Neal J. Thomas and Frank A. Maffei

Severe Asthma

CHAPTER OUTLINE

LEARNING OBJECTIVES

- Discuss the impact of asthma on the pediatric population.
- Review the pathophysiology of status asthmaticus
- Describe the usual triggers of asthma and appreciate potential iatrogenic triggers of bronchospasm in the PICU
- Describe the evaluation of a child admitted to the PICU with status asthmaticus
- Identify the major therapies for status asthmaticus
  - Inhaled beta agonists
  - Inhaled anticholinergic agents
  - Corticosteroids
  - Magnesium
  - Helium/Oxygen Mixture
  - Intravenous beta agonists
  - Methylxanthines
  - Leukotriene receptor antagonists
  - Ketamine and inhalational anesthetics
  - Non-invasive ventilation
- Outline a general treatment algorithm for asthmatic patients who require critical care
- Review the theoretical and practical difficulties with mechanical ventilation in patients with status asthmaticus
- Discuss the complications that may occur with status asthmaticus during positive pressure ventilation

EPIDEMIOLOGY

Despite vast improvements in the care of children with asthma over the past decades, asthma remains a common cause of admission to pediatric intensive care units. During the 1990s asthma prevalence and hospital admissions increased in the United States and worldwide. The increase occurred in both males and females and across all ethnic groups. However, the largest increases occurred in children of low socioeconomic status living in urban settings. Recent asthma statistics should be interpreted with consideration of changes made in the method for reporting asthma prevalence (Fig. 23-1). From 1980 to 1996, the National Health Interview Survey (NHIS) conducted by the CDC measured pediatric asthma prevalence as the percentage of children with asthma in the past 12 months. Since 1997, asthma prevalence estimates have been defined as: having received an asthma diagnosis, currently having the disease at the time of the interview, and experiencing an attack in the past year. The more specific definition may have led to a reduction in the number of children reported to have asthma.
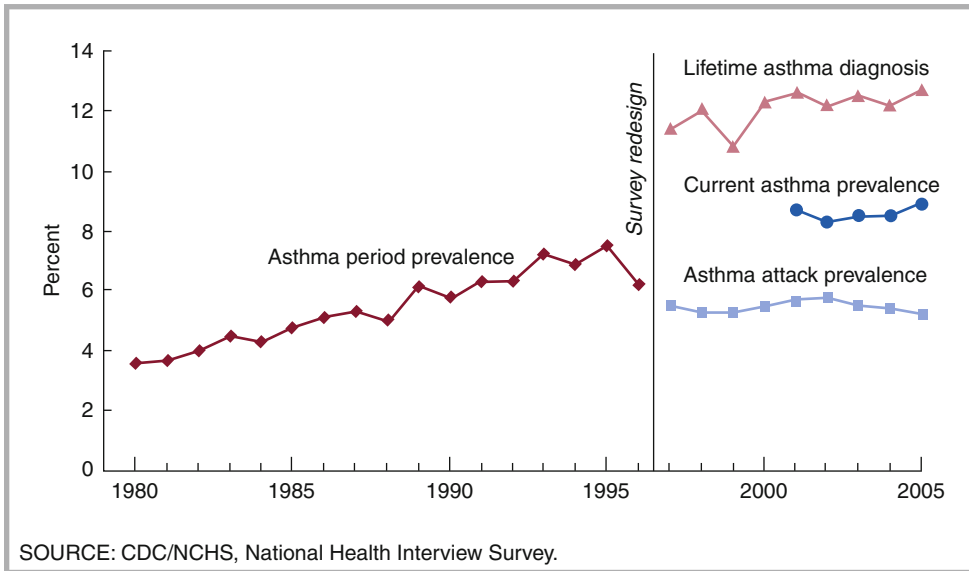
Graphical representation of childhood asthma prevalence using national health interview data (Source: CDC/NCHS. National Health Interview Survey)
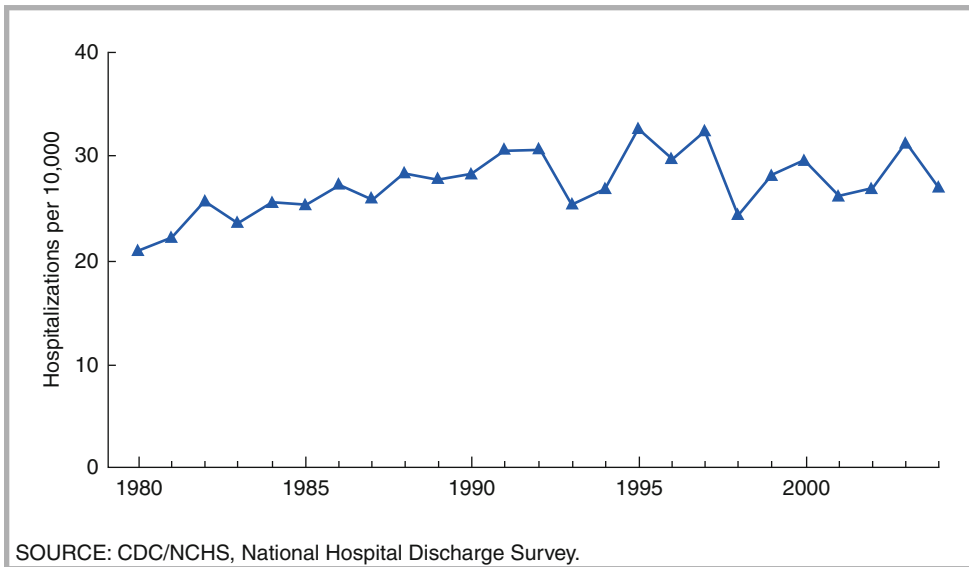
Hospitalizations for childhood asthma per 10,000 children (0−17 years) in the US from 1980 to 2004 (Source: CDC/NCHS. National Hospital Discharge Survey)

The most recent NHIS reveals the following important demographic data:

■ From 1980 to 1996, asthma prevalence among children more than doubled, from 3.6% in 1980 to 7.5% in 1995.

■ Post-1997 asthma prevalence has not increased and has remained relatively stable although the difference between asthma period prevalence may be due to changes in the NHIS questionnaire as noted above.

■ In 2005, 8.9% of children in the US had asthma (6.5 million children).

■ Asthma death rates appear to have declined recently following a rise from 1980 through the mid-1990s. In 2004, the rate of asthma deaths was 2.5 asthma deaths per 1 million (total of 186 pediatric asthma deaths)

■ Racial disparities persist in childhood asthma; black and Puerto Rican children have high prevalence rates, and black children have far higher mortality rates when compared with white children

Asthma remains the most common cause of hospitalization among children. In 2004 there were 198,000 asthma admissions accounting for 3% of all US pediatric hospitalizations (Fig. 23-2). Respiratory failure occurs in 8–20% of children admitted to a PICU for an asthma exacerbation.

ENVIRONMENTAL AND GENETIC FACTORS

Numerous theories have been offered to explain the increase in asthma prevalence over time; many of which continue to be sharply debated. One proposed mechanism is the "hygiene hypothesis". This theory assumes natural exposure to microbial infections occurring early in life can cause an organism to develop a natural immunity against asthmatic triggers. A decrease in the number and intensity of exposures in the past century may have placed children at risk of forming less natural immunity to asthma. Despite extensive study, this theory still lacks the scientific evidence to move this proposition past speculation.

An alternative hypothesis to explain the rise in asthma is based on apparent association between exposure to irritants (i.e. second-hand tobacco smoke, air pollution) and the subsequent development of asthma in childhood. This theory can be extended to early infection with respiratory viruses (respiratory syncytial virus is the most extensively studied), which have been linked to the development of asthma. However, this theory is also speculative, as it is unclear whether the exposure to an asthma trigger during a time of rapid lung growth leads to airway remodeling, or whether the respiratory symptoms that occur with these early exposures are simply the initial presentation of a child who is "prone" to the development of asthma.

The phenotype of asthma and the variability in therapy responsiveness is likely the result of a complex interaction between environmental and genetic factors. Although it is clear that inheritable factors are important to the development of asthma, it is unlikely that a single gene is responsible for this the disease or its response to therapy. A smaller number of genes displaying some effect, either additively or synergistically, is a more plausible explanation. Through case–control studies, family-based association studies, and linkage analysis studies, several candidate genes have been proposed. Two genes that have been investigated extensively are the beta-2-adrenergic receptor gene and the interleukin-4 receptor gene, both of which are located on an area of chromosome 5q. Evidence suggests that polymorphisms of the gene for the β_2-adrenergic receptor may affect the clinical response to β agonists. Single nucleotide polymorphisms (SNPs) have been found at codons 16 and 27. Two substitutions may have particular importance. A change at base 46 from adenine to guanine causes a substitution of glycine for arginine at codon (amino acid position)16 and a change at base 79 from guanine to cytosine causes a substitution of glutamic acid for glutamine at codon 27. Patients with the glycine substitution have been found to be prone to beta receptor down regulation and therefore are clinically less responsive to beta-agonist therapy. Although the detrimental effect of the glycine substitution has been questioned, a meta-analysis revealed a significant association between favorable responses to inhaled beta 2-adrenergic agonists in asthmatic children with the native arginine phenotype at position 16 when compared with children with the glycine substitution. The poor response to beta-agonists was most pronounced in African-American asthmatic children with the glycine substitution. Most recently, a significant pharmacogenomic association was found between a SNP in the glucocorticoid-induced transcript 1 gene (GLCCI1) gene and the response to glucocorticoids in asthma.

Interleukin-4 (IL-4) is a pro-inflammatory cytokine important in the pathogenesis of asthma. IL-4 enhances the IgE mediated allergic response, induces the expression of vascular cell adhesion molecule-1 (VCAM-1), and promotes differentiation of T helper type 2 lymphocytes leading to further cytokine release. Variants of the gene that encodes for the IL-4 receptor have been shown to be associated with asthma. Recently, nucleotide polymorphisms for the IL4 receptor (IL-4R) have been identified as a genetic risk factor for severe persistent asthma. Further understanding into the role of IL 4R variants may lead to therapies that inhibit the biological actions of IL-4 by either blocking the receptor (via a monoclonal antibody directed at the receptor) or using a soluble recombinant human IL-4 receptor (consisting of the extracellular portion of human IL-4R) to bind and inactivate freely circulating IL-4. Both approaches are areas of active research.

Other loci containing possible genetic influences on asthma are located on chromosomes 11q and 12q, and recently, the surfactant protein genetic variants have been found to be associated with asthma in adults. While it is clear that genetic influence plays an important role in the development and severity of asthma, further study is necessary to delineate the clinical importance of these genes and their polymorphisms especially as they relate to the clinical response to pharmacological treatments.

| Asthma prevalence continues to increase, but the etiology of this increase is unknown

| The phenotype of asthma is likely due to a complex gene-environment interaction

PATHOPHYSIOLOGY

Despite the many triggers of status asthmaticus, the underlying pathophysiology remains constant and is composed of three mechanisms: airway mucosal edema, airway smooth muscle spasm, and airway mucous plugging from copious secretions. As the diameter of the pediatric airway is proportionally smaller than that of an adult, the child is more prone to mechanical obstruction from each of the three mechanisms, and therefore, more likely to demonstrate symptoms of respiratory failure. The effect of a reduction in airway diameter is best appreciated when considering Poiseuille's Equation, which states:

$$R = 8\eta L / \pi r^4$$

where: R=resistance, η=viscosity of the air (or fluid), L=length of the tube (airway), r=radius of the tube (airway).

Accordingly, decreasing the radius by 50% (as can occur readily in the small airway of a child) will result in a 16-fold increase in airway resistance. Bronchospasm, endobronchial edema and mucous plugging each cause a reduction in airway diameter. The relative contribution of each mechanism may vary between asthmatic children and individual exacerbations. Each mechanism of lower airway dysfunction may require distinct therapy. An enhanced inflammatory response contributes to all three mechanisms of lower airway dysfunction and merits further discussion.

> The three mechanisms responsible for airway obstruction in asthma are airway mucosal edema, airway smooth muscle spasm, and airway mucus plugging from copious secretions.

> Decreasing the airway radius by 50% leads to a 16-fold increase in resistance.

INFLAMMATION IN ASTHMA

Airway inflammation and subsequent cytokine production, originating from either resident airway inflammatory cells or those cells infiltrating the airway due to certain triggers, are the major underlying components of airway obstruction during asthma. Even in asymptomatic asthmatic children, the airway is in a state of low-grade, but persistent inflammation. Although every inflammatory cell may be responsible for some portion of this airway edema, those thought to be the most active during status asthmaticus are the infiltrative lymphocytes, eosinophils and the resident mast cells and airway epithelial cells.

During asthma exacerbations, lymphocytes (specifically the TH2 subtype) are drawn to infiltrate the airway by signaling from a variety of chemokines, with eotaxin being the most studied. Once activated, lymphocytes release a host of inflammatory cytokines (interleukins 4 and 5, among others) that further stimulate the inflammatory response, leading to increased edema. Other inflammatory mediators, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), regulated on activation, T-cell expressed and secreted (RANTES), and interleukin-8 have also been found to be important to the ongoing inflammatory response that occurs during status asthmaticus. Eosinophils play a major role in this up-regulated inflammation, leading to release of leukotrienes and the formation of oxygen free radicals, all of which worsen airway edema and mucus production. A study of adults with asthma demonstrated that the number of eosinophils found in bronchoalveolar lavage fluid is directly proportional to the degree of asthma severity, proposing this cell line as the major contributor to asthma severity.

Resident airway cells are also important in the inflammation that is central to asthma pathogenesis. Mast cells are up-regulated when stimulated to enhance the pro-inflammatory response. These cells appear to be responsible for airway changes as a result of specific allergens and, when stimulated, release a host of cytokines and chemokines that activate downstream inflammation. Airway epithelial cells also produce a number of cytokines and chemokines that regulate inflammation during severe asthma. Interleukin 1-beta is the most intensely studied. Bronchoalveolar lavage fluid interleukin 1-beta concentrations have been correlated with asthma severity in adults. The interleukin 1-beta inflammatory pathway has been manipulated in attempts to gain control over the inflammatory response that triggers worsening asthma with some success *in vitro*.

The cellular events initiated by an asthma trigger ultimately leads to a decrease in airway diameter secondary to a combination of smooth muscle contraction, endobronchial edema,

> Lymphocytes and eosinophils are important *infiltrative* cells in asthma pathogenesis.

> Mast cells and airway epithelial cells are important *resident* cells in asthma pathogenesis.

and thick, copious secretions. Thus, the increase in airway resistance leads to the clinical features of asthma that are described in later portions of this chapter.

Given the importance of inflammation, some experts suggest that methods to non-invasively measure inflammation may have a role in asthma therapy. An inflammatory mediator that is readily measurable is exhaled nitric oxide (NO). L-arginine and L-citrulline are oxidized by NO synthases (NOS), which synthesize NO. There are three isoforms of NOS: inducible NOS (iNOS), which is activated by pro-inflammatory cytokines, and two isoforms of constitutively expressed NO (cNOS), which are expressed on most cells. The fraction of exhaled NO (FeNO) is now moving beyond preliminary research and may become a clinically useful, point-of-care marker of acute as well as chronic asthma. The FeNO has been found to decrease after steroid therapy in asthmatics. It has also been found to be useful in predicting asthma exacerbations in adults.

> The fraction of exhaled nitric oxide may be a clinically useful marker for inflammation in children with asthma.

TRIGGERS OF ASTHMA

There are many different external and internal stimuli that can incite acute episodes of status asthmaticus. The most well understood mechanism is IgE-mediated allergic asthma. This immediate type of hypersensitivity occurs when IgE molecules bound to resident mast cells interact with the allergic antigen and lead to the inflammatory response governed by lymphocytes. This stimulus can lead to immediate airway obstruction that is generally short-lived, but can also create a late reaction which can be more severe and persistent. While infections from both viral and bacterial sources can also trigger severe asthma in children, viruses appear to be the major infectious trigger. In the very young child, respiratory syncytial virus and parainfluenza predominate, while in older children, influenza and rhinovirus become more prevalent. Human metapneumovirus and bocavirus have recently been suggested to be viral etiologic factors for acute bronchospastic disease in children. Environmental air pollution, including second-hand smoke, can result in episodes of severe asthma in those children who are predisposed to bronchial hypersensitivity. Some authors suggest that the rise in asthma seen in the past decades is a result of the environmental changes, especially related to ozone. In children, second-hand smoke from caretakers is known to play a major role in triggering status asthmaticus. Exercise is also a very common trigger of severe asthma, especially in the older child. The worsening of airway obstruction generally occurs after the exercise and not during it, and pre-treatment with pharmacological therapies can have some success in preventing exacerbations of exercise-induced asthma. In all age groups, but particularly noteworthy in infants, gastro-esophageal reflux can produce bronchospasm. The etiology is likely due to direct irritation of the airways by refluxed gastric material, or alternatively, by neurally-induced bronchospasm secondary to irritation of vagal nerve fibers located in the distal esophagus. The control of reflux and gastric acidity remains an important component of asthma treatment. Bronchoconstriction secondary to vagal efferent nerve activity can also be triggered by emotional stress in the older child. This trigger is particularly important when tailoring treatment for a child with asthma. It is possible that an external stimuli such as an allergen commence airway obstruction, but increasing emotional distress can further the severity of the exacerbation. Therefore, the judicious use of low dose sedation may be required in children admitted to the PICU with status asthmaticus who are not mechanically ventilated.

> There are many external triggers of asthma that require careful assessment by history upon PICU admission.

Not all triggers of severe asthma are the result of exposure outside of the PICU. Certain drugs and mechanical ventilation are well known to trigger bronchospasm when initiated for the treatment of other disease processes requiring critical care. The most common medications that are administered in critically ill children that may trigger asthma are beta–adrenergic antagonists. When used for cardiovascular reasons, these agents have been demonstrated to incite severe bronchospasm, and should therefore, be avoided or used with extreme caution in a child with a known history of asthma. The cardioselective beta-adrenergic antagonists may incite less bronchospasm, but should still be used with caution. Other agents that can trigger airway reactivity are aspirin, other non-steroidal anti-inflammatory agents, and sulfating agents. The influence of a foreign body in the trachea on the development of asthma

symptoms is well-known. For example, it is not uncommon to treat a child for bronchospasm after the initiation of mechanical ventilation secondary to a disease process unrelated to the lungs (i.e., neurologic, cardiovascular). Therefore, it is of prime importance to obtain a history related to reactive airway episodes children admitted to the PICU.

Recently, a rapid-onset, severely progressive form of asthma exacerbation has been appreciated. Acute asphyxial asthma (AAA), or rapid-onset near-fatal asthma, is well described in adults. AAA has a predilection for young adult males and is characterized by a brief duration of symptoms (usually less than 6 h), few identifiable triggers and a rapid progression to respiratory failure. Often, the patient will present *in extremis*, cyanotic, with little to no air movement, and obtundation. Despite the severity of presentation, response to therapy is prompt. When mechanical ventilation is warranted, its duration is usually short, due to rapid improvements in gas exchange. The pathophysiology of AAA may be distinct. An initial neurogenic event that mediates intense bronchospasm may be of primary importance and be independent of the submucosal cellular profile. The challenge remains in identifying asthmatic children who have a propensity for rapid progression and stressing early evaluation and therapy.

EVALUATION OF STATUS ASTHMATICUS

Although there are numerous evaluation tools available to gauge the severity of an asthma exacerbation, serial clinical examinations remain the cornerstone for ongoing assessment. The presence of cough is almost uniform and, together with shortness of breath, is commonly the chief complaint. Wheezing audible upon chest examination is commonly heard, but the absence of wheezing may signify severe airflow obstruction. A visual assessment of accessory muscle should be done serially. Maximal use of intracostal and abdominal muscles during breathing may signify impending respiratory failure. Cerebral function is monitored closely as children with carbon dioxide retention or hypoxia may exhibit signs of central nervous system dysfunction such as agitation or lethargy. A validated, reliable, objective measure of status asthmaticus is the Wood-Downes clinical asthma score, which is outlined in Table 23-1.

> Serial clinical examinations are of paramount importance in the child with severe asthma.

This score allow clinicians to make judgments as to the severity of asthma, and allows multiple caregivers to follow the course of an asthma exacerbation and gauge the effectiveness of therapeutic modalities. As with any clinical scoring tool, interobserver variability may limit the clinical usefulness of the tool.

> The clinical asthma score will allow multiple caregivers to assess progression or improvements in a child with severe asthma. However, reproducibility may be difficult.

A proven examination finding that is often neglected is the presence of a pulsus parodoxicus. When measured in a normal child, the decrease in systolic blood pressure during inspiration is generally 5 mm Hg. In moderate asthma a decrease of 10–20 mm Hg is often noted. A systolic pressure decrease of > 20 mm Hg during inspiration is seen in children with severe exacerbations.

Measurement of expiratory airflow with a peak flow meter is very useful in older children who can reliably perform this maneuver. This measurement is safe, inexpensive, and it also can be performed repeatedly, allowing the clinician to assess therapy effectiveness and overall improvement (or worsening) over time. A chest radiograph will allow the clinician to detect a pneumothorax or pneumomediastinum in the asthmatic child, which may correlate with asthma severity and require evacuation. A pneumothorax large enough to warrant intervention is often apparent from the clinical examination. Infiltrates, such as pneumonia, may only be apparent

TABLE 23-1

WOOD-DOWNES ASTHMA SCORE

VARIABLES	0 POINTS	1 POINT	2 POINTS
Oxygenation saturation	≥95% in room air	<95% in room air	<94% in 40% O_2
Inspiratory breath sounds	Normal	Unequal	Decreased or absent
Accessory muscles	None	Moderate	Maximal
Expiratory wheezing	None	Moderate	Marked
Cerebral function	Normal	Depressed/agitated	Coma

FIGURE 23-3

Common findings on a chest radiograph of a child with status asthmaticus. The hallmark is hyperinflation, and air leaks can occur which can lead to pneumomediastinum and subcutaneous interstitial air as seen
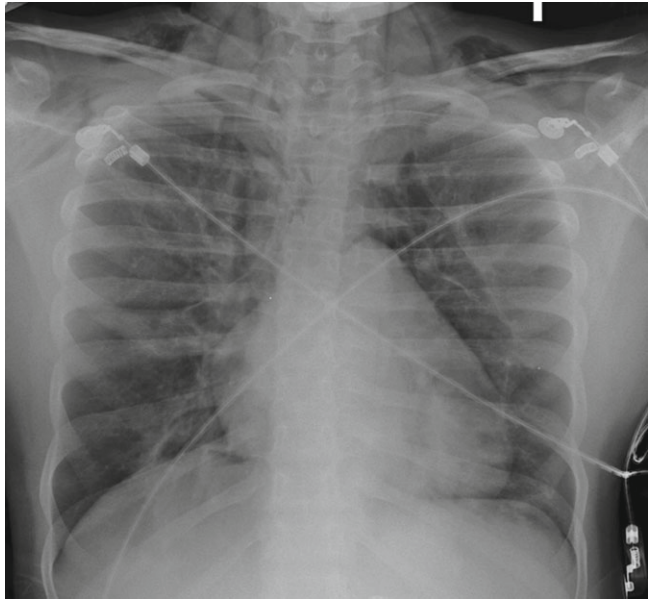
on radiograph, especially in the younger age groups. In a mechanically ventilated child, the radiograph will also determine appropriate depth of the endotracheal tube (Fig. 23-3).

An arterial blood gas may aid in determining asthma severity, but must be interpreted in the context of the clinical examination. A $PaCO_2$ of greater than 45 mm Hg in a child with severe work of breathing during an asthmatic exacerbation likely warrants PICU admission and serial arterial blood gas monitoring. In a child with severe tachypnea, increasing work of breathing and an increasing alveolar-arterial gradient, a "normal" $Pa\,CO_2$ may not be physiologically appropriate and indeed may signify worsening gas exchange. Clinical symptoms, such as the ability to speak, mental status, and diaphoresis are likely as reliable if not more reliable to determine respiratory failure when compared to an arterial blood gas.

It is important to remember the old adage "All that wheezes is not asthma". The differential diagnosis of the wheezing child includes laryngomalacia and bronchomalacia (especially in children less than 2 years of age), cystic fibrosis, viral bronchiolitis, foreign body aspiration (usually a sudden onset of wheezing in a previously healthy child), cardiac wheezing secondary to congenital heart disease or myocardial failure, viral croup, bacterial tracheitis, psychogenic wheezing and vocal cord dysfunction. A thorough history and physical examination will often exclude many of these disorders that can mimic severe asthma.

Vocal cord dysfunction is often difficult to distinguish from true asthma. The exact etiology of vocal cord dysfunction is unclear, but the condition is thought to be initiated by inappropriate vagal nerve stimulation causing an increase in laryngeal tone and precipitation of paradoxical adduction of the vocal cords. True lower airway obstruction is not a predominate feature of vocal cord dysfunction. Organic triggers are often lacking, and exacerbations are refractory to standard asthma treatments. The diagnosis can be made using pulmonary function testing confirming extrathoracic inspiratory obstruction, or more definitively, with direct laryngoscopic visualization of the paradoxical adduction of the vocal cords during inspiration.

An arterial blood gas in a child with asthma should never substitute for serial physical examinations.

THERAPIES FOR STATUS ASTHMATICUS

Oxygen delivery is the key treatment goal in caring for a child with severe asthma.

Severe asthma that requires admission to the PICU deserves aggressive therapy aimed at reducing airway resistance induced by the three mechanisms described above. Avoidance of hypoxia remains the key treatment goal in status asthmaticus, as ventilation/perfusion mismatch with the development of an intrapulmonary shunt routinely develops with severe asthma and air-trapping. As opposed to adults with chronic obstructive pulmonary disease,

supplemental oxygen will not suppress the respiratory drive in children with asthma. Therefore, oxygen therapy at high concentrations should be rapidly administered. Most children with severe asthma, especially those with a history of progressive worsening for days, are dehydrated, and fluid replacement with a goal of euvolemia should be undertaken. Unless there is a known bacterial infection or suspected infiltrate, antibiotics are not routinely indicated. However, the clinician must consider an infection with an atypical organism such as *mycoplasma pneumonia* as a potential trigger for the asthma exacerbation.

Current proven therapies that can be utilized in a child with severe asthma include:

Inhaled beta agonists remain the mainstay for asthma therapy. These medications can stimulate both beta-1 and beta-2 adrenergic receptors, and the beta-1 effects result in the toxicity seen with these agents. Therefore, a relatively selective beta-2 agonist would be preferable. In the United States, albuterol is the most commonly used selective beta-2 agonist. These medications have their effect by stimulation of the beta-2 receptors on bronchial smooth muscle cells, leading to bronchodilation by the adenosine 3′,5′-cyclic monophosphate (cAMP) mediated pathway. When delivered by aerosol, their effectiveness is dictated by distal drug delivery to the bronchial smooth muscle cells. Therefore, their delivery is dependent upon dose, spontaneous tidal volume, gas flow, device used to deliver the gas, and the subject's breathing patterns. Even under ideal conditions only a small percentage of drug actually reaches the target cells. Therefore, dosing must be titrated accordingly. While the use of serial, fixed-dose, inhaled beta-agonist treatments are appropriate for moderate exacerbation, multiple studies support the use of continuous nebulization in severe cases. This continuous therapy also appears to be well tolerated by the patients, and is less labor intensive for respiratory staff, thereby leading to a degree of cost effectiveness when compared to many intermittent treatments. The adverse effects of the inhaled beta-agonists are mostly related to their beta-1 cardiac effects. Tachycardia is the most common side effect, and is usually well tolerated in children without cardiac disease. Excitability, tremor, and hypokalemia also result from the use of these agents. Albuterol is an equal mixture of the active enantiomer, R-albuterol, and the inactive L-albuterol. Recently, there have been studies investigating levalbuterol, the pure R-isomer for racemic albuterol, in children with asthma. It has been suggested that the use of levalbuterol will have lower cardiac side effects with clinically comparable efficacy. There is also some evidence that this pure R-isomer results in decreased hospitalization rates in children with asthma. As the cost are markedly higher with levalbuterol, and no studies to date have been performed in the PICU setting, clinicians should use their best judgment in selecting a form of racemic albuterol to utilize in severe asthma in the PICU. The use of inhaled beta agonists should continue if the child requires mechanical ventilation due to respiratory failure. Delivery via high dose metered dose inhalers can optimize distal drug delivery while on mechanical ventilation.

> Inhaled beta agonists are the mainstay of therapy for the child with severe asthma.

Inhaled anticholinergic agents, particularly ipratropium bromide, are now considered standard therapy in combination with beta-agonists in severe asthma. Ipratropium exhibits bronchodilatory effects through inhibiting parasympathetic mediated bronchoconstriction, and has the advantage of less cardiac toxicity than beta-agonists. Unlike the parasymapatholytic atropine, ipratropium bromide does not impede mucociliary function. When utilized in conjunction with standard therapy, ipratropium improves in pulmonary function in both adults and children in the emergency setting, and appears to have the greatest benefit in severe asthma exacerbations. Despite the fact that studies of efficacy in the child with status asthmaticus admitted to the PICU are lacking, these agents should be added to the treatment plan of a child with severe asthma. Clinicians should be aware of concomitant pupillary dilation (unilateral or bilateral), if the inhaled anticholinergic agent inadvertently comes in contact with the eye of the patient.

As inflammation is the hallmark finding with severe asthma, corticosteroids are required therapy due to their potent anti-inflammatory effects. The effect of steroids on airway inflammation may take up to 6 h to become apparent, and therefore, children with severe asthma should receive their first dose of steroids as soon as possible. Numerous studies have demonstrated benefit in relieving bronchospasm and alleviating the need for hospitalization in both adults and children treated early with corticosteroids. Children requiring PICU admission for status asthmaticus should be treated with intravenous rather than enteral

steroids. The intravenous route will assure bioavailability of the steroids that will not be hindered by delayed gastric absorption, intestinal dysmotility, or vomiting leading to a delay in achieving the therapeutic goals of anti-inflammation. There has been no demonstrated advantage from one steroid preparation to another, and the commonly used intravenous corticosteroids are methylprednisolone, dexamethasone and hydrocortisone. The adverse effects of short-term treatment with this therapy include hyperglycemia, gastritis, sodium and water retention, hypertension, and increased susceptibility to infection. If long-term therapy is required for children with asthma, suppression of the hypothalamic-pituitary-adrenal axis, demineralization of bones, myopathy, and growth failure may occur.

<u>Magnesium</u> is an intracellular cation that is a key cofactor for cellular homeostasis. By inhibiting calcium intake into the smooth muscle cell of the airway, magnesium results in bronchodilation, leading to its use in asthma for many years. The use of intravenous magnesium as adjunctive therapy for severe asthma has been found to improve airflow in adults. Moreover, magnesium has gathered favor for use in children requiring critical care. Optimal dosing and duration is unknown, Intravenous dosing of 25–50 mg/kg given over 30 min every 4 h is the most common method of administering magnesium for severe asthma. Higher doses or rapidly infused magnesium may cause vasodilatation with resultant hypotension, and therefore, close hemodynamic monitoring is required. Other potential side affects of magnesium administration include flushing, arrhythmia, weakness and CNS depression. A meta-analysis of emergency room use of nebulized magnesium demonstrated that the number of children needed to treat to prevent hospitalization was only four. This route of administration deserves further study in children with severe asthma requiring critical care.

<u>Helium</u> is a biologically inert gas without inherent bronchodilatory or anti-inflammatory properties. Its use in the therapy of severe asthma is directly related to its physical properties that produce favorable flow characteristics. Normally, gas flow in the lung periphery is laminar because the large cross sectional area of the distal bronchioles allow for slow, streamlined flow. In contrast, upper airway flow is turbulent. Although the diameter of the upper airway is far greater than an individual bronchial, the total cross sectional area available for flow is far less in the upper airway. This results in a high velocity chaotic flow pattern. The pathophysiologic changes that asthma produces in the lower airway (edema, constriction and mucous plugging) result in a reduction in the cross sectional area available for flow. A greater pressure gradient and higher velocities are required to achieve distal flow in the setting of bronchoconstriction, and thus, the flow pattern becomes turbulent. Turbulent flow can be predicted based upon the Reynold's number (Re) of a gas. Flow is turbulent when the Re > 2,500. The formula for the Reynold's number is:

$$Re = VD\rho / \mu$$

where V is gas velocity, D is the diameter of the airway, ρ is gas density and μ is gas viscosity. Since helium possesses a lower gas density (approximately seven to eight times less dense than air), it results in a lower Reynold's number, and thus, reduces the likelihood of turbulent gas flow through narrowed airways. The conversion of turbulent to laminar flow allows distal gas delivery with a lesser pressure gradient and reduced velocity. Clinically, this results in improvement in gas exchange and a reduction in the work of breathing. Helium/ oxygen mixtures may also inherently improve ventilation as carbon dioxide diffuses at a four times faster rate when compared to an oxygen/nitrogen mixture. These physical characteristics have led to the addition of <u>helium/oxygen mixtures</u> to the armamentarium of asthma treatments. However, further study is needed to determine the impact of helium/oxygen mixtures in children with severe asthma exacerbations. The most beneficial mixture (i.e. the lowest Reynold's number) will have the highest concentration of helium (80% helium/20% oxygen), but the amount of oxygen required for the patient will dictate the mixture that is tolerated. Whether there is any benefit to mixtures utilizing lower than 70% helium is unknown. In addition, there is increased aerosol deposition in patients with asthma who received a helium/oxygen mixture when compared to air. Using a helium/oxygen mixture to deliver aerosolized medications to patients with severely obstructed small airways may increase the administration of the pharmacologic agents. This, in turn, may lead to a faster resolution of bronchospasm. When this mixture is utilized in a child with asthma who is

Intravenous corticosteroids should be administered as soon as possible to a child with severe asthma.

Helium/oxygen mixtures have a lower Reynold's number, leading to less turbulence through narrowed airways.

being mechanically ventilated, the PICU clinician must be cautious in flow and pressure related readings from most conventional ventilators, which are calibrated with only oxygen/nitrogen mixtures, and therefore may display inaccurate readings.

Intravenous beta-agonists should be considered when patients are unresponsive to increasing doses of inhaled bronchodilators, and the addition of these parenteral agents may either decrease the need for intubation or shorten the course of mechanical ventilation for severe asthma. The advantage of utilizing the intravenous route is that medication delivery is not dependent upon airflow and particle delivery to the airways. However, due to the side effects such as tachycardia, dysrhythmias, and specifically cardiac ischemia, intravenous beta-agonists should be utilized only in children without heart disease and be administered in the pediatric ICU. The two most commonly used medications are isoproterenol and terbutaline. Although studies of nebulized therapy with these two medications revealed no difference in either efficacy or adverse events, some authors believe that there are fewer cardiac side effects with terbutaline. However, the choice of which intravenous medication to be instituted must also take into account cost of the medication, and terbutaline is markedly more expensive to utilize when compared to isoproterenol. Until comparative studies are performed with these two agents, clinicians should use their best judgment in making their choice of intravenous beta-agonists.

It has been long known that the class of medications known as methylxanthines, and most notably theophylline and aminophylline, are potent bronchodilators. There are two mechanisms of action of methylxanthines on bronchial smooth muscle cells. They are potent, but non-selective inhibitors of the phosphodiesterases (PDE), including type 4, which is expressed in many of the cells that are key to the development of asthma. Intracellular cAMP is metabolized to AMP by the PDEs. By inhibiting this enzyme, the intracellular concentration of cAMP increases and displays a negative effect on phospholipase C contraction. This leads to decreased bronchoconstriction. In addition, the PDE inhibiting effect is thought to down-regulate the inflammatory burst from pulmonary inflammatory cells. The second mode of action occurs via inhibition of adenosine-induced bronchoconstriction. Despite these two mechanisms and a long history of efficacy in asthma, these medications are now considered second-line for both chronic asthma therapy as well as during acute exacerbations. One reason for the decrease in use is due to their narrow therapeutic window, in which significant adverse effects (nausea, vomiting, agitation, and tachycardia) can occur with even therapeutic levels. Drug concentrations can also increase or decrease due to multiple interactions with medications that interact with the hepatic cytochrome P450 enzymes. Methyxanthines have been found to improve clinical asthma scores and airflow during acute exacerbations, but have not consistently been shown to reduce PICU or hospital length of stay. Clinicians should consider the use of methylxanthines in the beta agonist refractory asthmatic while appreciating the potential for drug toxicity.

Methylxanthines may have a role in the treatment of some children with severe asthma, but they possess a small therapeutic window.

Leukotriene receptor antagonists have been demonstrated to have benefit in the treatment of chronic asthma symptoms, but their advantage as adjunctive therapy in severe acute asthma is presently unknown. It also appears as if only a portion of asthmatic subjects benefit from these medications. Whether this is due to certain leukotrienes receptor genetic variants or related to certain asthma phenotypes is unknown. The mechanism of action of these medications is based on their ability to inhibit 5-lipooxygenase, the enzyme responsible for the synthesis of the cysteinyl leukotrienes (LTC4, LTD4, and LTE4), which play a key role in asthma pathogenesis.

In children with severe asthma that fail to respond to any of the above therapies, sedation with ketamine has been attempted. Ketamine is a hypnotic anesthetic that possesses some bronchodilatory effects. This medication has been demonstrated to have benefit in acute asthma in both adults and children, but its use must be cautioned due to potentially serious adverse effects. These include hallucinations, bronchorrhea, laryngospasm, tachycardia, hypertension, and seizures. Low dose ketamine may play a role in avoiding mechanical ventilation in the child with severe asthma. Ketamine should be considered as an adjunct to endotracheal intubation and may be used as a sedative for the mechanically ventilated asthmatic children, in conjunction with a benzodiazepine.

The bronchodilatory effects of ketamine lead to a role in the treatment of severe asthma, but the serious adverse effects require close observation during its use.

There may be a role for non-invasive ventilation for the treatment of severe asthma, based on its effectiveness in avoiding the need for intubation in adults with chronic obstructive

pulmonary disease. The use of this mode of respiratory support requires a patient to be cooperative, and therefore, will likely be reserved for older children. Further study is necessary to determine the efficacy of non-invasive ventilation in critically ill asthmatic children.

A child with a refractory exacerbation and progressive hypoxemia despite maximal therapy and mechanical ventilation warrants a trial of <u>inhalational anesthetic agents</u>. Halothane, isoflurane, and sevoflurane have all been found to have bronchodilating effects, although the mechanism of action is unknown. Halothane has both significant negative inotropic and arrhythmogenic properties and should be avoided. Anesthetic delivery may be problematic, as anesthesia machines often do not have the capacity to properly ventilate the severe asthmatic for prolonged periods. A standard ICU ventilator can be fitted to deliver anesthesia, but ongoing delivery requires the presence of an anesthesiologist at the bedside.

MECHANICAL VENTILATION FOR SEVERE ASTHMA IN CHILDREN

Most children who are treated promptly and aggressively for severe asthma will improve and not develop respiratory failure requiring mechanical ventilation. However, a small subset of children may have progressive or rapid respiratory deterioration that requires endotracheal intubation and mechanical ventilation. These patients represent a clinical challenge, both in the decision and process of endotracheal intubation, as well as in the strategies utilized to provide on-going ventilatory support. The goal of mechanical ventilation of the child with severe asthma is to provide adequate oxygenation and ventilation until the airway obstruction subsides, and to allow respiratory muscles to rest by assuming the work of breathing.

> The goal of mechanical ventilation during asthma is to provide adequate oxygenation and ventilation and allowing respiratory muscles to rest.

There are some absolute indications for the initiation of mechanical ventilation in severe asthma. These include respiratory or cardiac arrest, refractory hypoxemia, or a rapidly worsening sensorium. There also exist some relative indications for endotracheal intubation, in which the decision must be made in the context of disease progression and therapy refractoriness. Relative indications include a rapidly increasing pulsus paradoxus, the loss of the ability to speak, and increasing lactate levels (signifying increased work of breathing). It is important to appreciate that an increasing respiratory acidosis alone does not define a need for mechanical ventilation.

Once the decision is made to intubate, preparation is essential, as the majority of morbidity (and mortality) that occurs as a consequence of severe asthma is during or soon after endotracheal intubation. Due to the predictable hemodynamic response to the initiation of positive pressure and the likelihood of concomitant volume depletion, appropriate fluid resuscitation should commence prior to intubation. Ketamine with a benzodiazepine is an effective combination to provide sedation. Use of atropine or glycopyrrolate should be considered to decrease bronchorrhea due to asthma or secondary to ketamine. Propofol is an acceptable alternative sedative if hypotension does not exist. Neuromuscular blockade can be achieved with the use of a rapidly acting nondepolarizing paralytic such as rocuronium. Due to the potential side effects of histamine release and hyperkalemia, succinylcholine is generally avoided, especially in infants. Opioid agonists such as morphine can worsen bronchospasm secondary to a release of histamine and should be avoided. Fentanyl causes less histamine release and may be considered if analgesia is required.

> Preparation is paramount during intubation, as the majority of morbidity and mortality of childhood asthma occurs during or shortly after endotracheal intubation.

Once intubated, the severe asthmatic child may also develop air plugging due to copious secretions obstructing the endotracheal tube. Pneumothorax secondary to air trapping and over-distention should be considered with any acute hemodynamic or respiratory deterioration.

In determining the most appropriate mechanical ventilator settings for the patient with severe asthma, the goal should be to provide an acceptable (but not necessarily normal) level of oxygenation and ventilation, and to avoid lung hyperinflation that may result from incomplete exhalation. Mechanical ventilation is complicated in these children by rapid, changes (both improvements and worsening) in airway resistance during the course of ventilation.

While the ventilator needs to be tailored to each patient specifically, some general guidelines on initial settings include: volume-cycled ventilation with an initial tidal volume set at approximately 10–12 mL/kg, a ventilation rate between 6 and 12 breaths/min, a relatively short inspiratory time (1 s) with an inspiratory to expiratory ratio as long as possible (1:4 or higher depending on the rate), and possibly the application low positive end expiratory pressure (PEEP) while monitoring auto-PEEP closely (see below). Newer generations of mechanical ventilators offer newer modes of ventilation, such as pressure-regulated volume control, which may have some benefits over volume-cycled ventilation. The oxygen concentration should initially be set at 100% and weaned as tolerated. The key to deciding on the appropriate respiratory rate and exhalation time is the physical exam. With the patient placed on the initial ventilator settings, the clinician should auscultate breath sounds and visualize chest excursion with each breath. Each positive pressure breath tidal volume should be completely exhaled prior to commencement of the next breath. If not, residual volume from each breath will lead to breath stacking, hyperinflation, and an increased risk of pneumothorax and hemodynamic compromise. If the exhaled flow is not completed, then either the mechanical respiratory rate must be decreased, or the expiratory time must be increased. However, in order to obtain minute ventilation sufficient for carbon dioxide removal, higher tidal volumes and peak inspiratory pressures may need to be tolerated. Normal carbon dioxide levels are not necessary and indeed may lead to preventable barotrauma. Clinicians should allow "permissive hypercapnia" to limit ventilator-induced lung injury. Pa CO_2 levels as high as 100 mm Hg may need to be tolerated during the early phases of mechanical ventilation.

> Mechanical ventilator settings must be tailored toward each child.

MONITORING AIRWAY PRESSURES AND GAS FLOW DURING MECHANICAL VENTILATION

Although mechanical ventilation may be life-saving in the asthmatic with respiratory failure, there exists the potential for further worsening of gas exchange after the institution of positive pressure. Monitoring changes in airway dynamics during mechanical ventilation of the asthmatic child is essential. Serially measurements of peak inspiratory pressures (PIP), plateau pressures and monitoring for the development of progresive hyperinflation enables the clinician to respond to dynamic airway changes that are common during mechanical ventilation for asthma.

Peak inspiratory pressures are often used as a proxy for distal alveolar pressure. However, during asthma, elevated airway resistance causes peak inspiratory pressure to be poorly reflective of peak alveolar pressure. Instead, serial measurements of both plateau and peak pressures better evaluate airway and lung changes during the mechanical ventilation of asthmatic child.

Measurement of peak inspiratory pressure allows assessment of the dynamic compliance of the respiratory system:

$$\text{Dynamic Compliance} = V_t/(PIP - PEEP)$$

Because PIP is measured during ongoing gas flow, it is not only reflective of lung compliance but also the resistance to airflow present in the proximal and distal airways. The peak pressure is inversely related to dynamic compliance. Increasing PIP can reflect a reduction in dynamic compliance of the lung due to worsening parenchymal disease if the plateau pressure is also elevated *or* reflect increased airway resistance if the plateau pressure remains constant.

Plateau pressure is obtained after instituting a flow pause (3 s) at end inspiration (Fig. 23-4). Plateau pressure is related to the static compliance of the respiratory system (RS) as:

> Increasing PIP can reflect a reduction in dynamic compliance of the lung due to worsening parenchymal disease if the plateau pressure is also elevated or reflect increased airway resistance if the plateau pressure remains constant.

$$\text{Static Compliance}_{RS} = V_t / (P_{plat} - PEEP)$$

Reduction in static compliance of the lung is usually due to inherent lung changes such as reduced functional residual capacity and/or increased elastic recoil. Since measurement of plateau pressure occurs during a state of zero flow through conducting airways it does not reflect changes in airway resistance. The plateau pressure is inversely related to static

FIGURE 23-4

Pressure during end inspiratory pause. Note the delta between the peak and plateau (EIP = end inspiratory pause)
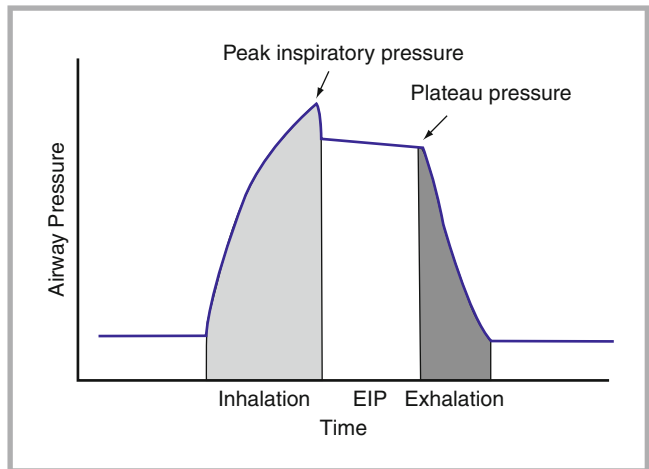
compliance. Increasing plateau pressure is usually reflective of worsening parenchymal (alveolar) disease. To minimize ventilator induced lung injury, some authors suggest that plateau pressure should be kept < 30 cm H_2O.

In summary, normally PIP is only slightly greater than plateau pressure. Concomitant elevations in PIP and plateau pressure are usually reflective of parenchymal disease such as ARDS or hyperinflation due to excessive tidal volume or auto-PEEP. Increased PIP with little change in plateau pressure usually reflects increased airway resistance. It is not uncommon for peak inspiratory pressures to be much higher than plateau pressures during mechanical ventilation for asthma. An increased PIP-plateau pressure delta is reflective of increased airway resistance and a decrease in the delta serves as a useful marker for clinical improvement.

Auto-PEEP occurs if an insufficient expiratory time impedes full exhalation of alveolar gas. Auto-PEEP is reflective of air trapping and is not uncommon in mechanically ventilated asthmatic children. Auto-PEEP can be quantified by occluding the expiratory port of the ventilator at end-expiration. The proximal airway pressure will equilibrate with alveolar pressure and permit measurement of auto-PEEP. Of note, auto–PEEP measured by the end-expiratory occlusion maneuver can have inconsistent results and requires paralysis as expiratory muscle contraction can cause artificial elevation. In addition, auto-PEEP can underestimate the severity of hyperinflation if there is poor communication between the distal alveoli and the proximal airways. This can occur if premature airway closure occurs prior to end expiration. Therefore, elevations in plateau pressures may be a more reliable and practical method to monitor lung hyperinflation.

Extrinsic PEEP may not be required in patients requiring neuromuscular blockade as significant elevation in total lung volume may occur. Use of low levels of extrinsic PEEP in mechanically ventilated children with spontaneous breaths may decrease the inspiratory work of breathing by decreasing the pressure gradient required to overcome auto-PEEP. Therefore, when selecting a PEEP setting, the intrinsic auto-PEEP must be carefully considered. The extrinsically applied PEEP should always be lower than the auto-PEEP. Adding excessive PEEP may result in overinflation, air leak and hemodynamic compromise from increased intrathoracic pressure.

The airway obstruction that occurs in severe asthma can be detected and monitored by a number of flow waveforms. The first is a flow-volume loop. In Fig. 23-5 increased airway resistance lead to decreased maximum expiratory flow, resulting in the concave shape to the expiratory limb on the flow-volume loop.

Flow-time loops can also be helpful in monitoring airway obstruction in the asthmatic child. This measure of expiratory flow can be tracked by assuring a return of flow to baseline zero prior to commencement of the next positive pressure breath. This is demonstrated in Fig. 23-6, in which end expiratory flow has not reached zero prior to the next breath (**arrow**). This will result in air-trapping and "auto-PEEP".

Increased peak inspiratory pressure with little change in plateau pressure usually reflects increased airway resistance.

Auto-PEEP occurs if an insufficient expiratory time impedes full exhalation of alveolar and is reflective of air trapping.
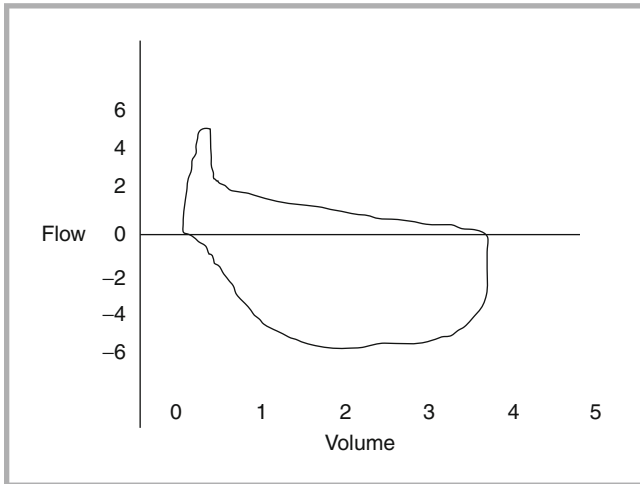
FIGURE 23-5

Concave expiratory flow pattern seen with lower airway obstruction
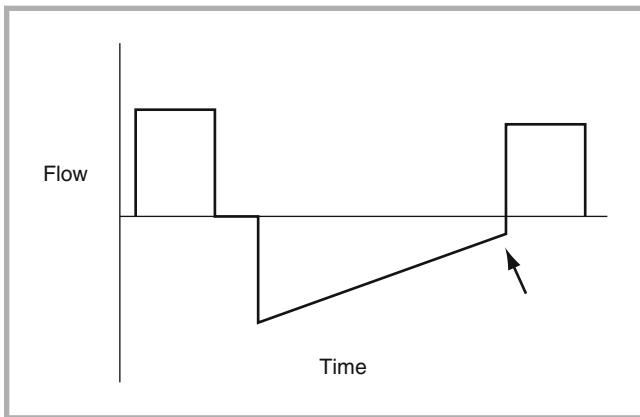
FIGURE 23-6

Flow-time relationship during mechanical ventilation of asthma. Note (*arrow*), expiratory flow has not returned to baseline indicating ongoing air trapping
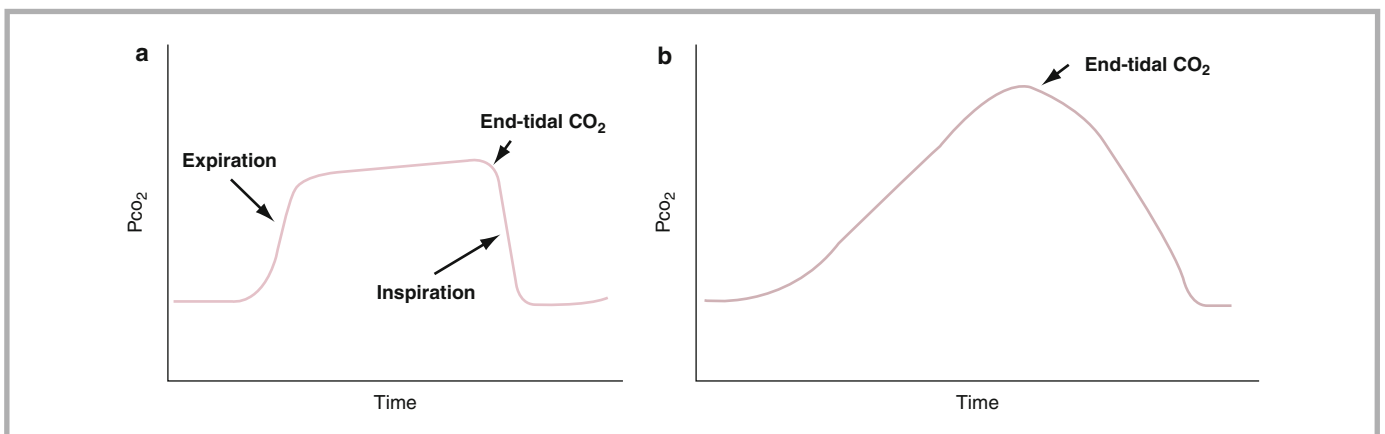
FIGURE 23-7

(**a**) Normal capnograph revealing normal early expiratory upstroke followed by alveolar plateau phase. (**b**) Capnograph during bronchospasm revealing prolonged expiratory phase, poor plateau and elevated end tidal CO_2 level

Lastly, the end tidal carbon dioxide tracing may also display evidence of expiratory obstruction and prolongation. There will be a delayed upstroke prior to reaching the expired carbon dioxide level transforming the waveform into a "shark fin" appearance. Normally there is a relative plateau that occurs prior to reaching the end tidal carbon dioxide value (Fig. 23-7).

COMPLICATIONS DURING MECHANICAL VENTILATION OF ASTHMA

There are a number of complications that can occur during the initiation and maintenance of mechanical ventilation in severe asthma. These complications include air leak due to positive pressure ventilatory breaths (pneumomediastinum, pneumothorax, subcutaneous emphysema), nosocomial tracheitis and pneumonia, and mucus plugging and atelectasis. Complications such as pneumothorax and hemodynamic compromise can be limited if plateau pressures are maintained less than 30–35 cm H_2O and auto-PEEP is less than 15 cm H_2O. There is also a risk of prolonged weakness that occurs in children ventilated for severe asthma. This myopathy appears to increase with the use of steroids and neuromuscular blocking agents, both of which are commonly used in children with asthma, as well as with aminoglycoside antimicrobials. The etiology of this myopathy is not presently understood, but may be related to a loss of protein synthesis or altered electrical excitability of muscle fibers. This weakness can be severe enough to require a physical rehabilitation hospital course once a child is medically ready for PICU discharge.

The degree of pulsus paradoxus that occurs during asthma is of prime importance during periods of hemodynamic compromise.

Marked hemodynamic compromise can occur during the course of a severe asthma exacerbation. The cardiopulmonary interactions that occur in the spontaneously breathing child with severe asthma are exemplified as previously noted by the presence of a pulsus paradoxus. In adults, the presence of a pulsus paradoxus in asthma has been correlated with disease severity. While many life-threatening disease processes related to the cardio-respiratory system can cause pulsus paradoxus (cardiac tamponade, pulmonary embolism, tension pneumothorax), it is best described in severe asthma.

In the spontaneously breathing asthmatic patient, increased left ventricular afterload, in addition to relative hypovolemia, compromises cardiac output. Once positive pressure ventilation is instituted, left ventricular afterload may be reduced, but it is offset by a marked reduction in venous return in combination with pre-existing hypovolemia, that may result in a dangerous reduction in cardiac output. This decrease in venous return may be exacerbated by the "auto-PEEP" frequently encountered in severe asthma. It is often necessary to fluid resuscitate the asthmatic child upon intubation, with close attention being required to avoid pulmonary edema. If at all possible, volume loading should be initiated in anticipation of intubation. Positive pressure ventilation, by increasing intrathoracic pressure, decreases left ventricular afterload, and therefore, leads to an improved stroke volume and will increase cardiac output as long as preload is constant. Thus, once an asthmatic patient is volume resuscitated, mechanical ventilation may actually improve hemodynamics. Finally, because the work of breathing in severe asthma can result in a lactic acidosis that may decrease cardiac function, mechanical ventilation may improve inotropy by reducing the work of breathing and decreasing anaerobic metabolism.

With close attention to fluid management, mechanical ventilation can improve hemodynamic instability in the child with severe asthma.

TREATMENT ALGORITHM FOR SEVERE ASTHMA IN CHILDREN

Asthma therapy in the PICU must be tailored to each individual patient's disease severity, age, level of maturity, response to therapeutic interventions, adverse effect of therapies attempted, and the presence or absence of other organ dysfunction and co-morbidities. Figure 23.8 outlines a general algorithm for the treatment of severe asthma in children. The key to the treatment of severe asthma is reassessment, and every therapeutic intervention should be assessed for both efficacy and adverse events. The algorithm outlines possible therapeutic strategies up until the point of mechanical ventilation. Extracorporeal membrane oxygenation should be considered in a ventilated asthmatic with refractory hypoxemia or hemodynamic collapse. Although there have been limited asthma patients that have required ECMO support, outcome has been highly favorable.

Asthma therapy must be tailored for each child, taking into account disease severity, response to therapeutics, and adverse effects of therapies attempted.

FIGURE 23-8

A clinical treatment guideline for severe asthma in children admitted to the PICU

```
                    ┌─────────────────────────────────┐
                    │      Initial monitoring          │
                    │  Vital signs, continuous EKG     │
                    │       Pulse oximetry             │
                    │     Peak flow (if able)          │
                    │    Clinical asthma score         │
                    │  Check serum electrolytes        │
                    │   (potassium, magnesium)         │
                    │  Consider arterial blood gas     │
                    │  Consider chest radiograph       │
                    └─────────────────────────────────┘
                                  │
  ┌───────────────────────────┐  +  ┌────────────────────────────┐
  │    Inhalational therapy   │     │  Corticosteroids (Intravenous) │
  │ Inhaled beta agonists     │     │                            │
  │ (continuous or            │     │                            │
  │ intermittent) and Inhaled │     │                            │
  │ anticholinergic agents    │     │                            │
  └───────────────────────────┘     └────────────────────────────┘
                                  │
                    ┌─────────────────────────────────┐
                    │        Reassessment              │
                    │         Vital signs              │
                    │       Pulse oximetry             │
                    │    Clinical asthma score         │
                    │  Consider arterial blood gas     │
                    └─────────────────────────────────┘
                                  │    ┌──────────────────┐
                                  │    │ If no improvement │
                                  │    └──────────────────┘
                    ┌─────────────────────────────────┐
                    │      Second tier therapy         │
                    │    Intravenous magnesium         │
                    │    Intravenous beta-agonists     │
                    │        Methylxanthines           │
                    │     Helium/oxygen mixture        │
                    │     Intravenous ketamine         │
                    │   Non-invasive ventilation       │
                    └─────────────────────────────────┘
                                  │    ┌──────────────────┐
                                  │    │ If no improvement │
                                  │    └──────────────────┘
                    ┌─────────────────────────────────┐
                    │        Reassessment              │
                    │         Vital signs              │
                    │       Pulse oximetry             │
                    │    Clinical asthma score         │
                    │ Consider arterial line placement │
                    └─────────────────────────────────┘
                                  │    ┌──────────────────┐
                                  │    │ If no improvement │
                                  │    └──────────────────┘
                    ┌─────────────────────────────────┐
                    │ Initiation of mechanical ventilation │
                    └─────────────────────────────────┘
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Algorithm for the step-wise approach to escalating therapy in acute asthma

REVIEW QUESTIONS

1. **Which of the following statements regarding the epidemiology of childhood asthma is correct?**
   A. A child with asthma has a high likelihood of requiring intubation and mechanical ventilation if hospitalization is required for his/her care.
   B. Although the prevalence of pediatric asthma has increased, the associated mortality has sharply decreased due to improved critical care services.
   C. The "hygiene hypothesis" which suggests that the early exposure to microbial infections results in asthma has become accepted as the sole explanation for the increased prevalence of asthma.
   D. The phenotype of asthma is likely the result of a complex interaction between environmental factors and a single gene mutation.
   E. The prevalence of asthma continues to rise especially among children of pre-school age and those living in urban settings.

2. **Poiseuille's Equation is used to explain the laminar flow rate of an incompressible fluid down a column. Which of the components of this equation best explains why children are at greater risk for airway obstruction than adults?**

A. The airway radius
B. The density of gas
C. The distance of the airways
D. The laminar flow of air
E. The pressure gradient from the trachea to the alveolus

3. **The pathophysiology of asthma involves a triad of three components mediated by an underlying inflammatory response. These three pathophysiological mechanisms consist of bronchospasm, mucosal edema, and which of the following?**
A. Diffusion block
B. Hypoxic vasoconstriction
C. Mucous plugging
D. Pulmonary edema
E. Surfactant depletion

4. **A 4 year old male is admitted to the pediatric intensive care unit with respiratory distress secondary to an acute exacerbation of asthma. He was started on albuterol as a continuous nebulized solution of 10 mg/h. He is awake and agitated, his oxygen saturation is 92% on 40% face mask oxygen, and he has normal inspiratory sounds. However, his Wood-Downes score is 7 because he has marked expiratory wheezing with maximal accessory muscle use. In light of these clinical findings, it would be MOST important to initiate which of the following medications:**
A. Azithromycin
B. Ipratroprium
C. Magnesium
D. Solumedrol
E. Theophylline

5. **A 9 year old male is transferred to the pediatric intensive care unit with respiratory distress secondary to an acute exacerbation of asthma. He has marked expiratory wheezing with maximal accessory muscle use. Despite aggressive therapy consisting of intravenous steroids, continuous β-agonist aerosol therapy, and anticholinergic aerosols, the young man continues to deteriorate and ultimately requires intubation. Which of the following induction medications for the intubation would MOST likely benefit his respiratory condition?**
A. Etomidate
B. Fentanyl
C. Ketamine
D. Propofol
E. Thiopental

6. **A 6 year old male is admitted with an acute exacerbation of status asthmaticus. He has significant expiratory wheezing with moderate retractions. He is well saturated on 40% face mask oxygen. He is treated with intravenous solumedrol, β-agonist aerosol therapy, and anticholinergic aerosols. He currently does not appear to need intubation, but must be monitored closely for signs of deterioration. Which of the following is the most effective means of monitoring this child?**
A. Daily fluid balance
B. Serial blood counts, temperature assessments, and respiratory cultures
C. Serial blood gases assessing for carbon dioxide retention
D. Serial chest x-rays assessing for atelectasis and air leaks
E. Serial clinical exams using a validated asthma score

7. **Although every inflammatory cell may be responsible for the inflammation and airway edema associated with asthma, those thought to be the most active during status asthmaticus include all of the following EXCEPT:**
A. Airway epithelial cells
B. Eosinophils
C. Lymphocytes
D. Mast cells
E. Neutrophils

8. **Inhaled β-agonists remain the mainstay for asthma therapy. Which of the following is true regarding their pharmacological actions?**
A. Their beneficial effects are mediated by a combination of β-1 and β-2 receptor stimulation.
B. Their beneficial effects are mediated by β-1 receptor stimulation while their toxicity is mediated by alpha-1 receptor stimulation.
C. Their beneficial effects are mediated by β-1 receptor stimulation while their toxicity is mediated by β-2 stimulation.
D. Their beneficial effects are mediated by β-2 receptor stimulation while their toxicity is mediated by alpha-2 receptor stimulation.
E. Their beneficial effects are mediated by β-2 receptor stimulation while their toxicity is mediated by β-1 receptor stimulation.

9. **Which of the following medications used in the treatment of status asthmaticus exerts its effect by inhibiting the inward movement of calcium into smooth muscle thereby preventing further bronchoconstriction?**
A. Albuterol
B. Aminophylline
C. Helium
D. Ipratropium
E. Magnesium

10. **Which of the following medications used in the treatment of status asthmaticus exerts its effect via a combination of inhibition of phosphodiesterase and adenosine-induced bronchoconstriction?**
A. Albuterol
B. Aminophylline
C. Helium
D. Ipratropium
E. Magnesium

11. **Pathophysiological conditions such as status asthmaticus result in increased turbulent airflow through the lower airways. Turbulent flow can be predicted based upon the Reynold's number (*Re*) of a gas. The formula for the Reynold's number is:**

$$Re = VD\rho / \mu$$

where *V* is gas velocity, *D* is the diameter of the airway, ρ is gas density and μ is gas viscosity. Helium/oxygen mixtures exert their effect on the Reynold's number by primarily influencing which of the following parameters?
A. Airway diameter
B. Gas density
C. Gas diffusion
D. Gas velocity
E. Gas viscosity

12. A 12 year old male with a known history of refractory asthma is transferred to the pediatric intensive care unit (PICU) with a severe exacerbation of his asthma. En route to the PICU, the emergency medical team places him on a non-rebreather oxygen mask because his oxygen saturation ranges from only 84–89%. He is promptly started on intravenous solumedrol, continuous inhaled albuterol, and intermittent ipratropium bromide. A few hours into his admission he is becoming progressively more lethargic and his respiratory distress persists. Intravenous magnesium and an aminophylline infusion are added to his therapeutic regimen. His vital signs reveal a temperature of 38.8°C, a heart rate of 160 bpm, a respiratory rate of 36 breaths/min, and a blood pressure of 125/82 mm Hg. His air exchange is fair with expiratory wheezing and marked retractions. He has bounding pulses. The nurse reports that he has anisocoria with his right pupil 7 mm and his left 4 mm. Which of the following is the MOST appropriate course of action?

   A. Perform a more thorough neurologic exam, and if reassuring, continue his current care with frequent monitoring of his neurologic exam and serum drug levels.

   B. Perform a more thorough neurologic exam, and if reassuring, decrease the dose of albuterol and/or ipratropium as their combined effect may be resulting in a tachydysrhythmia that is potentially compromising organ perfusion.

   C. Perform a more thorough neurologic exam, and if reassuring, discontinue his aminophylline as it may be associated with subclinical seizures manifested as anisocoria.

   D. Perform a more thorough neurologic exam, and if reassuring, discontinue his magnesium as high levels of magnesium may be associated with neuromuscular changes.

   E. Perform a more thorough neurologic exam, and if reassuring, order a stat computerized axial tomogram of the brain in light of his history of hypoxia.

13. A 7 year old male with an acute severe exacerbation of his asthma has a rapidly deteriorating level of consciousness. An arterial blood gas reveals a pH 7.26, $PaCO_2$ 56 mm Hg and PaO_2 52 mm Hg with pulse oximeter readings persistently 88%. A decision is made to urgently intubate the child. The child receives ketamine (1 mg/kg), glycopyrrolate, and rocuronium (0.9 mg/kg) to facilitate the intubation. The child is successfully intubated on the first attempt, but while taping the endotracheal tube he becomes profoundly hypotensive with significant respiratory variation in his arterial pressure waveform. Which of the following most likely represents the primary pathophysiology of the hypotension?

   A. A tension pneumothorax secondary to over distension of the lungs and increased auto-PEEP as a result of bagging in the face of increased airway resistance and prolonged exhalation.

   B. Decreased cardiac output from persistent hypoxia and acidosis exacerbated by the intubation process.

   C. Decreased cardiac output secondary to ketamine use in a catecholeamine-depleted patient.

   D. Inaccurate zeroing of the arterial catheter pressure transducer as the bed was raised to facilitate intubation of the child.

   E. Relative intravascular volume depletion secondary to increased insensible losses, decreased oral intake, and increased intrathoracic pressure.

14. A 9 year old, 30 kg young girl with an acute exacerbation of severe asthma has required intubation and mechanical ventilation. She is placed in a pressure regulated, volume control mode with the following ventilator settings:

   IMV rate: 20 breaths/min
   Peak End Expiratory Pressure (PEEP): 5 cmH_2O
   Tidal volume: 300 mL
   I-time: 1.0 s
   Fraction of inspired oxygen: 0.40

   In addition, she has an auto PEEP of 5 cmH_2O, a peak inspiratory pressure of 42 cmH_2O, a plateau pressure of 34 cmH_2O, and an end expiratory flow of 3 L/min. The nurse hands you her most recent arterial blood gas result:
   pH: 7.31
   $PaCO_2$: 59 mm Hg
   PaO_2: 68 mm Hg
   Which of the following is the most deleterious next intervention?

   A. Decrease the I-time
   B. Decrease the PEEP
   C. Decrease the tidal volume
   D. Increase the respiratory rate
   E. Make no ventilator changes

ANSWERS

1. E
2. A
3. C
4. D
5. C
6. E
7. E

8. E
9. E
10. B
11. B
12. A
13. E
14. D

SUGGESTED READINGS

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