Status asthmaticus in children

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Purpose of review

The prevalence of severe asthma in children has risen in the past few decades. The present review explores our current understanding of epidemiology, pathophysiology and treatment of status asthmaticus in children.

Recent findings

The pathophysiology of inflammation and airway hyperactivity continues to be a source of research. Early initiation of inhaled β-agonists and oral or parenteral steroids remain the standard of care in the treatment of status asthmaticus. Other treatment modalities such as magnesium and intravenous β-agonists show some benefit. There is a resurgence of interest in the use of methylxanthines. Alternatives to endotracheal intubation show some promise in preventing respiratory failure.

Summary

Asthma remains the third leading cause of hospitalization in children younger than 15 years old. Researchers continue to explore the efficacy of old and new treatment modalities. Future research efforts targeting at-risk populations could dramatically decrease asthma morbidity and mortality.

Keywords

children, respiratory distress, review, status asthmaticus

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Introduction

In the past few decades, the prevalence of severe asthma has been rising in American children. Asthma management, too, continues to evolve. Physicians are often faced with an asthmatic child in severe respiratory distress. The following review explores the current understanding of epidemiology, physiology, and treatment of severe, life-threatening asthma in children.

Definition

The exact definition of status asthmaticus varies between authors. For this article, we have defined status asthmaticus as a wheezing patient who does not respond to initial doses of nebulized bronchodilators [1].

Epidemiology

According to the 2003 National Health Interview Survey [2], 13% of children had been diagnosed with asthma at some time in their lives, although some of those children may no longer have asthma. About 9% of children were reported to currently have asthma in 2003. Clinicians should be somewhat encouraged by the fact that asthma prevalence has stabilized in the past few years and asthma mortality and hospitalizations have decreased in that time period, possibly indicating a higher level of disease management [3]. The disease burden of asthma is still high, however, and the American Lung Association [3] cites asthma as the third leading cause of hospitalization among children under the age of 15 years.

Risk factors

Clinicians have had difficulty identifying children at risk for fatal asthma attacks.

In their review of 51 pediatric deaths from asthma in Australia, Robertson *et al.* [4] found that only 39% had potentially preventable elements. Numerous previous studies have shown that nonwhite children in the United States with poor access to healthcare are at the highest risk for severe disease [5,6].

Pathophysiology

Asthma is characterized by reversible, diffuse lower-airway obstruction, caused by airway inflammation and edema, bronchial smooth-muscle spasm, and mucous plugging. Improved understanding of the pathophysiology of asthma has led to improved treatment modalities as well as strategies for prevention.

Clinicians and researchers have recognized the importance of chronic airway inflammation, rather than bronchospasm alone, as key to the pathogenesis of asthma [7–9]. Inflammatory submucosal infiltrates in the respiratory tree activate mast cells, epithelial cells, and T lymphocytes that in turn produce proinflammatory cytokines [7–9]. Mediators such as histamine, leukotrienes, platelet-activating factor, and others are found both locally in the airways as well as systemically in the blood and urine, and these mediators correlate with disease severity [8,9]. The inflammatory changes and resultant epithelial destruction expose nerve endings that lead to airway hyperreactivity [8,10]. The hyperreactive airway of the asthmatic child is thus primed for acute obstruction by triggers such as infections, allergens, environmental irritants, smoke, gastroesophageal reflux, exercise and stress [8,10–17]. The autonomic nervous system, which regulates bronchoconstriction and bronchodilation, as well as mucous secretion and possibly mast cell degranulation, plays a significant role in the pathophysiology of asthma [8].

Inflammation and bronchospasm lead to limitation of airflow, airtrapping, and increased functional residual capacity. In order to counteract this increased functional residual capacity, inspiratory muscle activity persists throughout exhalation, attempting to keep the airway open and allow air to flow out [18]. The heterogeneous nature of the microareas of hyperinflation causes ventilation/perfusion mismatching and hypoxemia. Increased work of breathing under hypoxemic conditions and some degree of dehydration combine to cause accumulation of lactate, ketones, and other inorganic acids. This acidosis is initially offset by respiratory alkalosis, but once respiratory failure ensues, a precipitous decrease in pH will occur.

Increased functional residual capacity and more negative pleural pressures have a significant effect on ventricular function. Children with severe asthma have increased negative intrapleural pressures that become more negative with increasing severity of the attack [18]. Negative intrapleural pressure causes increased left ventricular afterload, resulting in a high risk for pulmonary edema. Overhydration furthers the risk of development of pulmonary edema. Right ventricular afterload is increased secondary to hypoxic pulmonary vasoconstriction, acidosis, and increased lung volume. Pulsus paradoxus, an exaggeration of the normal inspiratory drop in arterial pressure, is the result of a marked inspiratory decrease in left-sided cardiac output, as described above.

Clinical presentation

The presentation of status asthmaticus varies by severity, the asthmatic trigger, and patient age. Most children present with cough, wheezing, and increased work of breathing. Acute bronchospasm may lead to rapid respiratory failure especially in patients with an allergic trigger. The degree of wheezing does not correlate well with severity of the disease [19]. The noisy chest is a reassuring sign, however, as this wheezing represents sufficient airflow to cause turbulence and vibration, and thus wheezing. Distant or absent breath sounds ('silent chest') in the face of increased respiratory effort forebodes respiratory failure. Agitation or dyspnea, especially in adolescents, should be recognized as severe respiratory compromise. Other findings indicative of impending respiratory failure include disturbance in level of consciousness, inability to speak, markedly diminished or absent breath sounds, central cyanosis, diaphoresis, and an inability to lie down [20]. The presence of pulsus paradoxus correlates with the severity of the asthma attack and may be useful in following the severity of illness [21,22].

Assessment

The assessment of status asthmaticus relies mostly on clinical observations, although diagnostic tests may supply additional useful information in the critically ill child.

Chest radiography

Clinically significant radiographic abnormalities are rare in the unintubated asthmatic child and chest films do not often produce changes in clinical behavior [23]. Hederos *et al.* [24] found that chest radiographs were of clinical significance in only one of 60 children with a new diagnosis of asthma. Radiographs have a limited role but may be indicated when there is suspected airleak, evidence of pneumonia, or the underlying cause of wheezing is in doubt.

Blood gas

Noninvasive oximetry and sidestream capnography have replaced routine blood gas determination. Oximetry is not a reliable measure of adequate ventilation. The decision to intubate an asthmatic child should not depend on blood gas determination, but should be made on clinical grounds (as above). Arterial blood gas measurement, however, is useful to assess pulmonary gas exchange. Hypocarbia is found early in the presentation; normalizing CO_2 in the face of persistent respiratory distress may herald impending respiratory failure. Once the decision has been made to intubate a patient in status asthmaticus, frequent blood gas assessment through an indwelling arterial line is useful to follow clinical progress.

Treatment

The mainstays of treatment for status asthmaticus continue to be β-agonists and steroids. Useful adjuvants

including anticholinergics, magnesium, and positive pressure ventilation are discussed below.

General

Any child in status asthmaticus requires cardiorespiratory monitoring. A comfortable and supportive environment can ameliorate the situational anxiety though hypoxemia and anxiety will also lead to agitation and restlessness. Sedatives are contraindicated in the nonintubated asthmatic patient.

Supplemental oxygen, via partial or nonrebreather facemask, should be administered. Caution should be used for children with underlying chronic respiratory disease as oxygen may decrease the respiratory drive and precipitate worsening respiratory acidosis.

Poor fluid intake, increased loss of insensible fluids and vomiting may cause dehydration in the asthmatic child. Fluid replacement should be aimed towards restoration of euvolemia. Overhydration may lead to pulmonary edema. Fluid balance should be monitored carefully as the syndrome of inappropriate antidiuretic hormone has been described in severe asthma [25].

While physicians have previously eschewed the use of antibiotics, recent evidence [26] suggests that therapy targeted to patients with evidence of atypical bacterial infection may confer additional advantage to standard therapy alone.

β-Agonists

β-Receptor agonists remain the mainstay of therapy in status asthmaticus. β-Agonists produce smooth-muscle relaxation by binding to β_2-receptors in the smooth muscles of the airways. β-Agonists can be administered via the inhaled, intravenous, subcutaneous, or oral routes. Nebulization is the most common route of administration. Orally administered β-agonists are not effective in the treatment of severe, acute asthma. Given the effectiveness of inhaled β-agonists, subcutaneous epinephrine is rarely indicated and should be utilized only in extreme circumstances where inhaled β-agonists are unavailable or undeliverable (no aeration, intubated patient without proper delivery device), when there are other systemic signs of anaphylaxis, and when intravenous access has not been established in a patient with impending respiratory failure.

Albuterol is the most commonly used β-agonist in the United States. Other common agents include epinephrine, isoproterenol, and terbutaline. Albuterol and terbutaline are generally preferred by clinicians for their relative β_2-selectivity. Many clinicians have recently adopted the use of levalbuterol, the pure or homochiral formulation of (*R*)-albuterol. Conventional or racemic albuterol is an equal mixture of (*R*)-albuterol and (*S*)-albuterol. Previously thought to be an inert compound, (*S*)-albuterol may exaggerate airway hyperresponsiveness and also may have a proinflammatory effect [27]. There is controversy in the literature as to whether levalbuterol leads to improved clinical response with fewer side effects [28–30]. Most recently, Qureshi *et al.* [30] found no difference in clinical asthma score in children presenting to the emergency room with moderate to severe asthma exacerbations after treatment with racemic albuterol when compared with levalbuterol. No recommendation regarding the use of the much more expensive levalbuterol in children with status asthmaticus can presently be made.

Even under ideal conditions, less than 10% of nebulized drug will reach the lung. Alterations in tidal volume, breathing pattern, and nebulizer gas flow can further decrease the amount of drug delivery [31,32]. Some experts recommend much higher doses of nebulized β-agonists [33]. There is growing evidence that the use of a metered-dose inhaler with a valved holding chamber is more effective than nebulized albuterol in young children with moderate to severe asthma exacerbations [34]. For children who need more frequent doses of β-agonist, however, continuous nebulization appears to be superior to intermittent doses [35–37]. Use of continuous nebulization with albuterol may lead to more rapid improvement, improved sleep, and may also be more cost-effective [38].

Intravenous β-agonists should be considered in patients unresponsive to treatment with continuous nebulization as well as those in whom nebulization is not feasible (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 β-agonist of choice in the United States, while other countries use albuterol. Most adverse effects of β-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. In a prospective cohort study, Chiang *et al.* [39] found no clinically significant cardiac toxicity in 114 pediatric patients receiving intravenous terbutaline.

Anticholinergics

When used in conjunction with β-agonists, anticholinergics are now standard of care in the treatment of acute asthma in children. Anticholinergic agents are usually administered via the inhaled route. The most commonly

used compound is ipratropium bromide, a quaternary derivative of atropine. Rodrigo and Castro-Rodriguez [40] conducted a metaanalysis of 32 randomized controlled trials using anticholinergics in children, adolescents and adults, and concluded that multiple doses of inhaled ipratropium bromide in combination with β-agonists significantly reduced hospitalizations and significantly improved spirometric parameters in pediatric patients.

Steroids

Corticosteroids are a mandatory first-line treatment for status asthmaticus. Glucocorticoids work in a myriad of ways: they control airway inflammation; modify the activation of lymphocytes, eosinophils, mast cells, and macrophages; inhibit vascular leakage induced by proinflammatory mediators; restore disrupted epithelium; normalize the ciliated cell to goblet cell ratio; decrease mucus secretion; and downregulate production and release of proinflammatory cytokines. Aerosolized corticosteroids, whose efficacy depends on adequate air movement, have a limited role in the treatment of status asthmaticus [41–43,44••]. Oral or parenteral corticosteroids are equally efficacious, although parenteral steroids are preferred for critically ill children and those patients with emesis or delayed gastric emptying. A 2001 Cochrane Database review demonstrates improved outcomes for children who receive corticosteroids early in their emergency department course [45]. Commonly used parenteral steroid agents include hydrocortisone, methylprednisolone, and dexamethasone. Duration of steroid therapy will depend on severity of the attack and on chronicity of underlying inflammation. Although short-term use of high-dose steroids is usually not associated with significant side effects, hyperglycemia, hypertension, and acute psychosis have been reported [46]. The immunosuppressive effects of corticosteroids are mostly associated with long-term use though even a single course of steroids can increase the risk for fatal varicella [47].

Magnesium

Magnesium for the treatment of asthma was first described in 1936 [48]. The suggested mechanism of action is smooth-muscle relaxation secondary to inhibition of calcium uptake. A recent metaanalysis by Cheuk *et al.* [49] of five randomized, placebo-controlled studies showed some benefit of adding intravenous magnesium to nebulized β-agonists and corticosteroids. A Cochrane review showed similar benefit to inhaled magnesium [50]. Intravenous magnesium is preferable to the nebulized form.

Methylxanthines

Theophylline and its water-soluble salt aminophylline are methylxanthines that have experienced a recent resurgence in clinical interest. Once a mainstay of treatment, the methylxanthines had fallen out of favor due to concerns about toxicity. The mechanism of effect of the methylxanthines in asthma remains unclear. In addition to their action as phosphodiesterase inhibitors, the class of drugs has been postulated to stimulate endogenous catecholamine release, to act as a β-adrenergic agonists, to act as diuretics, to augment diaphragmatic contractility, to increase binding of cAMP, to act as prostaglandin antagonists, and to have other, unspecified, anti-inflammatory effects.

The role of the methylxanthines in the treatment of children with severe asthma remains controversial. Several recent studies, however, suggest that methylxanthines may offer some benefit [51,52]. The dosage needs to be adapted to age groups and individual patients based on serum levels; the narrow therapeutic range of theophylline overlaps with its toxicity range. Toxicity includes nausea and vomiting, tachycardia, and agitation. Severe and life-threatening toxicity in the form of cardiac arrhythmias, hypotension, seizures, and death is usually associated with high theophylline serum concentrations. Clinicians should use aminophylline and theophylline carefully and in conjunction with specialists familiar with the use of methylxanthines.

Leukotriene inhibitors

There are no large studies to date that show any role for leukotriene inhibitors in the setting of status asthmaticus.

Helium–oxygen

Inhaled mixtures of helium–oxygen (heliox) reduce turbulent airflow, and thereby allow better O_2 delivery to the distal airways. Heliox mixtures have a high helium fraction (60–80%) and a relatively low oxygen fraction, making the therapy not useful in profoundly hypoxic patients. In a prospective, randomized, double-blind, crossover study of heliox in 11 nonintubated children with severe asthma [53], heliox failed to show an effect on respiratory mechanics or dyspnea scores. A 2003 Cochrane systematic review of heliox for asthma showed similar results [54]. Other investigators continue to find uses for heliox, especially in the cases of density-dependent increases in airway resistance [55]. Most recently, Kim *et al.* showed that children treated with continuous albuterol delivered by heliox showed greater clinical improvement than those treated with oxygen-alone delivered albuterol [56].

Intubation and mechanical ventilation

Intubation of the asthmatic child should be avoided unless respiratory failure is impending. Intubation may aggravate bronchospasm, precipitate circulatory collapse and greatly increase the risk of barotrauma through positive pressure ventilation. Several recent studies

showed that use of noninvasive positive pressure ventilation may obviate the need for invasive techniques [57,58].

Absolute indications for intubation include cardiopulmonary arrest, severe hypoxia, or rapid deterioration in the child's mental state. Progressive respiratory embarrassment despite maximal treatment, including noninvasive techniques, constitutes a relative indication for mechanical ventilation. The decision to intubate should not depend on arterial blood gas findings alone; many hypercarbic patients can be managed without invasive support while other patients with mild hypercarbia may need emergent airway support.

Once the decision to intubate has been made, the child must be preoxygenated with 100% oxygen. Time permitting, a fluid bolus should be given to prevent the hypotension associated with positive pressure ventilation. Suction for the oropharynx and a nasogastric tube should be available. Rapid sequence intubation should proceed with atropine (if indicated), a sedative or anesthetic, followed by a rapid-acting muscle relaxant. Ketamine, because of its bronchodilatory action, is a preferred induction agent in patients with severe asthma. A cuffed or sufficiently large endotracheal tube is recommended to minimize air leak with the anticipated high inspiratory pressures. Newth *et al.* [59] found no increased risk for postextubation complications in young children intubated with cuffed endotracheal tubes. Indeed, most of the complications in asthmatic patients receiving ventilation occur during or immediately after intubation. Hypotension, oxygen desaturation, pneumothorax/subcutaneous emphysema, and cardiac arrest are the most frequently observed complications [60]. Marked hypotension is not uncommon after intubating the asthmatic child, and most often is the result of hyperinflation with decreased venous return to the heart, augmented by the vasodilatory and myocardial depressant effects of sedatives and paralytics. Hypotension should improve with volume administration and slowing of the respiratory rate. If hypotension and/or hypoxemia do not rapidly respond to fluid administration and alteration in ventilatory pattern, a tension pneumothorax must be considered.

The severely obstructed expiratory air flow of the asthmatic child requires an extremely long expiratory time. Great care must be taken to avoid too rapidly administered manual breaths. Barotrauma can be limited by several strategies including pressure-control, pressure support, and permissive hypercapnia. The use of positive end-expiratory pressure in the asthmatic patient receiving mechanical ventilation remains controversial [61,62].

The intubated asthmatic child receiving mechanical ventilation should be given heavy sedation to avoid tachypnea and ventilator dyssynchrony. Long-term neuromuscular blockade should be reserved for those patients in whom adequate ventilation cannot be achieved at acceptable inspiratory pressures.

Inhalational anesthetics

Inhalational anesthetic agents have been effectively used in the treatment of refractory status asthmaticus [63–65]. Proper and safe administration of inhalational anesthetics in the pediatric intensive care unit requires either an anesthesia machine or a custom-fitted ventilator with scavenging system and continuous analysis of inspiratory and expiratory vapor concentrations.

Ketamine

Ketamine is a dissociative anesthetic agent with strong analgesic action. It also mediates bronchodilation. Ketamine has been used in children with severe asthma receiving mechanical ventilation because of its anesthetic and bronchodilatory properties [66,67].

Conclusions

The disease burden of asthma remains quite high and nonwhite populations seem to have a higher prevalence of severe disease. The pathophysiology of asthma continues to be a topic of basic science research. Despite many recent advances in understanding of the pathophysiology of this disease, β-agonists and steroids remain the cornerstones of treatment for acute exacerbations. Current literature supports the use of adjuvant therapies such as magnesium and anticholinergics as well as a resurgence in the use of methylxanthines. Noninvasive positive pressure ventilation may forestall intubation, which should be reserved for the direst of circumstances.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 362–363).

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