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Acute Severe Asthma

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Asthma is the most common chronic pediatric respiratory disease and remains one of the most common reasons children in the United States require hospitalization. Acute exacerbations of asthma can be life-threatening. While most of these acute exacerbations can be managed successfully in the office or in the emergency department, a few children with severe exacerbations may require admission to the intensive care unit. These severe exacerbations have been referred to as status asthmaticus, acute severe asthma, life-threatening asthma, or near-fatal asthma.[1-5] The following review explores the current understanding of epidemiology, physiology, and treatment of acute severe asthma in children.

Definition

The exact definition of acute severe asthma or status asthmaticus varies between authors.[1] For this article, the authors define acute severe asthma as a wheezing patient who does not respond to initial doses of inhaled bronchodilators.

Risk Factors

Although few children have life-threatening asthma episodes, these episodes may be associated with potential mortality, a high morbidity, and a high cost of treatment.[3]

There appear to be two clinical subsets of children who die from acute severe asthma.[3,6] The first group of children with fatal asthma has a long history of poorly controlled asthma, often with a previous history of respiratory failure. In these children, death occurs secondary to acute respiratory failure and asphyxia or complications associated with mechanical ventilation.[6-8] Pathologic examination in these children reveals extensive bronchial mucous plugging, edema, and eosinophilic infiltration of the airways. In the second group, the children have only a mild history of asthma, experience the sudden onset of bronchospasm, and can rapidly progress to cardiac arrest and death. If recognized and managed early, these children respond to beta-adrenergic agonists and mechanical ventilatory support better than children with the slow-onset fatal asthma.[3,6,9,10] Pathologic examination in this rapidly fatal group of children shows empty airways devoid of mucous plugging with a greater proportion of neutrophils rather than eosinophils.[3,6,9,10] Although the existence of this second type of fast onset has been controversial, many studies have shown a high percentage of death occurring within 1-2 hours of onset of symptoms.[3,6-13] Some of these studies reveal an over-representation of obese children and African American children in this rapidly progressive, type 2 cohort, which invites speculation about an alternative pathophysiology or possible health care disparities in this group of children.[3,14] These studies indicate the need to recognize children at risk for sudden asphyxial asthma. Accordingly, several authors have attempted to define

Executive Summary

Acute exacerbations of asthma are one of the key clinical complications that result in adverse patient outcomes, and they also are keenly monitored by managed care companies. Primary care physicians typically are looked to for championing performance improvement to reduce these rates and the need for escalating care and cost.

- There are two subsets of children who die from acute severe asthma: those with a long history of poorly controlled asthma and those with a history of mild asthma who experience a sudden onset of bronchospasm that rapidly progresses to cardiac arrest and death.
- Risk factors for potentially fatal asthma include history of previous attacks, attacks precipitated by food allergy, failure to perceive the severity of illness, noncompliance, lack of social support, and non-white children.
- The Becket asthma score is a quick assessment of severity of an attack.
- Common pharmacologic agents include corticosteroids, beta-agonists, ipratropium bromide, magnesium sulfate, aminophylline, and leukotriene modifiers.

risk factors for children who die from asthma.[3,6,15,16] (*See Table 1.*) Patients who have had a life-threatening episode of asthma should receive ongoing care from a physician who specializes in asthma.[8,15]

Pathogenesis/ Pathophysiology

Asthma is now considered a disease of inflammation. During the past 2 decades, tremendous gains have been made with regard to the understanding of asthma.[6,17-19] Asthma frequently begins during childhood and is often associated with atopy, the genetic susceptibility to produce IgE specific to common airborne allergens. Atopic children respond to these airborne allergens with a T helper type 2 (Th2) immune response. Th2 cells produce interleukin (IL)-4, IL-5, IL-6, IL-9, and IL-13 and are involved in activating B cells for the production of immunoglobulins, particularly IgE. Th2 responses stimulate antibody-mediated responses and activation of mast cells and eosinophils. All of these factors result in the main pathophysiologic components of the asthmatic response — airway inflammation, bronchial airway hyper-responsiveness, airway remodeling, and reversible airway obstruction.

"Severe airway obstruction resulting from inflammation, bronchoconstriction, and excessive mucus production is at the heart of the gas exchange abnormalities and symptomatology in children with acute severe asthma."[6] The increase in airway resistance leads to an increase in the work of breathing and reductions in FEV_1 and FEV_1/FVC.[6,20] In acute severe asthma, transpulmonary pressures greater than 50 cm H_2O are not uncommon.[19] As the degree of airway obstruction worsens, expiration becomes active rather than passive; air flow rates are low and expiratory times become progressively longer. Inspiration often occurs before termination of the previous expiration, resulting in air-trapping and lung hyperinflation and, because of this, residual volume and functional residual capacity is increased.[20]

Air-trapping and lung hyperinflation lead to an intrinsic positive end-expiratory pressure (PEEPi), or auto-PEEP, a phenomenon also termed dynamic hyperinflation. Dynamic hyperinflation has several adverse effects in the cardiovascular and respiratory systems. The increased lung volumes shift tidal breathing to a less compliant portion of the pressure volume curve. In addition, flattening of the diaphragm produces additional mechanical disadvantage.[21] Dynamic hyperinflation also results in premature closure of the airways, which produces a further increase in air resistance, thereby

Table 1: Risk Factors for Potentially Fatal Asthma

- History of previous attack with:
  - Severe, rapid progression of symptoms
  - Respiratory failure requiring endotracheal intubation and ventilatory support*
  - Pediatric intensive care unit admission
- Attacks precipitated by food allergy
- Denial or failure to perceive the severity of illness
- Noncompliance
- Lack of social support network (dysfunctional family)
- Non-white children (especially African American and Hispanic children)

*May include noninvasive positive pressure ventilation

Adapted from:Wheeler DS, Page K, Shanley TP. Status asthmaticus, in Wheeler DS et al (eds.) *The Respiratory Tract in Pediatric Critical Illness and Injury*. London, Springer-Verlag, 2009:169-193.

worsening gas exchange. These factors collectively increase the work of breathing and increase the physiologic dead space. The gas exchange abnormalities produced by dynamic hyperinflation result in ventilation-perfusion mismatch.[6]

The effects of dynamic hyperinflation on cardiorespiratory interactions are quite complex.[22] Right ventricular afterload is increased by a combination of factors, including lung hyperinflation (increased pulmonary vascular resistance), hypoxic pulmonary vasoconstriction, and acidosis. During expiration, the increase of intrathoracic pressure secondary to dynamic hyperinflation impedes systemic venous return, worsening left ventricular preload. During inspiration, the exaggerated negative intrathoracic pressure required to overcome airway resistance increases left ventricular afterload.[6,22] These changes can be detected clinically as an increase in the pulsus paradoxus.[23,24] Pulsus paradoxus is a valuable clinical sign of disease severity in children with asthma.[1,24]

Clinical Presentation and Assessment

The onset of asthma symptoms may result from exposure to "triggers" such as exercise, air pollutants, weather conditions, viral infections of the upper respiratory tract (particularly rhinovirus and respiratory syncytial virus), or allergen exposure, all of which increase inflammation in the lower airways.[2]

Table 2: Markers of Acute Severe Asthma

- Inability to speak in full sentences or unable to speak at all (infants will have shorter periods of crying and will have difficulty or will stop feeding)
- Drowsy/confused/altered level of consciousness
- Seated upright; unable to lie supine
- Respiratory rate is elevated (bradypnea is an ominous sign)
- Use of accessory muscles, tracheal tugging, head bobbing
- Loud wheeze; quiet chest is ominous sign
- Tachycardia; bradycardia is ominous sign
- Pulsus paradoxus (> 15 mmHg drop with inspiration); absence may indicate fatigue
- Decreased FEV_1 or PEFR < 40% of best or predicted
- Oxygen saturation < 90% in room air

The presentation of acute severe asthma varies by severity, asthmatic trigger, and patient age.[2] This variability often leads to poor recognition of the severity of illness, which, in turn, results in greater morbidity.[25,26] The clinical examination can be misleading, and key clinical features must be taken into consideration when assessing a patient with acute asthma. [5,25-27] (*See Table 2.*)

The immediate assessment of patients with acute asthma exacerbations should include the degree of respiratory distress (ability to speak, respiratory rate, use of accessory muscle, air entry, inspiratory:expiratory ratio), degree of hypoxia (cyanosis, pulse oximetry, level of consciousness), and cardiovascular status (heart rate and rhythm, pulsus paradoxus, blood pressure).

Accessory muscle use, wheeze, and tachypnea might diminish as the patient tires.[5] This may be misinterpreted as an improvement, when in fact the patient has worsened. Clinicians must pay close attention to these changes.

There are many "asthma scores" based on these observations that have been developed to assess the severity of the asthma exacerbation; at least 18 different "asthma scores" are available.[3,28,29] The Becker asthma score is a quick assessment of severity by using respiratory rate, wheezing, inspiratory:expiratory ratio, and accessory muscle use.[30] (*See Table 3.*) A score > 4 is considered moderately severe status asthmaticus, while a patient with a score of ≥ 7 may be admitted to the

Table 3: Assessing Asthma Severity — Becker Asthma Score

Score	Respiratory Rate (per min)	Wheezing	I/E Ratio	Accessory Muscle Use
0	< 30	None	1:1.5	None
1	30-40	Terminal expiration	1:2	1 site
2	41-50	Entire expiration	1:3	2 sites
3	> 50	Inspiration and entire expiration	> 1:3	3 sites or neck strap muscle use

Score ≤ 4 = mild; Score > 4 to < 7 = moderate; Score ≥ 7 = severe (needs PICU)

Source: Ducharme FM, Chalut D, Ploynick L, et al. The Pediatric Respiratory Assessment Measure: A valid clinical score for assessing acute asthma severity from toddlers to teenagers. *J Pediatr* 2008;152:476-480.

Table 4: Asthma Severity

Parameter*	Mild	Moderate	Severe	Imminent Respiratory Arrest
Breathlessness	Walking Can lie down	Talking (infant: shorter cry/difficult feeding); Prefers sitting	At rest (infant will stop feeding) Hunched over	
Talks in	Sentences	Phrases	Words	
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy/confused
Respiratory rate	Increased	Increased	Increased	Bradypnea
Accessory muscles and suprasternal retractions	Usually not	Usually	Usually	Paradoxical movement
Wheeze	Moderate (end expiration)	Loud	Usually loud	Absence of wheeze
Pulse/min	< 100	100-120	> 120	Bradycardia
Pulsus paradoxus (mm HG)	Absent (< 10)	10-25	> 25	Absence suggests respiratory muscle fatigue
PEFR (after bronchodilator)	> 80%	60-80%	< 60%	
PaO_2 on room air and/or $PaCO_2$ (mm Hg)	Normal (need not be tested)	< 45	> 45	
Saturation	> 95%	91-95%	90% or less	

*The presence of several parameters, but not necessarily all, indicates the severity of the attack
PEFR = peak expiratory flow rate

Source: Becker AB, Nelson NA, Simons FE. The pulmonary index. Assessment of a clinical score for asthma. *Am J Dis Child* 1984;138:574-576

pediatric intensive care unit (PICU). A more detailed asthma score provided by the National Heart, Lung, and Blood Institute is given in Table 4.[31] The physician also needs to consider the wide range of potential complications, as attention to these problems when assessing and managing acute asthma might significantly improve outcome.[5] (*See Table 5.*)

Pulse oximetry may be useful to differentiate between patients who are likely to improve with therapy and those who are likely to progress to respiratory failure.[6] An increase in oxygen saturation following albuterol nebulization predicts patients who are likely to improve, and respiratory failure rarely occurs in patients with an initial oxygen saturation > 92%.[6] The degree of hypoxemia significantly correlates with the degree of airway obstruction, as determined by FEV_1.[32] Furthermore, hypoxemia appears to be an independent risk factor for both hospitalization and increased length of stay.[33-35]

Hypoxemia is multifactorial in origin, resulting from a combination of factors including ventilation-perfusion mismatch, alveolar hypoventilation, and hypercarbia. Significant hypoxemia, however, is relatively uncommon in children with acute severe asthma.[6,19,35] Therefore, the presence of significant hypoxemia should alert the physician to search for some additional underlying cause, such as atelectasis secondary to mucous plugging, pneumonia, or pneumothorax.[5,6]

The degree of airway obstruction is rapidly determined by assessment of pulmonary function using the FEV_1 and the peak expiratory flow rate (PEFR). Although FEV_1 is considered to be the more reliable test, the PEFR is more easily obtained. Unfortunately, the correct performance of both tests is extremely dependent on the patient's cooperation and effort; the values obtained may vary widely and may not be reliable. PEFR and FEV_1 less than 30-50% of predicted, or of the patient's personal best, indicate severe airflow obstruction.[6,27] If the child is in significant distress, the use of pulmonary function tests may need to be deferred.

Monitoring carbon dioxide levels, invasively or non-invasively, might be useful. Although initial $PaCO_2$ may be below normal levels, a progressive increase in $PaCO_2$ is considered an early warning sign of severe airway obstruction and impending respiratory failure.[6]

Metabolic acidosis is well described in patients with acute severe asthma.[36,37] One reported cause of metabolic acidosis is accumulation of lactic acid, presumably from a prolonged and marked increased work of breathing; additional factors include tissue hypoxia secondary to oxygen supply/demand imbalance in respiratory muscles, dehydration accompanying acute severe asthma from poor oral intake and increased insensible losses, and decreased cardiac output associated with hyperinflation.[6] These causes are often labeled as type A and represent impairment in oxygen delivery as the cause of lactic acidosis. Other authors have shown that lactic acidosis is common in acute severe asthma but is primarily type B lactic acidosis, which occurs in the presence of normal oxygen delivery.[36] Type B lactic acidosis is often seen with the use of beta-adrenergic agents to treat acute severe asthma, which leads to derangements in glucose metabolism and the development of type B lactic acidosis.[36,38,39] Support for this mechanism includes clinical observations demonstrating a resolution of lactic acidosis with decreasing or discontinuation of bronchodilator therapy.[36] Lactic acidosis developing during acute severe asthma is important to recognize because the compensatory hyperventilation that ensues to maintain body pH may lead to increased dyspnea. Lactic acid-induced hyperventilation has been mistaken as a sign of worsening airway obstruction, leading to inappropriate escalation of bronchodilator therapy, and has contributed to respiratory failure and the institution of mechanical ventilation.[36]

The mechanism for lactic acidosis during acute severe asthma is important to determine because effective treatment must address the underlying cause. If it is determined that the lactic acidosis is primarily type B associated with normal oxygen delivery and in the presence of adequate ventilation, a reduction in beta-adrenergic therapy may be appropriate.[36]

Hypokalemia is the most common electrolyte abnormality in children with acute severe asthma and is a well-recognized complication of beta-agonist administration.[38,40,41] In addition, glucocorticoids used in the management of asthma can result in unwanted mineralocorticoid effects, leading to hypokalemia.[40,41]

Serum potassium levels should be monitored and, if needed, replaced if sufficiently low. Oral supplementation should be avoided due to the patient's respiratory distress and supplementation should be given intravenously.

Another common abnormality seen is hyperglycemia. Treatment with beta-agonists and systemic steroids has been associated with changes in glucose metabolism.[42] The resultant hyperglycemia may result in osmotic diuresis and dehydration; this would be aggravated by utilization of intravenous fluid supplements containing glucose, a common practice during hospitalization of children.

Complicating the hyperglycemia, fluid balance abnormalities are also seen in children with acute severe asthma, and these children are often dehydrated because of increased insensible fluid losses from the respiratory tract, coupled with poor oral intake of fluids. Dehydration may produce thicker, more tenacious bronchial secretions, leading to worsening bronchial mucous plugging. Although the majority of children require intravenous fluid rehydration, an inappropriate type of fluid (hypotonic or glucose-containing) or overzealous fluid administration may lead to fluid retention and pulmonary edema.[6,42-45] Children with acute severe asthma may have elevated plasma antidiuretic hormone levels and are at risk for hyponatremia and fluid overload if given large volumes of hypotonic fluid.[44-46] In addition, the high negative transpulmonary pressures associated with acute severe asthma promote fluid accumulation around the respiratory bronchioles, leading to pulmonary edema and worsening respiratory status.[6,47]

Table 5: Asthma Complications

- Pneumothorax
- Pneumomediastinum
- Pneumopericardium
- Pulmonary interstitial emphysema
- Pneumoretroperitoneum
- Cardiac arrhythmias
- Myocardial ischemia
- Mucous plugging
- Atelectasis
- Pneumonia
- Electrolyte imbalance (hypokalemia, hypomagnesemia, hypophosphatemia)
- Lactic acidosis
- Hyperglycemia

Management

Any child with acute severe asthma requires cardiorespiratory monitoring and close attention to fluid balance and neurologic status. A comfortable and supportive environment can ameliorate the situational anxiety, although hypoxemia and anxiety will also lead to agitation and restlessness. Sedatives should be avoided in the nonintubated patient with acute severe asthma, as it may cause hypoventilation and worsen the respiratory distress leading to failure.

There has been a great deal of interest in phenotypic classification of severe or difficult to treat asthma.[4] Although childhood asthma is generally an allergic, eosinophilic inflammatory disease, many patients with severe asthma have significant neutrophil inflammation.[4,48,49] Neutrophilic inflammation may be due to chronic infection with organisms such as *Mycoplasma* or *Chlamydia*.[50,51] While antibiotics are not recommended in the therapy of acute asthma, this recent evidence suggests that antibiotic therapy targeted to patients with evidence of atypical bacterial infection may confer additional advantage to standard therapy alone.[50,51] Additional use of

Table 6: Grades of Evidence of Interventions in Acute Severe Asthma

Grade A
• Oxygen should be administered to maintain peripheral oxygen saturation between 0.89 to 0.95
• Use inhaled β2-agonists as primary bronchodilators
• Give steroids in all cases of acute asthma
Grade B
• Add nebulized ipratropium bromide
Grade C
• A single dose of magnesium sulfate can be used
Grade D
• A single dose of intravenous montelukast should be considered

The quality of the evidence was given a grade of A, B, C, or D for high, moderate, low, and very low, respectively.

Adapted from: Rubin BK, Pohanka V. Beyond the guidelines: Fatal and near-fatal asthma. *Paediatr Resp Rev* 2012;13:106-111.

antibiotics involves using macrolide antibiotics as immunomodulatory drugs that can reduce neutrophil inflammation and decrease asthma severity and the need for corticosteroids.[4,50]

Oxygen Therapy

Hypoxemia is always present in life-threatening asthma and is a major contributing factor to asthma death.[4,52] The administration of supplemental oxygen is considered standard therapy for children with acute severe asthma/status asthmaticus.[6,31] (*See Table 6.*) While oxygen therapy is essential, unregulated oxygen therapy — the provision of high amounts of oxygen beyond what is necessary to obtain physiologic oxygen saturation levels — has been shown to be unnecessary and potentially harmful.[4,53,54] Giving 100% oxygen can depress compromised ventilation and increase the partial pressure of carbon dioxide ($PaCO_2$). Therefore, some authors have recommended that only sufficient oxygen be administered to maintain peripheral oxygen saturation (SpO_2) between 89-94%.[4] It must be remembered that some bronchodilators, particularly the beta-agonists, reduce hypoxic pulmonary vasoconstriction and, thus, worsen hypoxemia by increasing V/Q mismatch.[6] Therefore, these medications should be administered concurrently with supplemental oxygen.[6,52]

Systemic Corticosteroids

With the recognition that airway inflammation plays a prominent role in the pathophysiology of acute severe asthma, corticosteroids are standard treatment for children with acute severe asthma. (*See Table 6.*) Based on the wealth of available evidence, expert opinion and published guidelines recommend the administration of corticosteroids in the management of acute severe asthma/status asthmaticus within the initial 48 hours of treatment.[2,6,31] A 2003 Cochrane Database review supports improved outcomes for children who receive corticosteroids early in their emergency department course.[55] Corticosteroids speed the resolution of airflow obstruction, potentiate the effects of beta-agonist therapy, and have the potential to decrease hospitalization for sicker patients.

The optimal dosing of systemic corticosteroids for children with acute severe asthma remains an unresolved issue.[6,56] Several studies suggest that high-dose corticosteroid therapy offers few advantages over low-dose corticosteroids in the treatment of acute severe asthma.[6] Typically, oral or intravenous corticosteroids (e.g., methylprednisolone) have been given at a dose of 1-2 mg/kg as frequently as every 6 hours during an acute severe asthma attack. Although corticosteroids are often administered intravenously, data do not show that this is more effective than oral steroids, and no data show that giving prednisone 2 mg/kg/day (80 mg maximum for older children and adults) is less effective than higher doses.[4] (*See Table 7.*) Oral steroids generally are not recommended for children with acute severe asthma and impending respiratory failure because of the increased risk of intubating a patient with a full stomach.

Significant side effects may occur with the use of steroids, particularly if used at a high dose; these include hyperglycemia, hypertension, and acute psychosis.[2,57] Prolonged steroid use may cause immunosuppression, hypothalamic-pituitary-adrenal axis suppression, osteoporosis, myopathy, and weakness.[2,4,58,59]

Currently available evidence does not support the use of inhaled steroids in lieu of systemic corticosteroids.[6] While it is most common to discontinue inhaled corticosteroids in patients with acute severe asthma, the concomitant use of inhaled steroids along with systemic steroids may provide additional benefit for some, but not all, patients.[60,61]

Beta-Adrenergic Agonists

Table 7 provides details on the bronchodilators currently used in the management of acute severe asthma. Beta-2-adrenergic receptor agonists have emerged as the single most potent class of bronchodilator available.[26,62] Non-selective agonists such as isoproterenol or epinephrine are associated with a higher incidence of significant side effects (i.e., myocardial ischemia) and are often not used.[6,62,63]

Table 7: Common Drugs and Doses in Acute Severe Asthma

Corticosteroids

- Usually administered intravenously
- Methylprednisolone: 2-4 mg/kg/day, with a maximum dose of 60 mg/day (adult maximum 125 mg/day)

Beta-agonist (Albuterol)

- Hourly or continuously delivered albuterol via nebulizer
- Hourly: 0.15 mg/kg every hour (minimum 2.5 mg; maximum 5 mg)
- Continuous: 0.3-0.5 mg/kg/hour up to 20 mg/hr (consider 10 mg/hr for children who weigh 5-10 kg; 15 mg/hr for children who weigh 10-20 kg; and 20 mg/hr for children who weight > 20 kg)

Beta-agonist (Terbutaline)

- Continuous intravenous infusion
- Loading dose: 2-10 mcg/kg
- Infusion dose: 0.5 mcg/kg/min; dose may be increased by 0.1-0.2 mcg/kg/min every 15-30 min; doses up to 10 mcg/kg/min have been reported

Ipratropium bromide

- 250 mcg/dose for children < 20 kg; 500 mcg/dose for children ≥ 20 kg
- Consider 3 doses given every 4-8 hours

Magnesium sulfate

- 50-75 mg/kg (max dose 2 g given every 4-6 hours)
- Optimal magnesium level 4-5.5 mg/dL

Aminophylline

- Aminophylline is the ethylenediamine salt of theophylline; pharmacokinetic parameters are those of theophylline; 100 mg aminophylline = 80 mg theophylline
- Monitoring parameter: theophylline level; recommend level < 15 mcg/mL (see text)
- Loading dose (inpatients not currently receiving aminophylline or theophylline): 5-6 mg/kg (based on aminophylline) over 20-30 minutes
- Continuous infusion follows, and dose depends on patient age and desired level
- Suggested infusion rates:
  - 6 months-1 year: 0.7 mg/kg/hr aminophylline
  - 1-9 years: 1.2 mg/kg/hr aminophylline
  - 10-16 years: 0.9 mg/kg/hr aminophylline
- Metabolism is influenced by multiple medications
- Effect as a respiratory muscle inotrope is dose-dependent; lower doses are effective

Leukotriene Modifiers

- Montelukast (Singulair) oral tablets
- Dose:
  - 1-5 years: 4 mg po QD
  - 6-14 years: 5 mg po QD

Subcutaneous epinephrine has been used for decades for the treatment of acute severe asthma.[6,62] The use of subcutaneous epinephrine has fallen out of favor because of the widespread availability, ease of administration, and efficacy of the newer beta-adrenergic agonists such as albuterol. However, subcutaneous/IM epinephrine continues to have a role in the treatment of critically ill children with impending respiratory failure secondary to acute severe asthma.[64-66] Subcutaneous/IM administration of epinephrine should be considered in children who are rapidly decompensating despite inhaled beta-adrenergic agonists and

in children who are unable to cooperate with inhalation therapy secondary to anxiety, altered mental status, or apnea.[6] Subcutaneous epinephrine (0.01 mg/kg) may be administered every 20 minutes for three doses. Severe airflow obstruction may be relieved by subcutaneous/IM epinephrine to a degree sufficient to allow adequate delivery of aerosolized beta-adrenergic agonists to the distal airways, thereby allowing these agents to take effect.

For the majority of patients with acute severe asthma, inhaled beta-adrenergic agonists have superior efficacy compared with subcutaneous epinephrine.[1,6] Furthermore, although the duration of action appears to be dose-dependent, sequential inhalation of these agents (most commonly albuterol) produces a more rapid, greater improvement in airway obstruction than nebulizing higher doses less frequently.[6,67] Based on the available evidence, the consensus is that frequent albuterol nebulization should be considered standard therapy for children presenting with acute severe asthma.[6,31] (*See Table 6.*)

Several studies have compared the efficacy of small-volume nebulizers vs metered-dose inhalers (MDI) with spacers for the treatment of acute asthma exacerbation in children.[68] Although nebulizers allow for the concurrent administration of supplemental oxygen, some studies have suggested close to 90% of the drug is lost to the atmosphere.[1,6,64] The available evidence suggests that there are no differences between MDIs with spacers compared with nebulizers, and either option appears reasonable in the emergency department setting.[68,70] However, evidence is growing that the use of an MDI with a valved holding chamber is more effective than nebulized albuterol in young children with moderate to severe asthma exacerbations.[1,4,71]

Recent studies have evaluated the use of Breath Actuated Nebulizer (BAN).[72,73] These studies have revealed that BANs allow for a lower amount of albuterol while decreasing asthma severity scores, decreasing length of stay in the emergency department, and reducing the rate of hospitalization.[73] A BAN may prove to be an acceptable alternative to conventional nebulizer use.[73]

Continuous albuterol nebulization has been shown to be more effective in children with acute severe asthma and impending respiratory failure.[1,62,74,75] Continuous nebulization provides sustained stimulation of the beta-adrenergic receptors in the airways, thereby preventing the rebound bronchospasm that can occur with intermittent nebulization.[6] Although continuous nebulization of albuterol can be safely done, it should be done only in a closely monitored setting. Side effects occur with beta-agonists and include hypokalemia, cardiac arrhythmias, cardiac ischemia, tremor, ventilation-perfusion mismatch, lactic acidosis, and increased mucus secretion.[1,2,4,6,62] It is important to remember that beta receptors in the lung are down regulated and rapidly saturated with the use of inhaled beta-agonists.[4] This may result in no clinically beneficial effect of higher doses of beta-agonists but increasing side effects.[4,76]

Albuterol exists as a 50:50 mixture of two mirror-image enantiomers: the active R-albuterol and S-albuterol. Previously thought to be an inert compound, S-albuterol may exaggerate airway hyperresponsiveness and result in bronchoconstriction; it may also have a proinflammatory effect.[1,70,77] It appears that administration of only the R-enantiomer of albuterol would be an appropriate treatment rationale. Levalbuterol (Xopenex R) is pure R-albuterol and is available for nebulization. Unfortunately, the majority of studies in children with exacerbations of asthma suggest that there is not a clinical benefit to the use of levalbuterol vs racemic albuterol.[1,78-80] No recommendation regarding the use of the much more expensive levalbuterol in children with acute severe asthma can presently be made.[1,6]

Intravenous beta-agonists should be considered in patients unresponsive to treatment with continuous nebulization, as well as those for whom nebulization is not feasible (i.e., intubated patients, patients with prohibitively poor air entry). Decreased tidal volume and/or near complete airway obstruction in severe status asthmaticus may prevent effective aerosolized bronchodilator delivery. Terbutaline is the current intravenous beta-agonist of choice in the United States, while other countries use albuterol intravenously. Most adverse effects of beta-agonists in asthma are of cardiovascular nature, including tachycardia, increased QTc interval, dysrhythmia, hypertension, as well as hypotension. Induced severe hypokalemia may precipitate arrhythmias. Neither albuterol nor terbutaline, however, is known to cause clinically significant cardiac toxicity when used for pediatric status asthmaticus.[81,82]

The use of intravenous terbutaline is not recommended by the current National Asthma Education Program (NAEP) Expert Panel Report.[31]

Anticholinergic Therapy

The autonomic nervous system is involved in the regulation of airway smooth muscle tone and mucus secretion. The parasympathetic nerve fibers, which are confined to the larger, central airways, stimulate bronchoconstriction and mucus secretion (mediated through the neurotransmitter acetylcholine).[6] In contrast, the sympathetic nerve fibers are distributed more peripherally in the smaller airways and stimulate bronchodilation. This dual-innervation suggests that a therapeutic strategy aimed at both the cholinergic and adrenergic pathways would be beneficial in the treatment of acute severe asthma. Indeed, this is the case, and, when used in conjunction with beta-agonists, anticholinergic agents are now standard of care in the treatment of acute asthma in children.[1,4,6] (*See Table 6.*) A Cochrane review strongly suggests significant clinical benefit to the concomitant use of a beta-agonist and inhaled anticholinergic for treating acute severe asthma, and some studies have indicated an added

benefit with minimal risk in the most severely ill patients with asthma.[83,84] The most commonly used compound is ipratropium bromide, a quaternary derivative of atropine. (*See Table 7.*)

Magnesium

Magnesium is safe, and a meta-analysis has shown that when given systematically, it confers additional benefit in the treatment of life-threatening asthma.[85] Magnesium might be effective in acute asthma through a variety of mechanisms.[5,6]

Magnesium administration may serve to replace an underlying magnesium deficiency. Multiple studies have shown that patients with acute severe asthma have underlying hypomagnesemia, and frequent beta-agonist therapy has been demonstrated to result in decreased magnesium levels.[6]

Magnesium may act as a pharmacologic agent via one of several mechanisms.[5,6] It is clear that magnesium acts principally as a calcium antagonist, directly inhibiting calcium uptake in smooth muscle cells, thereby resulting in smooth muscle relaxation. Magnesium acts at the neuromuscular junction by decreasing acetylcholine release, diminishing the depolarization action of acetylcholine, and depressing the excitability of smooth muscle membranes.[6,89,90] Magnesium decreases histamine release from mast cells.[90-92] Finally, magnesium decreases superoxide production by neutrophils, thereby producing anti-inflammatory properties.[90,91]

A single dose of intravenous magnesium sulfate administered to patients with severe acute asthma has been shown to be effective.[5]

Several small, prospective, randomized, controlled trials comparing intravenous magnesium and placebo in children presenting to the emergency department with acute severe asthma have been performed.[91,93-96] Not all of these studies demonstrated beneficial effects with magnesium; a subsequent meta-analysis concluded that magnesium sulfate provides additional benefit to children with acute severe asthma when added to a regimen of frequent, nebulized beta-adrenergic agonists and corticosteroids.[92] Magnesium sulfate should be tried, at least a single dose, when respiratory failure is impending.[26,31] (*See Table 6.*)

The current dose and frequency of administration have not been adequately defined. (*See Table 7.*) There is evidence to suggest that increasing the serum magnesium level to greater than 4 mg/dL is necessary to produce bronchodilation.[26,97] Onset of action is within minutes and the effects last approximately 2 hours.[6,97] Side effects appear dependent upon serum magnesium concentration; mild effects include nausea, vomiting, facial flushing, and dry mouth. At serum magnesium levels greater than 12 mg/dL, loss of deep tendon reflexes, muscle weakness, and respiratory depression, as well as cardiac conduction defects, may be seen.[97]

Theophylline/ Aminophylline

Theophylline has been used as a bronchodilator for the treatment of asthma for many years and was once considered the bronchodilator of choice for the management of acute asthma.[100] The therapeutic effects of aminophylline in asthma include bronchodilation and improved diaphragmatic contraction.[101] Therapeutic effects occur at blood levels up to 20 mg/dL. Levels above this range may occur and cause toxic effects. These include diuresis, hypokalemia, insomnia, tachycardia, cardiac arrhythmias, convulsions, and sudden death.[101,102] In many centers, aminophylline has been supplemented by the use of beta-agonists for the treatment of acute severe asthma.

The NAEP Expert Panel has revised its original guidelines and concluded that methylxanthines are not recommended for treatment of hospitalized children with status asthmaticus.[31] However, current recommendations proscribing the use of theophylline are not based on analysis of treatment data in critically ill children with acute severe asthma.[6]

Theophylline offers several potential advantages for the treatment of acute severe asthma in the PICU population. Theophylline produces bronchodilation and improves air flow without adversely affecting ventilation-perfusion matching.[103] Theophylline's diuretic effect may reduce excess alveolar fluid and microvascular permeability.[6,103,104] Finally, theophylline increases respiratory drive, improves mucociliary clearance, reduces pulmonary vascular resistance, and improves contractility of the diaphragm, all of which may benefit the child with acute severe asthma.[101,103] For these reasons, there has been renewed interest in intravenous aminophylline.[101] Current guidelines assert that there may be a role for aminophylline in particularly severe asthma.[101] Aminophylline use in children may be appropriate if children have acute severe asthma and the response to aggressive therapy (inhaled bronchodilators and glucocorticoids) is poor. This recommendation is based on limited data and further work is needed.[101,105] Avoidance of toxic theophylline levels is critical. (*See Table 7.*) One study recommends an intravenous loading dose of 7 mg/kg, followed by age-adjusted rates of 0.5-0.65 mg/kg/hr.[105] Theophylline levels are kept between 12-17 mg/mL.

Helium-Oxygen Mixtures

Helium-oxygen mixtures (heliox) are available in concentrations of 80% helium/20% oxygen and 70% helium/30% oxygen. Helium mixtures have a low density compared with air (the 80/20 mixture is approximately one-third the density of air).[26] Heliox is a temporary measure to reduce respiratory resistive work and forestall muscle fatigue until airway obstruction improves with conventional therapy.[26] Evidence suggests heliox is more effective for the sicker patient.[106] The beneficial effects of heliox seem most efficacious when used early in the disease course (less than 24 hours).[106] The addition of heliox to the treatment regimen for acute asthma is not warranted for all patients.[107] Patients requiring FiO_2 greater than 0.30 will not tolerate the

use of heliox, as there is no way to titrate beyond the 70/30 mixture.

Heliox may also be effective as the driving gas for nebulized bronchodilators.[108,109] The low density of helium improves the deposition of aerosolized particles in the airways, which can lead to a more rapid response to treatment and more significant improvement in airway function.[26]

In the pediatric patient who requires conventional mechanical support of ventilation, heliox may assist in lowering peak inspiratory pressure (PIP) and improving blood gas pH and partial pressure of CO_2.[110] This benefit is lost once PIP is less than 30 cm H_2O.

Ketamine

Ketamine, a dissociative anesthetic agent, causes bronchodilation by a combination of factors, including drug-induced release of endogenous catecholamines, inhibition of vagal tone, and direct smooth muscle relaxation.[111] Although ketamine has been used successfully for the treatment of refractory bronchospasm in intubated patients, there is controversy concerning its use in nonintubated patients because it may cause increased pulmonary secretions and laryngospasm.[112-115] Literature exists supporting its use as an efficacious adjunct to standard therapy in the treatment of children with acute severe asthma and impending respiratory failure.[116-117]Ketamine should be used cautiously in unintubated patients and only in a monitored setting.

Leukotriene-Modifying Agents

The leukotrienes are biologically active fatty acids generated from arachidonic acid by the enzyme 5-lipoxygenase; 5-lipoxygenase generates leukotriene A4 (LTA4) from arachidonic acid. LTA4 is metabolized to LTC4, LTD4, and LTE4, which are referred to as the slow-reacting substances of anaphylaxis.[118-120] The leukotrienes produce bronchoconstriction, stimulate mucus secretion, decrease mucociliary clearance, increase vascular permeability, and recruit eosinophils and basophils into the airway, thereby perpetuating airway inflammation.[118] The leukotrienes are 1000 times more potent than either histamine or methacholine in airway challenge tests.[121] Activation of the leukotriene pathways during acute asthma exacerbations, as determined by urinary LTE4 levels, appears to correlate with the degree of airway obstruction.[122]

Several different leukotriene-modifying agents are currently available, each working via different mechanisms. The leukotriene receptor antagonists (LTRA), montelukast and zafirlukast, are the only leukotriene-modifying agents approved for use in children. At present, the main indications for LTRA in pediatric asthma are as add-on therapy to inhaled corticosteroids or as initial controller therapy in children with mild asthma, especially those who cannot or will not use inhaled corticosteroids.[120]

There has been growing interest in using these agents for the treatment of acute severe asthma, although few studies exist.[120,123,124] (*See Table 6.*)

Mechanical Ventilation

Despite maximum medical therapy, mechanical ventilation may be needed to manage respiratory insufficiency resulting from airway obstruction and respiratory muscle fatigue in acute severe asthma.[4,125] Acute severe asthma leading to respiratory failure is an important cause of morbidity and mortality because of the high risk of barotrauma and cardiovascular instability associated with the positive pressure mechanical ventilation in these children.[6,126] The goal of mechanical ventilation in acute severe asthma is twofold: to provide sufficient gas exchange to ensure survival until reversal of airway obstruction is accomplished and to minimize complications associated with mechanical ventilation.

In an effort to unload the respiratory muscles during a severe asthma exacerbation, noninvasive mechanical ventilation using bilevel positive airway pressure (BiPAP) may be used.[5,127,128] The presence of air-trapping in the alveoli results in auto-positive end-expiratory pressure (auto-PEEP), which requires the patient to generate a higher negative inspiratory force to overcome the auto-PEEP and generate inspiratory flow. The addition of end-expiratory pressure should allow for equilibration of pressure between the mouth and the alveoli, reducing the amount of force the patient needs to generate to achieve inspiratory flow.[127] The use of an inspiratory pressure in BiPAP helps to reduce the work of the respiratory muscles.

Early initiation of noninvasive ventilation in addition to standard therapy may be effective in decreasing work of breathing in children with acute severe asthma.[127,128] It may be safe and well tolerated by patients for at least 24 hours and may prevent the need for intubation.[128] Clinicians using noninvasive ventilation for acute severe asthma must be skilled in noninvasive ventilation and be aware of complications such as barotrauma and hemodynamic instability. These patients must be closely monitored; their condition may abruptly worsen, so the medical team must be ready for immediate intubation.[127]

There are few absolute indications for tracheal intubation in children with status asthmaticus (e.g., coma, cardiac arrest), although failure to maintain adequate oxygen saturations, a worsening metabolic acidosis, and decreasing mental status are all signs that respiratory arrest is imminent. The decision to tracheally intubate should be based on the clinical examination and not the results of an arterial blood gas. These children should be considered high risk for intubation, and a rapid-sequence intubation technique should be performed by the most experienced physician available. Ketamine (2 mg/kg intravenous [IV]) is an excellent choice for an induction agent because of its bronchodilatory properties.[129] Neuromuscular blockade with either succinylcholine (if there are no contraindications to its use) or a nondepolarizing agent such as

vecuronium or rocuronium produces acceptable conditions for laryngoscopy and tracheal intubation.[129]

These children will likely require high inspiratory pressures, so the use of a cuffed endotracheal tube is preferable.[6,126,130]

More than one-half of the complications in patients requiring mechanical ventilation for acute severe asthma occur at or around the time of tracheal intubation and include hypoxemia, hypotension, and cardiac arrest.[130] Hyperventilation should be avoided, and hypotension should improve with volume resuscitation and slowing the respiratory rate to avoid further air-trapping and dynamic hyperinflation. A tension pneumothorax should be considered if these measures fail to relieve hypotension and hypoxemia. In these cases, needle thoracentesis is life-saving.

The goal of mechanical ventilation is to obtain and maintain acceptable oxygenation, avoid complications, and allow time for the corticosteroids and bronchodilators to reduce the bronchospasm and inflammation.

Mechanical ventilation should not be targeted toward the results of an arterial blood gas.[6] Utilizing low tidal volumes and respiratory rates and tolerating the resultant hypercapnia dramatically reduces the frequency of barotrauma and death.[6,131] In children, strategies that use low tidal volumes (8-10 mL/kg or less), short inspiratory times (0.75-1.5 sec), long expiratory times, and lower than normal respiratory rates result in improved survival.[6,126,132] The degree of hypercapnia that can be safely tolerated is not known.[6,133]

The most appropriate mode of mechanical ventilatory support may differ among patients and their stage of illness. Pressure control, volume control, and pressure support have all been used in children with acute severe asthma.[3,19,125] Each mode of ventilation has its advantages and disadvantages. Most authors prefer pressure-controlled ventilation.[3,6] The use of positive end-expiratory pressure (PEEP) in these patients is controversial; however, low-level PEEP will minimize dynamic airway collapse and decrease trigger work in spontaneously breathing patients.[19,130]

The use of high-frequency oscillatory ventilation in children with respiratory failure secondary to status asthmaticus has been reported.[134] Extracorporeal life support may be life-saving in children with refractory acute severe asthma.[135,136]

Finally, inhaled nitric oxide has been utilized in children with refractory status asthmaticus.[137,138] The rapid improvement in ventilation described may be related to the action of inhaled nitric oxide as a bronchodilator, direct vascular effect, or both.

Volatile Anesthetics

Inhalational anesthetics are occasionally used for the treatment of status asthmaticus and acute respiratory failure.[6] The bronchodilatory properties of these agents are well-known, and proposed mechanisms include direct stimulation of the beta-adrenergic receptor, direct relaxation of bronchial smooth muscle, inhibition of the release and action of bronchoactive mediators (e.g., histamine, acetylcholine), and depression of vagally mediated airway reflexes.[139] Halothane appears to be particularly effective, although concerns regarding its potential toxicity, including direct myocardial depression, hypotension, and arrhythmias, have limited its use in this setting.[140] These adverse effects may be further potentiated in children with status asthmaticus who will have some degree of hypoxia, hypercapnia, and acidosis and who are frequently managed with the concomitant administration of beta-adrenergic agents and/or theophylline.[6]

The use of isoflurane in status asthmaticus and acute respiratory failure offers several advantages over halothane.[141] Isoflurane produces less myocardial depression and is less arrhythmogenic compared with halothane. Given its role as a general anesthetic, concomitant administration of sedation/analgesia and neuromuscular blockade is not necessary. Isoflurane has been used with some success in both children and adults with status asthmaticus refractory to conventional therapy.[141,142]

Summary/Conclusion

The burden of childhood asthma continues to rise, with increasing rates of asthma prevalence, severity, and death.[143] Background asthma management remains suboptimal in children needing hospitalization. This is despite our improved understanding of the pathophysiology of asthma and the availability of effective anti-inflammatory therapy.

Children will continue to present to the ED with acute severe asthma. The emphasis in treatment remains on the aggressive use of inhaled beta-agonist and steroid therapy to abort the acute attack and decrease both the mortality rate and need for hospitalization. For children who fail to respond, adjunctive therapies and advances in ventilatory management can lead to improved outcomes in these patients.

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CME Questions

1. An episode of acute severe asthma is associated with:
   a. reduced functional residual capacity.
   b. normal transpulmonary pressure.
   c. active expiration.
   d. prolonged inspiration.
   e. increased forced expiration volume fraction in 1 second (FEV_1).

2. Effects of dynamic hyperinflation are complex and include:
   a. increased preload.
   b. reduced left ventricular afterload.
   c. reduced physiologic dead space.
   d. increased right ventricular afterload.
   e. reduced pulsus paradoxus.

3. Which of the following contributes to the acidosis that may be present in the patient with acute severe asthma?
   a. Excessive dose of beta-adrenergic drugs
   b. Dehydration
   c. Reduced cardiac output
   d. Mismatch of oxygen delivery to oxygen demand in respiratory muscles
   e. All of the above

4. Corticosteroids can have which of the following effects?
   a. Antagonist to beta-adrenergic therapy
   b. Decreased neutrophil survival
   c. Hypoglycemia
   d. Induced apoptosis of eosinophils
   e. Hypotension

5. Regarding the use of steroids in the treatment of acute severe asthma, which of the following is true?
   a. The optimal dose is known.
   b. High-dose corticosteroid therapy offers few advantages over low-dose corticosteroid therapy.
   c. Data exist that demonstrate ineffectiveness of oral steroids.
   d. Inhaled steroids are as effective as systemic steroids.

6. Concerning the use of beta-agonists in the treatment of acute severe asthma, which of the following is true?
   a. Frequent albuterol nebulization should be considered standard therapy.
   b. Levalbuterol has been shown to be more beneficial than racemic albuterol.
   c. Use of intravenous terbutaline is recommended by the Expert Panel Report of the National Asthma Education Program.
   d. Subcutaneous epinephrine should be used as the initial bronchodilator of choice.

7. Magnesium may facilitate bronchodilation through which mechanism?
   a. Calcium antagonist with resultant smooth muscle relaxation
   b. Induced diuresis
   c. Increased histamine from mast cells
   d. Increased acetylcholine release at the neuromuscular junction

8. Which of the following effects of theophylline may be beneficial in the treatment of acute severe asthma?
   a. Bronchodilation
   b. Diuretic effect
   c. Improved contractility of the diaphragm
   d. Improved mucociliary clearance
   e. All of the above

In Future Issues: Osteoarthritis

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The essential monthly primary care update

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

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Extended Treatment of VTE with Dabigatran vs Warfarin

Source: Schulman S, et al. *N Engl J Med* 2013;368:709-718.

Current recommendations for treatment of uncomplicated venous thromboembolism (VTE) in the absence of persistent risk factors for recurrence (e.g., protein C, protein S deficiency) suggest at least 3 months of antithrombotic therapy, typically with warfarin. Risk of recurrence, however, is not insubstantial, and recent clinical trials have shown that extending the duration of antithrombotic therapy after a course of warfarin (with aspirin, for instance) reduces the risk for recurrent VTE.

When warfarin is used for extended VTE recurrence prophylaxis, serious bleeding risk is about 1% annually. In comparison trials to warfarin, major bleeding rates on dabigatran have been generally comparable to warfarin, and intracerebral bleeding was demonstrably less with dabigatran than warfarin. Since dabigatran does not require monitoring, monthly physician visits, or dietary modulation, and has infrequent potential for drug interaction, it provides an attractive alternative.

Schulman et al report the results of two randomized, controlled, double-blind trials of dabigatran 150 mg twice daily vs warfarin or placebo in patients who had completed at least 3 months of warfarin treatment. Dabigatran was found to be noninferior to warfarin for prevention of recurrent VTE, with less frequent bleeding than warfarin (0.9% vs 1.8%). Dabigatran may be a viable alternative for extending DVT prophylaxis after a "traditional" course of warfarin. ■

Selection Criteria for Lung Cancer Screening

Source: Tammemagi M, et al. *N Engl J Med* 2013;368:728-736.

The national lung screening trial (NLST) reported in 2011 that low-dose CT screening in selected smokers (n = 53,454) reduced mortality from lung cancer by 20%. Entry criteria for the NLST included age 55-74 years with at least a 30 pack-years smoking history (former smokers, if they had quit within the last 15 years, were also enrolled). Subsequently, national organizations have variously endorsed lung cancer screening for persons matching NLST eligibility criteria.

The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) developed a lung-cancer risk prediction model based on 154,901 subjects. The PLCO determined other predictors of lung cancer beyond age and smoking duration used in the NLST, including body mass index, family history of lung cancer, and presence of chronic obstructive pulmonary disease. Because the PLCO duration of follow-up was longer than NLST (9.2 years vs 6.5 years), the strength of the PLCO prediction model might be anticipated to be greater than NLST.

A comparison between the NLST and PLCO prediction models found that the PLCO criteria had greater sensitivity and specificity, ultimately missing 43% fewer lung cancers than NLST. The PLCO prediction model has the potential to improve outcomes for persons at risk of lung cancer. ■

Special Subgroups in Hypertension: Obese Hypertensives

Source: Weber MA, et al. *Lancet* 2013; 381:537-545.

The inter-relatedness of obesity, hypertension, and cardiovascular (CV) events is complex. Obesity is independently associated with high blood pressure, all-cause mortality, and CV mortality. Yet, some reports have suggested that when parsing out CV events among a secondary prevention population (persons with *existing* CV disease), subjects with *normal* body weight bear a disproportionately *greater* risk than overweight and obese persons.

To further clarify this counterintuitive knowledge base, Weber et al report on an analysis of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension trial (ACCOMPLISH). ACCOMPLISH was performed to determine the relative efficacy of an angiotensin-converting enzyme (ACE) inhibitor + hydrochlorothiazide (HCTZ) vs ACE + amlodipine (CCB) in patients (n = 11,506) with Stage 2 hypertension (blood pressure > 160 mmHg). The trial ultimately demonstrated that ACE + CCB provided a significant mortality advantage over ACE + HCTZ.

In this report, ACCOMPLISH study subjects were divided into normal weight (body mass index [BMI] < 25), overweight (BMI 25-29), and obese categories (≥ BMI 30). CV events were most

frequent in the normal weight group, and least frequent in the obese patients in the ACE + HCTZ arm of the trial. In the ACE + CCB arm, there were no differences between weight categories in outcomes.

The seemingly paradoxical relationship between overweight and outcomes in persons with established CV disease (myocardial infarction, cerebrovascular accident, or existing hypertension) is difficult to explain. It may be that obesity-related hypertension is mediated by a different, more benign pathophysiology, hence producing more favorable outcomes, although this concept has been insufficiently explored. Finally, because of relatively higher event rates with ACE + HCTZ in normal-weight patients, clinicians should select ACE + CCB since event reduction is equivalent across weight groups for this combination. ■

Omalizumab for Asthma in Real Life

Source: Grimaldi-Bensouda L, et al. *Chest* 2013;143:398-405.

In evidence-based medicine terminology, "efficacy" is the term used to reflect results achieved within a clinical trial, whereas "effectiveness" indicates the results seen in "typical practice settings," commonly called "real-life settings." Clinical trials are anticipated to provide results superior to those in practice settings, where patients cannot be so readily de-selected or excluded, where resources may be more limited, and where rigorous regimentation for administration of treatment is less abundant.

Omalizumab (OMA) is not generally regarded as a first-line asthma medication, but rather an appropriate add-on when guideline-based foundation therapies (inhaled steroids, long-acting beta agonists, and leukotriene receptor antagonists) are insufficient to provide control. Although only 30-50% of asthmatics have a prominent underlying allergic component, among difficult-to-control asthmatics, the number may be as high as 80%. Clinical trials indicate that OMA, by blocking IgE, is a useful add-on in such resistant asthma cases. But do "real-life" settings reflect similar benefit?

Grimaldi-Bensouda et al report on refractory asthma patients (n = 767) recruited by more than 100 physicians who prescribed OMA as an add-on treatment. During a follow-up period of almost 2 years, study subjects who received any doses of OMA enjoyed a 43% relative risk reduction in likelihood of hospitalization or emergency department visits for asthma. Subjects on treatment with OMA demonstrated an even greater benefit: 60% relative risk reduction.

In real-life settings, OMA provides substantial improvement in clinically important endpoints for patients with difficult-to-treat asthma. ■

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Tenofovir: New Hope for Hepatitis B Patients

Source: Marcellin P, et al. *Lancet* 2013; 381:468-475.

Hepatitis B (HEP-B) is responsible for approximately half of hepatic carcinoma cases worldwide. While HEP-B treatment has been shown to reduce risk for liver failure and hepatic cancer in cirrhosis, whether currently available antiviral therapies actually reverse the underlying disease process is less well studied. Indeed, previous prevailing wisdom had opined that the fibrotic changes of cirrhosis might not be amenable to attempts at regression.

Tenofovir (TFV) is a potent HEP-B polymerase/reverse transcriptase inhibitor. Marcellin et al report on the results of an open-label trial of TFV in patients who had completed a 48-week antiviral treatment with either adefovir or TFV. Subjects were subsequently assigned to once-daily TFV for up to 7 years. Approximately one-fourth of patients had cirrhosis at baseline, and all subjects agreed to follow-up liver biopsy in the fifth year of the trial (240 weeks).

TFV was well tolerated and confirmed to be associated with regression of fibrosis (in the cirrhosis group) and improvement in liver histology (in the non-cirrhosis group) at 240 weeks. This large dataset is very supportive of a role for TFV not just in arresting disease progression, but actually in regression of cirrhosis. ■

H. pylori: Frequency of Recurrence After Successful Eradication

Source: Morgan DR. *JAMA* 2013;309: 578-586.

Worldwide, *Helicobacter pylori* appears to be responsible for the majority of cases of gastric cancer. A Chinese clinical trial of *H. pylori* eradication through pharmacotherapy noted an almost 40% reduction in gastric cancer over the subsequent 15-year observation period. Initial eradication of *H. pylori* provides important risk reduction. Of course, initial treatment is sometimes not effective, and even when initial treatment is effective, there is potential for recurrence.

From a population of study subjects (n = 1091) cleared of *H. pylori* (confirmed by post-treatment negative urea breath tests), only 125 evidenced recurrence over a 1-year follow-up (11.5%). Factors associated with recurrence included non-adherence to *H. pylori* treatment regimens and methodology of the treatment regimen (i.e., 14-day triple therapy, sequential therapy, or concomitant therapy, with sequential therapy being most successful). These recurrence rates are typical of low-income countries, whereas recurrence rates are as much as 30% less in high-income countries. Overall, *H. pylori* treatment is well tolerated, provides important risk reduction for gastric cancer, and is associated with few recurrences that can be managed by appropriate retreatment. ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

New Study on Chelation Therapy Proves Controversial

In this issue: Chelation therapy for cardiovascular disease; statins and kidney injuries; chlorthalidone for hypertension; and FDA actions.

Does chelation therapy work?

The National Center for Complementary and Alternative Medicine (NCCAM) is attempting to fulfill its mandate to prove or disprove the value of alternative treatments. A division of the National Institutes of Health, NCCAM has done research on everything from supplements to meditation. This latest study looks at chelation therapy in patients with cardiovascular disease. Chelation therapy with ethylene diamine tetra-acetic acid (EDTA) has been used for decades to treat lead toxicity, and it has also been found to reduce metastatic calcium deposits. Despite the fact that small studies have never shown a benefit for chelation in treating cardiovascular disease, many alternative clinics continue to tout its value in this role. A recently published NCCAM-funded study to evaluate the value of chelation enrolled more than 1700 patients ≥ 50 years of age with a history of myocardial infarction (MI) at least 6 weeks prior. The study was a double-blind, placebo-controlled, 2 × 2 factorial randomized trial from 2003 through 2011. There were 289 patients who withdrew consent from the study, of which 60% were in the placebo group. The study consisted of 40 EDTA/vitamin infusions vs placebo infusions (given weekly for 30 weeks then at 2-8 week intervals). About 15% of patients in both groups dropped out during therapy. The primary outcome was a composite of total mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for angina. The primary endpoint occurred in 222 (26%) in the chelation group and 261 (30%) in the placebo group (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.69-0.99; $P = 0.35$). There was no effect on total mortality, but there was slight improvement in other outcomes with chelation. The authors conclude that among stable patients with a history of MI, chelation therapy modestly reduced the risk of adverse cardiovascular outcomes. They conclude that this study provides evidence to guide further research but is not sufficient to support the routine use of chelation therapy in patients with cardiovascular disease (*JAMA* 2013;309:1241-1250). Editorialists in the same issue of *JAMA* immediately leveled strong criticisms, ranging from allegations of noncompliance with regulations for the protection of research participants to questioning the professional credentials of the study sites and investigators. The *JAMA* editorial board did an extensive review of the data, and despite concerns, decided to publish the study with the caveat that "these findings do not support the routine use of chelation therapy as secondary prevention for patients with previous myocardial infarction and established coronary disease." (*JAMA* 2013;309:1291-1292.) Another editorialist, however, suggests that "limitations in the design and execution" of this trial compromise the findings. For example, the high number of withdrawals of consent in the placebo group suggests that the study was not truly blinded. There is also concern about the use of "softer" endpoints such as coronary revascularization and hospitalization for angina.

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

Also, the trial design was altered midway through the study because of the length of the trial. Given these concerns, "including missing data, potential investigator or patient unmasking, use of subjective endpoints, and intentional unblinding of the sponsor, the results cannot be accepted as reliable and did not demonstrate a benefit of chelation therapy." (*JAMA* 2013;309:1293-1294.) ■

Statins and renal function

When prescribing a high-dose statin, physicians no longer need to monitor liver function tests, but might want to consider monitoring renal function, at least for the first 3 months. Last year, the FDA removed labeling requiring periodic monitoring of liver enzyme tests, but now a Canadian study suggests that high-potency statins (defined as doses of at least 40 mg simvastatin, 20 mg atorvastatin, or 10 mg rosuvastain) may be associated with acute kidney injury. Researchers reviewed records of more than 2 million patients from nine population-based cohort studies comparing current and past use of high-potency vs low-potency statin therapy. Patients hospitalized for acute kidney injury were matched with 10 controls. About 3% of patients had chronic kidney disease (CKD) at the onset of the study. Within 120 days of starting therapy, there were 4691 hospitalizations for acute kidney injury in patients without CKD and 1896 hospitalizations in patients with CKD. In patients without CKD, current users of high-potency statins were 34% more likely to be hospitalized with acute kidney injury compared to low-potency statin users (fixed effect rate ratio 1.34; 95% CI, 1.25-1.43). In patients with CKD, the increase was about 10% with high-potency statins (risk ratio, 1.10; 95% CI, 0.99-1.23). The authors conclude that use of high-potency statins is associated with an increased rate of acute kidney injury compared to low-potency statins, with the effect strongest in the first 120 days of treatment. The authors further suggest that since there is a relatively small incremental cardiovascular benefit between high-potency and low-potency statins, and given the increased risk of rhabdomyolysis, diabetes, and acute kidney injury, patient selection for risk-benefit is important (*BMJ* 2013;346:f880). ■

Chlorthalidone for hypertension

Thiazide diuretics are recommended as first-line treatment for hypertension. Hydrochlorothiazide (HCTZ) is the most commonly used diuretic in North America, but some experts have recommended chlorthalidone in this role, suggesting that it may be superior. A new study, however, suggests that chlorthalidone may cause more electrolyte abnormalities than HCTZ. Nearly 30,000 patients ≥ 66 years of age who were newly treated for hypertension were evaluated. About one-third were treated with chlorthalidone and the rest with HCTZ. None of the patients had been hospitalized for heart failure, stroke, or MI within the last year. The primary outcome was a composite of death or hospitalization for heart failure, stroke, or MI, and safety outcomes included hospitalization with hypokalemia or hyponatremia. After 5 years of follow-up, there was no difference in the primary outcome between the two drugs — 3.2 events per 100 person years for chlorthalidone vs 3.4 events per 100 person years for HCTZ. However, patients treated with chlorthalidone were three times more likely to be hospitalized with hypokalemia (adjusted HR, 3.06; CI, 0.81-1.06). Hyponatremia was also more common (HR, 1.68; CI, 1.24-2.28). The findings suggest that in typical doses, chlorthalidone is not associated with fewer adverse cardiovascular events or deaths compared to hydrochlorothiazide, but it is associated with a greater incidence of electrolyte abnormalities, especially hypokalemia (*Ann Intern Med* 2013;158:447-455). ■

FDA actions

The FDA has issued a warning regarding azithromycin and cardiac toxicity. The drug has been associated with fatal heart rhythms — especially in patients already at risk — including those with prolonged QT intervals, torsades de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure. Other patients may be at risk as well, including those with low potassium or magnesium levels, those using drugs that prolong the QT intervals, and elderly patients with cardiac disease. The warning was based on a study published in *The New England Journal of Medicine* last year.

An FDA advisory committee is recommending against the use of calcitonin salmon (Miacalcin and Fortical nasal sprays, and Miacalcin injection) for the treatment of osteoporosis in postmenopausal women because the risk of cancer outweighs any potential benefit. The recommendation is based on an FDA review that questions the drug's effectiveness in reducing fractures. Another review found a small increased risk of cancer associated with the drug. The drug could still be used for Paget's disease, acute bone loss due to immobilization, and hypercalcemia. The FDA has yet to rule on the advisory committee's recommendations. ■