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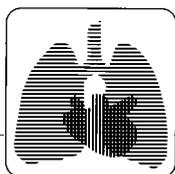
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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]



review

Status Asthmaticus in Children*

A Review

Heinrich A. Werner, MD

About 10% of American children have asthma, and its prevalence, morbidity, and mortality have been increasing. Asthma is an inflammatory disease with edema, bronchial constriction, and mucous plugging. Status asthmaticus in children requires aggressive treatment with β -agonists, anticholinergics, and corticosteroids. Intubation and mechanical ventilation should be avoided if at all possible, as the underlying dynamic hyperinflation will worsen with positive-pressure ventilation. If mechanical ventilation becomes necessary, controlled hypoventilation with low tidal volume and long expiratory time may lessen the risk of barotrauma and hypotension. Unusual and nonestablished therapies for severe asthma are discussed.

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Key words: asthma; β -adrenergic agonists; children; corticosteroids; helium-oxygen; ipratropium; ketamine; magnesium sulfate; mechanical ventilation; status asthmaticus

Abbreviations: cAMP = cyclic adenosine monophosphate; DHI = dynamic hyperinflation; ECLS = extracorporeal life support; e-NANC = excitatory or stimulatory nonadrenergic-noncholinergic; i-NANC = inhibitory nonadrenergic-noncholinergic; NANC = nonadrenergic-noncholinergic; NO = nitric oxide; PC = pressure control; PEEP = positive end-expiratory pressure; PKA = protein kinase A; PRVC = pressure-regulated volume control; PS = pressure support; PSV = pressure-support ventilation, VIP = vasoactive intestinal peptide

Severe asthma is becoming more prevalent in American children, and mortality has risen sharply in the past decade. Any physician may be faced with an asthmatic child in severe respiratory distress and impending respiratory failure, and will have to initiate aggressive treatment quickly. The following text reviews the current understanding of epidemiology, physiology, and treatment of severe, life-threatening asthma in children. The term *status asthmaticus* will be used to describe the condition of severe asthma.

DEFINITION

Status asthmaticus is the condition of a patient in progressive respiratory failure due to asthma, in whom conventional forms of therapy have failed.¹

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The exact definition differs between authors. For practical clinical purposes, any patient not responding to initial doses of nebulized bronchodilating agents should be considered to have status asthmaticus.²

EPIDEMIOLOGY

About 10% of children in the United States have asthma.³ Asthma has become the most common chronic illness of childhood in the United States.⁴ Dramatic worldwide variations in asthma prevalence have been found, with the highest rates in the United Kingdom, Australia, and New Zealand, and the lowest prevalence in Eastern Europe, China, and India.^{5,6} Its prevalence is increasing, especially in children < 12 years of age.^{4,7} Diagnostic shift, *ie*, the use of "asthma" for conditions previously classified differently, cannot fully account for this development, as asthma prevalence has been increasing worldwide.⁸

Asthma morbidity is also on the increase in the United States; annual hospitalization rates for asthma have nearly doubled for children aged 1 to 4

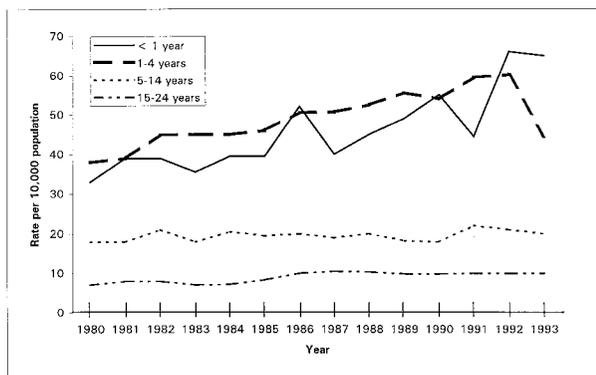


FIGURE 1. Hospital discharge rates for asthma in the United States, from 1980 to 1993. From MMWR.⁴

years from 1980 to 1992 (Fig 1).⁴ This trend is also shared by other nations worldwide.⁸

Asthma mortality is rising worldwide for reasons poorly understood. Among American children aged 5 to 14 years, asthma death rates almost doubled from 1980 to 1995 (Fig 2).^{4,22} Other countries have observed a similar increase in severity and mortality (New Zealand, Canada).^{23,24}

It has been estimated that 3 to 16% of hospitalized adult asthmatic patients will progress to respiratory failure and require intubation,^{25,26} but this figure may be considerably lower for children.^{12,27}

RISK FACTORS

The definition of criteria to identify children with potentially fatal asthma has proven to be difficult. Although several contributors to the mortality risk have been described, as many as one third of children who die from asthma may have only had mild asthma before, and were not previously classified as

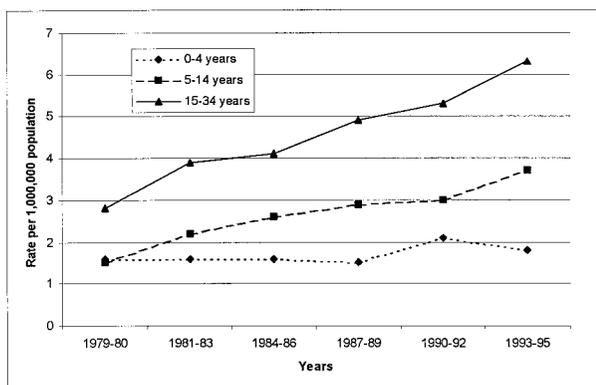


FIGURE 2. Rates of death in children with asthma as the underlying cause of death diagnosis in the past 2 decades. Adapted from Mannino et al.²²

Table 1—Risk Factors for Potentially Fatal Asthma

Medical factors
Previous attack with:
Severe, unexpected, rapid deterioration ^{9,10}
Respiratory failure ^{11,12}
Seizure or loss of consciousness ^{13,14}
Attacks precipitated by food ¹⁴
Psychosocial factors
Denial or failure to perceive severity of illness ¹⁵⁻¹⁷
Associated depression or other psychiatric disorder ¹⁸
Noncompliance ^{16,19}
Dysfunctional family unit ¹⁷
Inner-city residents ²⁰
Ethnic factors
Nonwhite children (African American, Hispanic, other) ^{20,21}

“high risk” by any available criteria. In their review of 51 pediatric deaths from asthma in Australia, Robertson et al¹⁰ found that only 39% had potentially preventable elements. Known predictors of severe, life-threatening asthma can be grouped in medical, psychosocial, and ethnic factors (Table 1).⁹⁻²¹ In the United States, nonwhite children with poor access to health care have the highest risk for near-fatal and fatal asthma.^{20,21} Black children have long shared disproportionately in the increase of prevalence, morbidity, and mortality of asthma.²⁸ During the last decade, black children were four to six times more likely to die from asthma than white children.⁴

PATHOPHYSIOLOGY

Asthma is characterized by reversible, diffuse lower-airway obstruction, caused by airway inflammation and edema, bronchial smooth-muscle spasm, and mucous plugging. During the last 2 decades, chronic airway inflammation, rather than smooth-muscle contraction alone, has been recognized as playing the key role in the pathogenesis of asthma.^{29,30} Lymphocytic and eosinophilic submucosal infiltrates, seen on tracheal and bronchial biopsy specimens from adult asthmatic patients, appear to correlate with severity of disease.²⁹ Mast cells, epithelial cells, and T lymphocytes are activated and produce proinflammatory cytokines.³⁰ Mediators such as histamine, leukotrienes, platelet-activating factor, and others are found locally (airways) as well as systemically (blood and urine) in increased concentrations.³⁰ In addition to inflammatory changes, epithelial destruction renders the airways of the asthmatic patient hyperirritable. At all levels of the tracheobronchial tree, epithelial, especially ciliated, cells are destroyed and nerve endings are exposed.³¹ Correlation has been found between the degrees of epithelial denudation and airway reactivity.³¹ The hyperirritable and chronically inflamed airway is

susceptible to acute obstruction triggered by such factors as allergen exposure³²; respiratory tract infections³³; environmental irritants,³⁴ including second-hand smoke³⁵; exercise³⁶; emotional stress³⁷; gastroesophageal reflux³⁸; and drugs. Furthermore, inflammation causes hypertrophy and stimulation of goblet cells and mucous glands, leading to hypersecretion,³⁹ with bronchial mucous casts in extreme cases.^{40–42}

Autonomic Nervous System

The autonomic nervous system regulates bronchoconstriction and bronchodilatation, as well as mucus secretion and possibly mast cell degranulation.⁴³ Parasympathetic ganglia in the walls of small bronchi form the end points of vagal pulmonary innervation. Apart from vagal signals, these ganglia also receive input from the sympathetic and the nonadrenergic-noncholinergic (NANC) nervous systems. Postganglionic parasympathetic fibers end in airway epithelium, submucosal glands, and mast cells.⁴³ The densest cholinergic innervation is found in the walls of major bronchi, which is also the site of bronchoconstriction in asthma.⁴⁴ Sympathetic β -receptors are found on airway smooth muscle, epithelium, and mucous glands, and are stimulated by circulating catecholamines. Bronchomotor tone is a result of the balance of parasympathetic, sympathetic, and NANC input (Table 2).

Cholinergic mechanisms mediated by parasympathetic fibers are the predominant neural pathway for bronchoconstriction in humans.⁴⁵ Activation of these fibers causes release of postganglionic acetylcholine, which in turn activates M_3 muscarinic receptors in airway smooth muscle, causing bronchoconstriction.⁴⁴ M_3 postganglionic receptors also mediate mucus secretion.⁴³ M_2 receptors are of particular interest in asthma; located on the postganglionic nerves, they limit further acetylcholine release and thus have a powerful inhibitory function.⁴⁴ Mounting

evidence⁴⁴ suggests that dysfunction of M_2 receptors causes vagally mediated hyperreactivity; dysfunction of the M_2 receptor can be induced in guinea pigs by exposure to allergens, viral infection, ozone, eosinophil products, tumor necrosis factor, and interleukin 1.⁴⁵ Currently available anticholinergic agents are nonselective and antagonize both M_3 and M_2 receptors. M_2 -receptor antagonism may then cause bronchoconstriction, counteracting some of the M_3 -receptor-induced bronchodilatation.⁴⁶

There is no direct adrenergic innervation to human airway smooth muscle. Adrenergic bronchodilatation and other β -adrenergic effects in asthma are mediated via stimulation of β -receptors by circulating catecholamines.⁴⁷ β -Receptors are found on smooth muscle of large and small airways,⁴⁸ cholinergic⁴⁹ and sensory⁵⁰ airway nerves, submucosal glands,⁵¹ bronchial blood vessels,⁵² as well as inflammatory cells (mast cells,⁵³ eosinophils,⁵⁴ lymphocytes,⁵⁵ and macrophages⁵⁶). Occupation of a β -receptor by an agonist results in activation of protein kinase A (PKA) via 3',5'-adenosine monophosphate (cyclic adenosine monophosphate [cAMP]). PKA phosphorylates cell-specific proteins leading to the respective cellular response.⁵⁷ In airway smooth muscle, increased concentrations of PKA lead to muscle relaxation via several mechanisms: inhibition of myosin light-chain phosphorylation,⁵⁸ a fall in intracellular Ca^{2+} ,⁵⁹ and stimulation of Na^+/K^+ adenosine triphosphatase.⁶⁰

The NANC nervous system has both inhibitory nonadrenergic-noncholinergic (i-NANC) effects and excitatory or stimulatory nonadrenergic-noncholinergic (e-NANC) effects⁶¹ on bronchomotor tone. NANC relaxation (i-NANC) was first reported in human airways in 1976⁶² and remains the only known neurally mediated bronchodilator mechanism in man.⁴⁵ i-NANC appears to involve several neurotransmitters, including vasoactive intestinal peptide (VIP)⁶³ and nitric oxide (NO).⁶⁴ VIP receptors are found in smooth muscle, epithelial cells, and submucosal glands in humans.⁶³ Binding of VIP activates adenylyl cyclase, resulting in elevated cAMP levels.⁶⁵ Besides bronchodilatation, VIP has vasodilatory⁶⁶ and immunomodulatory functions.^{67,68} NO is produced by NO synthase found in nerves in tracheal and bronchial smooth muscle,⁶⁹ may be co-released with acetylcholine and VIP,⁷⁰ and mediates bronchodilatation.⁷¹

e-NANC bronchoconstriction is believed to be mediated by neuropeptides released from nociceptive sensory fibers in the airways.⁷² These afferent fibers, when stimulated, transmit signals to the brain, and simultaneously release tachykinins such as substance P and neurokinin A. Tachykinins act as potent bronchoconstrictors,⁷³ stimulate submucosal glands,⁷⁴

Table 2—Autonomic Influences on Bronchomotor Tone

Bronchodilatation	
Parasympathetic	M_2 -receptor stimulation leading to inhibition of acetylcholine release
Sympathetic	β -receptor stimulation by circulating catecholamines
i-NANC	Release of VIP and NO
Bronchoconstriction	
Parasympathetic	Activation of M_3 receptors by acetylcholine
e-NANC	Release of tachykinins (substance P, neurokinin A)

cause histamine release from mast cells,⁷⁵ and stimulate inflammatory cells, such as neutrophils, eosinophils, and lymphocytes.

Lung Mechanics and Gas Exchange

Pulmonary mechanics and volumes are markedly altered in asthma. Due to severe airflow limitation in the lower airways, premature airway closure leads to increases in closing capacity and functional residual capacity. Inspiratory muscle activity persists throughout expiration, attempting to counteract expiratory airway closure by increasing the forces holding the airway open.⁷⁶ Hyperinflation results. Inhomogeneous distribution of areas of premature airway closure and obstruction causes ventilation/perfusion mismatching resulting in hypoxemia. Increased work of breathing under hypoxic 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 rapid and often profound decrease in pH will occur.

Cardiopulmonary Interactions

The marked changes in lung volume and pleural pressures impact on the function of both left and right ventricles. Spontaneously breathing children with severe asthma have negative intrapleural pressures during almost the entire respiratory cycle, with peak inspiratory pressures as low as -35 cm H₂O during a severe attack.⁷⁶ Mean pleural pressure becomes more negative with increasing severity of the attack.⁷⁶ Negative intrapleural pressure causes increased left ventricular afterload⁷⁷ and favors transcapillary filtration of edema fluid into airspaces,⁷⁶ resulting in a high risk for pulmonary edema. Overhydration in this scenario would increase microvascular hydrostatic pressure and further favor development of pulmonary edema.

Right ventricular afterload is increased secondary to hypoxic pulmonary vasoconstriction, acidosis, and increased lung volume.⁷⁸ Pulsus paradoxus is a clin-

ical correlate of cardiopulmonary interaction during asthma. This actually inappropriate term describes an exaggeration of the normal inspiratory drop in arterial pressure (normally ≤ 5 mm Hg, but ≥ 10 mm Hg in pulsus paradoxus⁷⁹). Pulsus paradoxus is the result of a marked inspiratory decrease in left-sided cardiac output, caused by decreased left atrial return from increased capacitance of the pulmonary vascular bed, and increased left ventricular afterload from negative pleural pressures.

CLINICAL PRESENTATION AND ASSESSMENT

General

The child with status asthmaticus usually presents with cough and wheezing, and exhibits signs of dyspnea, increased work of breathing, and anxiety. However, the sick asthmatic child may also present in respiratory failure or even frank cardiopulmonary arrest. The degree of wheezing does not correlate well with severity of disease.⁸⁰ The clinician should be reassured by the noisy chest in a child with severe asthma, as sufficient airflow is present to cause turbulence and vibration, and thus audible wheezing. Far more ominous are distant or absent breath sounds ("silent chest") in the face of increased respiratory effort.

Clinical Predictors of Impending Respiratory Failure

Findings indicating impending respiratory failure include disturbance in level of consciousness, inability to speak, markedly diminished or absent breath sounds, and central cyanosis. Diaphoresis and inability to lie down are also ominous signs in asthmatic patients.⁸¹ Wood et al⁸² suggested a clinical asthma score to quantify the severity of acute asthma (Table 3).

The presence of pulsus paradoxus correlates with the severity of the asthma attack.^{79,83,84} The degree of pulsus paradoxus can be measured directly with a hand-operated BP cuff or estimated from a pulse

Table 3—Clinical Asthma Score*

Variables	Score		
	0	1	2
Cyanosis or PaO ₂ , mm Hg	None 70–100 in 21% O ₂	In 21% O ₂ < 70 in 21% O ₂	In 40% O ₂ < 70 in 40% O ₂
Inspiratory breath sounds	Normal	Unequal or absent	Decreased
Accessory muscles used	None	Moderate	Maximal
Expiratory wheezing	None	Moderate	Marked
Cerebral function	Normal	Depressed or agitated	Coma

*From Wood et al.⁸² A score of ≥ 5 indicates impending respiratory failure; a score of ≥ 7 is consistent with respiratory failure.

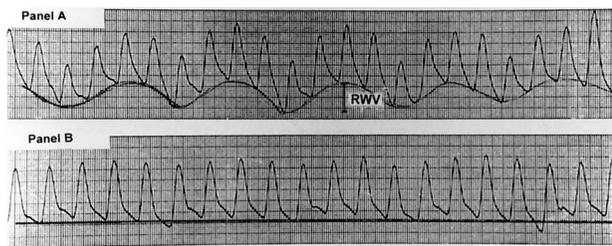


FIGURE 3. Marked variation in the baseline of an asthmatic patient's pulse oximeter tracing is observed in the presence of pulsus paradoxus. *Top, panel A:* pulse oximeter tracing of a patient with acute exacerbation of obstructive lung disease, pulsus paradoxus of 16 mm Hg. RWV = respiratory waveform variation. *Bottom, panel B:* pulse oximeter tracing after clinical improvement and resolution of pulsus paradoxus. The degree of variation correlates with degree of pulsus paradoxus, as well as with the degree of air trapping, in both spontaneously breathing patients and in patients receiving mechanical ventilation. From Hartert et al.⁸⁵

oximetry tracing (Fig 3).⁸⁵ As long as the patient is not experiencing frank fatigue and respiratory failure, the trend in pulsus paradoxus may be useful in following severity of the illness.⁸⁴

Chest Radiography

Chest radiographs are not routinely indicated in the unintubated asthmatic child, as unexpected radiographic abnormalities are very rare.⁸⁶ Exceptions are situations in which the clinical examination suggests the possibility of barotrauma or pneumonia, or when there is doubt that the wheezing is caused by asthma.

Blood Gas

Arterial blood gas measurement yields quantitative information on pulmonary gas exchange. Typical findings during the early phase of severe asthma are hypoxemia and hypocarbia. With increasing airflow obstruction, hypercarbia will develop and indicate impending respiratory failure.⁸⁷ However, the decision to intubate an asthmatic child should not depend on blood gas determination, but should be made on clinical grounds.^{88,89} Close observation of respiratory effort, pulse oximetry, and level of consciousness serve as continuous clinical correlates of pulmonary gas exchange. The sedated and intubated patient, however, requires frequent blood gas determination, best from an indwelling arterial line, to assess adequacy of ventilatory support and progression of illness.

TREATMENT

General

Any child in status asthmaticus requires cardiopulmonary monitoring. A comfortable and supportive

environment should be provided, ideally with a parent or family member present. While hypoxemia and anxiety will lead to agitation and restlessness, sedatives are contraindicated in the nonintubated asthmatic patient.

Oxygen

All patients with asthma have ventilation/perfusion mismatch and thus require humidified oxygen. High-flow supplemental oxygen is best delivered via a partial or nonrebreather mask. In the absence of preexisting chronic pulmonary disease, there is no evidence that oxygen will suppress the respiratory drive.⁹⁰

Fluid

Most asthmatic patients are dehydrated on presentation (poor fluid intake, vomiting, increased insensible fluid loss from the respiratory tract). Fluid replacement and maintenance of euvolemic state are necessary to minimize thickening of secretions. However, increased hydration in acute asthma has no purpose and may lead to pulmonary edema (see above). The syndrome of inappropriate antidiuretic hormone release may be common in severe asthma⁹¹; therefore, urine output and fluid balance need to be monitored carefully.

Antibiotics

Asthma attacks triggered by infection mostly involve viral pathogens⁹²; therefore, antibiotics are not indicated as a routine measure.

β -Agonists

β -Receptor agonist bronchodilators are a crucial element of therapy in status asthmaticus. These agents mediate bronchodilatation via stimulation of β_2 -receptors on airway smooth muscle, which in turn mediates smooth-muscle relaxation.

Commonly used agents include epinephrine, isoproterenol, terbutaline, and albuterol. Terbutaline and albuterol are generally being preferred for their relative β_2 selectivity, with decreased likelihood of β_1 cardiovascular effect. β -Agonists can be administered via the inhaled, IV, subcutaneous, or oral routes. Recently, some attention has turned to levalbuterol, the pure or homochiral formulation of (R)-albuterol. Conventional, or racemic albuterol is a 50/50 mixture of (R)-albuterol and (S)-albuterol. (S)-albuterol, previously thought to be an inert compound, may exaggerate airway hyperresponsiveness⁹³ and also may have a proinflammatory effect.⁹⁴ As (S)-albuterol is metabolized much more slowly than

(R)-albuterol,⁹⁵ it has been postulated⁹⁶ that (S)-albuterol may accumulate during frequent, repeated use of racemic albuterol and thus lead to increased frequency of potentially adverse effects. To date and to my knowledge, only two blinded, randomized studies^{96,97} comparing (R)-albuterol and racemic albuterol involved children, the number of children enrolled having been very small. Presently, no recommendation regarding the use of the much more expensive (R)-albuterol in children with status asthmaticus can be made. Orally administered β -agonists are ineffective in severe asthma. Subcutaneous epinephrine, once the standard of therapy in children with severe asthma, has become obsolete because of its marked cardiac side effects compared to equally effective nebulized agents.

The most common means of administering a β -agonist in an asthmatic patient is nebulization. In the United States, the most frequently used agent is albuterol (salbutamol). Dosage has often been recommended as 0.05 to 0.15 mg/kg.^{2,98} The correct dose remains controversial, but much less than 10% of nebulized drug will reach the lung even under ideal conditions.⁹⁹ Tidal volume, breathing pattern, and nebulizer gas flow further vary the amount of drug delivery.¹⁰⁰ Much higher doses of nebulized β -agonists, if delivered while the patient is being closely monitored, are being recommended by recent publications.^{101–103} This author commonly nebulizes albuterol, 2.5 mg (diluted to 4 mL), in uncomplicated asthma, and readily doubles the concentration or uses undiluted drug for severe status asthmaticus.

Continuous nebulization appears to be superior to intermittent doses.^{104–106} In a randomized study¹⁰⁶ comparing intermittent with continuous nebulization, children receiving continuous albuterol improved more rapidly. Use of continuous nebulization may also be more cost effective,¹⁰⁶ and offers more hours of uninterrupted sleep to an exhausted child.¹⁰⁷ Most published studies used rather low doses for continuous albuterol nebulization (4 to 10 mg/h), but much higher doses up to continuous nebulization of undiluted drug (equal to 150 mg/h for most nebulizers at 10 to 12 L/min flow) are being used by some authors.^{88,101,103} In severe status asthmaticus, I commonly administer 40 to 80 mg/h of albuterol.

For any form of nebulization, the nebulization device should be driven by oxygen. Care must be taken to utilize the correct flow rate; aerosol particle size depends, among other factors, on nebulizer flow rate. The higher the flow rate, the smaller will be the particle size. Only aerosol particles with a median diameter of 0.8 to 3 μ m are deposited in the alveoli, larger particles are mostly deposited in the pharynx

and upper airway, and smaller particles tend to be exhaled.^{108,109} Each nebulizer device has a different flow-particle size relationship, but most devices require 10 to 12 L/min in order to deliver particles in the 1- to 3- μ m range.

IV β -agonists should be considered in patients unresponsive to treatment with continuous nebulization. Decreased tidal volume and/or near complete airway obstruction in severe status asthmaticus may prevent aerosolized bronchodilator delivery to the areas most affected. Terbutaline is the current IV β -agonist of choice in the United States. In countries where albuterol (salbutamol) is available in the IV form, this compound is preferred for its increased β_2 -receptor affinity over terbutaline.¹¹⁰ Recommended dosages for IV terbutaline are 0.1 to 10 μ g/kg/min,¹¹¹ and 0.5 to 5 μ g/kg/min for albuterol (salbutamol).^{101,112}

Most adverse effects of β -agonists in asthma are of cardiovascular nature. Tachycardia, increased QTc interval, dysrhythmia, hypertension, as well as hypotension have been reported^{23,111,113} for unselective and selective β_2 -agonists, both with IV and inhalational administration. Other than tachycardia or diastolic hypotension,¹¹¹ neither albuterol nor terbutaline is known to cause clinically significant cardiac toxicity when used for pediatric status asthmaticus. A recent prospective cohort study¹¹⁴ of children receiving IV terbutaline for severe asthma found no clinically significant cardiac toxicity. However, myocardial ischemia is a documented complication with administration of IV isoproterenol to asthmatic children.¹¹⁵ Other adverse effects of β -agonists include hypokalemia,^{116–119} tremor,¹²⁰ and worsening of ventilation/perfusion mismatch.¹²¹ Cardiovascular adverse effects and tremor show tachyphylaxis, whereas bronchodilator response usually does not.¹²² Long-acting β -agonists, such as salmeterol, are contraindicated in status asthmaticus, and have been associated with fatalities in this setting.¹²³

Anticholinergics

Cholinergic bronchomotor tone mediated by the parasympathetic nervous system is a major determinant of airway caliber.⁴³ Anticholinergics, such as ipratropium, lead to bronchodilatation and have long been thought to be most effective in COPD. However, significant improvements in pulmonary function in response to anticholinergics have been demonstrated^{124–127} in asthmatic adults and children. Anticholinergics are now an integral part of the treatment of acute asthma in children. Anticholinergic agents are usually administered via the inhaled route. The most commonly used compound is ipratropium, a quaternary derivative of atropine.

In a randomized, controlled trial of 199 asthmatic adults, Rebusck et al¹²⁶ showed significant patient improvement when ipratropium was added to the inhaled β -agonist. The addition of three doses of ipratropium (250 μ g) to an emergency department treatment protocol for acute pediatric asthma was associated with reductions in duration and amount of treatment before discharge.¹²⁵ Schuh et al¹²⁴ studied 128 children with severe asthma, and found significant improvement in pulmonary function when nebulized ipratropium was added to albuterol. The most severely ill children benefited most. Davis and colleagues¹²⁷ determined dose-response relationships for ipratropium in asthmatic children between 9 years and 17 years of age. Ipratropium treatment produced dose-dependent bronchodilatation that becomes significant at doses $> 75 \mu$ g, and no further increase in bronchodilatation was seen beyond 250 μ g. Thus, the recommended dose is 250 to 500 μ g¹²⁷ at a dosing interval of 6 h.⁴³ Ipratropium is not absorbed into the bloodstream. Thus, its cardiovascular side effects are minimal.⁴³

Steroids

As asthma is mainly an inflammatory disease, corticosteroids are a mandatory first-line treatment for status asthmaticus.¹²⁸ Glucocorticoids have been shown to control airway inflammation: they reduce the number and activation of lymphocytes, eosinophils, mast cells, and macrophages; inhibit vascular leakage induced by proinflammatory mediators; restore disrupted epithelium; normalize ciliated cell to goblet cell ratio; decrease mucus secretion; and downregulate production and release of proinflammatory cytokines.^{129–131} The beneficial effect of corticosteroid treatment on airway mechanics in status asthmaticus has been demonstrated,¹³² usually becoming evident between 6 h and 12 h after administration of the first dose. Oral, or preferably parenteral, corticosteroid administration is accepted standard of care for children with status asthmaticus.¹²⁸ There does not appear to be a role for aerosolized steroids in acute, severe asthma in children.⁹⁸ Commonly used IV steroid agents include hydrocortisone and methylprednisolone. Suggested, effective plasma steroid concentrations are in the range of 100 to 150 mg of cortisol per 100 mL.¹³³ This is achieved with IV hydrocortisone, 2 to 4 mg/kg every 4 to 6 h, or methylprednisolone, 0.5 to 1.0 mg/kg every 4 to 6 h. Duration of steroid therapy will depend on severity of the attack and on chronicity of underlying inflammation. If treatment is required for longer than 5 to 10 days, slow dosage taper is recommended.¹²⁸

Although short-term use of high-dose steroids is usually not associated with significant side effects,¹³⁰ hyperglycemia, hypertension, and acute psychosis have been reported.^{130,134} The immunosuppressive effects of corticosteroid treatment may increase the risk for unusual or unusually severe infectious complications. Legionella as well as *Pneumocystis carinii* pulmonary infections have been described¹³⁵ in steroid-dependent asthmatic subjects. Disseminated varicella is a rare, but usually fatal complication of steroid therapy.¹³⁶ Even a single course of steroids can increase the risk for fatal varicella.¹³⁷ Children receiving long-term steroid treatment should have their varicella immune status assessed. If not immune, they would be candidates for varicella zoster immune globulin on exposure.¹³⁶ Children with acute asthma and recent exposure to chickenpox should not receive steroids, unless they are considered to be immune. Clinicians should also be aware that allergic reactions, ranging from rash to anaphylaxis and death, have been described with the use of methylprednisolone,^{138–141} hydrocortisone,¹³⁸ and oral prednisone¹⁴² in asthmatic patients.

Theophylline

Theophylline and its water-soluble salt aminophylline (theophylline ethylenediamine) are methylxanthines. The mechanism of effect of theophylline in asthma remains unclear. In addition to its action as phosphodiesterase inhibitor, the drug has been postulated to stimulate endogenous catecholamine release,¹⁴³ to act as a β -adrenergic agonist¹⁴⁴ and as a diuretic,¹⁴⁵ to augment diaphragmatic contractility,¹⁴⁶ to increase binding of cAMP,¹⁴⁷ and to act as prostaglandin antagonist.¹⁴⁸

The role of theophylline in the treatment of children with severe asthma remains controversial. A frequently cited report published in 1973 suggested a linear relationship between theophylline levels and expiratory flow¹⁴⁹ but included only six patients. Improvement was significant only when the data were plotted semilogarithmically. Goodman et al¹⁵⁰ undertook a meta-analysis of randomized, controlled pediatric trials of theophylline and found no benefit. However, this analysis included children with only mild or moderately severe asthma, and not those admitted to intensive care. Yung and South²⁷ performed a careful, randomized, double-blinded, placebo-controlled trial of aminophylline in 163 children with severe status asthmaticus whose conditions had failed to improve with frequent nebulized albuterol, ipratropium, and IV steroid treatment. Patients in the aminophylline group had a greater improvement in oxygen saturation and pulmonary function testing. Five patients in the placebo group but none

in the aminophylline group required intubation. The authors²⁷ found no difference in lengths of ICU stay. Subjects treated with aminophylline had significantly more nausea and vomiting. The authors²⁷ conclude that aminophylline should maintain its place as emergency treatment for severe, acute asthma in critically ill children, after standard treatment has been unsuccessful.

Dosage needs to be adapted to age groups and individual patients based on serum levels (goal, 10 to 20 $\mu\text{g}/\text{mL}$). A reasonable starting point is a 6-mg/kg aminophylline load followed by a 1-mg/kg/h infusion.⁸⁸ Neonates and infants have decreased aminophylline clearance and require lower infusion rates (0.1 to 0.8 mg/kg/h).

The therapeutic range of theophylline (10 to 20 $\mu\text{g}/\text{mL}$) is narrow, and overlaps with its toxicity range ($> 15 \mu\text{g}/\text{mL}$). 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 theophylline serum concentrations $> 35 \mu\text{g}/\text{mL}$. Because of the ongoing controversy about the benefits of theophylline, its narrow therapeutic range, and high risk of serious adverse effects, this drug is not recommended as routine treatment for children with acute asthma exacerbations.

Magnesium

Magnesium for the treatment of asthma was first described in 1940.¹⁵¹ The suggested mechanism of action is smooth-muscle relaxation secondary to inhibition of calcium uptake.¹⁵² Thus, it could be classified as a pure bronchodilator and theoretically would work best in situations when airway edema is not the most prominent feature of status asthmaticus.¹⁵³

Evidence in adult asthmatic subjects suggests that magnesium, 2 to 3 g IV, will significantly improve expiratory air flow, and will increase the magnesium serum level to 2 to 4 mg/dL.^{154–156} High-dose magnesium therapy (10 to 20 g over 1 h) has been reported as effective and safe in five adult asthmatic patients receiving mechanical ventilation.¹⁵³

Apart from uncontrolled case reports,^{157,158} to my knowledge, only one randomized trial of magnesium sulfate in pediatric asthma has been reported.¹⁵⁹ These authors¹⁵⁹ found a significant improvement in pulmonary function in 15 asthmatic children receiving magnesium sulfate, 25 mg/kg, when compared to the placebo-treated group. Current dosage recommendation for magnesium in asthmatic children is 25 to 75 mg/kg IV over 20 min.^{159,160}

Adverse effects include flushing and nausea, usually during the infusion. Toxicity occurs at higher

serum levels ($> 12 \text{ mg}/\text{dL}$) in the form of weakness, areflexia, respiratory depression, and cardiac arrhythmias. To my knowledge, magnesium toxicity has not been observed in published pediatric reports.

Helium-Oxygen

Lowering the density of a gas reduces resistance during turbulent flow, and also will render turbulent flow less likely to occur.¹⁶¹ A helium-oxygen mixture, heliox, with a helium fraction of 60 to 80%, has a lower density than nitrogen-oxygen, and has been well established in alleviating respiratory distress from upper-airway obstruction in children and adults.^{162–165} Heliox may also have a role in patients with more distal, small-airway obstruction. Heliox was shown to improve aerosol delivery to intubated¹⁶⁶ and nonintubated¹⁶⁷ asthmatic subjects. Wolfson et al¹⁶⁸ observed decreased work of breathing when they administered heliox to infants with severe bronchopulmonary dysplasia. Anecdotal cases of improved respiratory mechanics with heliox in asthmatic children have been reported, both in spontaneously breathing children^{169,170} and in children receiving mechanical ventilation.^{170,171} However, a prospective, randomized, double-blind, crossover study¹⁷² of heliox in 11 nonintubated children with severe asthma failed to show an effect on respiratory mechanics or dyspnea scores.

In order to significantly lower the density of the inhaled gas mixture, helium needs to comprise 60 to 80% of the gas mixture. Heliox can therefore not be used in patients with a high oxygen requirement. Adverse side effects of heliox therapy have not been reported to this point (to my knowledge) but it has been postulated that the gas could worsen dynamic hyperinflation (DHI) by increasing gas flow to severely obstructed alveoli.¹⁷³ Heliox remains an unproven therapy for pediatric asthma.

Intubation and Mechanical Ventilation

Indications: The decision to intubate an asthmatic child must not be taken lightly, and intubation should be avoided if at all possible. Tracheal intubation may aggravate bronchospasm,¹⁷⁴ and positive-pressure ventilation will greatly increase the risk of barotrauma and circulatory depression (see below).^{175,176} The traditional rule that respiratory acidosis dictates intubation has become outdated.^{11,88,177} With the advent of more aggressive use of inhaled β -agonist therapy, $< 1\%$ of asthmatic children admitted to a children's hospital^{178,179} and 5 to 10% of asthmatic patients admitted to pediatric intensive care^{27,102,180} require intubation.

Absolute indications for intubation include cardiac and respiratory arrest, severe hypoxia, as well as rapid deterioration in the child's mental state.⁸⁹ Progressive exhaustion despite maximal treatment constitutes a relative indication for mechanical ventilation. Otherwise, even the child with severe asthma should receive an aggressive trial of high-dose, nebulized β -receptor agonists and anticholinergics as well as IV corticosteroids. The decision to intubate should not depend on arterial blood gas determination.⁸⁸ Some hypercapnic asthmatic patients can be managed successfully without ventilation,¹¹ whereas an exhausted asthmatic patient may require intubation regardless of the presence or absence of hypercarbia.⁸⁸

Intubation: Prior to intubation, the child must be preoxygenated with 100% oxygen, the oropharynx cleared of all secretions, and the stomach decompressed via a nasogastric tube.⁹⁸ The patient should be premedicated with a sedative or anesthetic, followed by atropine and a rapid-acting muscle relaxant. Ketamine, 2 mg/kg IV, because of its bronchodilatory action, is a preferred induction agent in patients with severe asthma. Neuromuscular blockade may avoid the large swings in airway pressure seen in nonparalyzed asthmatic patients after intubation.¹⁷⁸ A cuffed or sufficiently large endotracheal tube is recommended to minimize air leak with the anticipated high inspiratory pressures.^{98,178} After preoxygenation, rapid-sequence intubation (preoxygenation of the spontaneously breathing patient, administration of premedication and muscle relaxant while applying cricoid pressure, followed by intubation, all while trying to avoid manual ventilation) is performed via the orotracheal route by the most experienced clinician available. This technique may lessen the risk of aspiration of gastric contents. Subsequent conversion to nasotracheal intubation for patient comfort may be considered, provided a tube of equal and sufficient size can be used.

More than 50% of complications in asthmatic patients receiving ventilation occur during or immediately after intubation.¹⁸¹ Except for tube malposition, complications are largely due to gas trapping (see below).¹⁷⁶ Hypotension, oxygen desaturation, pneumothorax/subcutaneous emphysema, and cardiac arrest are the most frequently observed complications.^{176,181} In case of acute deterioration during or after intubation, the most likely causes are tube malposition, equipment malfunction, and/or complications of gas trapping. Endotracheal tube position and equipment function must be reconfirmed rapidly. A colorimetric carbon dioxide indicator or capnography will confirm endotracheal intubation, as long as the patient is not in cardiac arrest. Obstruc-

tion of the endotracheal tube with thick secretions will occasionally require early reintubation. 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. 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. Hypotension should improve with volume administration and slowing of the respiratory rate. The contribution of hyperinflation to hypotension can be assessed by observing BP response to abrupt reduction of respiratory rate or a period of apnea. In some patients with severe asthma, manual pressure on the rib cage during expiration may be required to avoid massive hyperinflation. If hypotension and/or hypoxemia do not rapidly respond to fluid administration and alteration in ventilatory pattern, a tension pneumothorax must be considered.

Dynamic Hyperinflation: The institution of positive-pressure ventilation in the asthmatic child dramatically alters cardiocirculatory and respiratory dynamics. Pleural pressures change from predominantly negative⁷⁶ to positive, leading to diminished venous return and hypotension. Hypotension will often respond to volume loading and slowing of the ventilatory rate.

The severe airflow obstruction in asthma results in incomplete exhalation already prior to intubation. Progressive DHI develops, and end-expiratory lung volume reaches a new equilibrium above the functional residual capacity.¹⁷⁶ The increased lung volume increases pulmonary elastic recoil pressure (thus increasing expiratory flow) and expands small airways (thus decreasing expiratory resistance). Therefore, lung volume will rise until a point is reached where the entire inspired tidal volume can be expired during the available exhalation time.¹⁷⁶ This process, however, becomes maladaptive in severe asthma, such that hyperinflation required to maintain normocapnia cannot be achieved, as it would exceed total lung capacity.¹⁸² During spontaneous ventilation, the asthmatic patient's inspiratory muscles become unable to achieve such end-inspiratory volume, and the patient becomes hypercapnic. Positive-pressure ventilation, especially if aimed at restoring normocapnia, can increase DHI well beyond total lung capacity. As the degree of DHI directly correlates with risk of barotrauma and hypotension, mechanical ventilation may be responsible for most of the observed morbidity in severe asthma.¹⁷⁵

Once positive-pressure ventilation has been insti-

tuted, the degree of DHI correlates with tidal volume and expiratory time, in addition to the degree of airflow obstruction.¹⁷⁶ Conventional ventilation patterns aimed at achieving normocapnia typically lead to massive hyperinflation with increased risk of barotrauma and hypotension.¹⁷⁶

Permissive Hypercapnia: Darioli and Perret¹⁸³ introduced the concept of controlled hypoventilation with lower-than-traditional respiratory rates and tidal volumes in adult asthmatic patients, and found a dramatically decreased frequency of barotrauma and death compared to historical control subjects. This concept meanwhile has been widely accepted and found to improve outcomes in adult asthmatic patients.^{184,185} Permissive hypercapnia has also been reported in children with asthma. Dworkin and Kattan¹⁷⁹ administered mechanical ventilation to 10 children with the goal of keeping peak inspiratory pressure < 60 cm H₂O and arterial pH > 7.10; PaCO₂ ranged from 40 to 90 mm Hg; they observed no air leak after intubation, and all of the children survived. Cox et al¹⁷⁸ reported on asthmatic children receiving mechanical ventilation with initial tidal volumes of 10 to 12 mL/kg at rates of 8 to 12 breaths/min, inspiratory time was set at 1 to 1.5 s (allowing for an expiratory time of around 5 s), and tidal volumes were adjusted to keep peak inspiratory pressures < 45 cm H₂O. Only two postintubation pneumothoraces were seen, and all children survived without sequelae despite significant hypercarbia during mechanical ventilation.¹⁷⁸

Initial Ventilator Settings: The most appropriate mode of ventilation may differ between individual patients and their stage of illness. Most clinicians prefer pressure-limited forms of ventilation as the initial mode. Because of their decelerating flow pattern, modes such as pressure control (PC), or pressure-regulated, volume control (PRVC) will result in lower peak inspiratory pressure, but higher mean airway pressure compared to the same tidal volume delivered in volume-control mode. I prefer to use PRVC with initial tidal volumes of 8 to 12 mL/kg, delivered at a rate well below that for a normal child of that age. Inspiratory time is chosen between 0.75 s and 1.5 s. Peak inspiratory pressures are likely to be very high in patients with severe asthma, largely due to a high inspiratory flow rate imposed on severe airflow obstruction. Therefore, peak pressures will not represent alveolar pressures, and thus are not as good an indicator of the risk of barotrauma as the inspiratory plateau pressure.¹⁷⁶ However, due to regional differences in airway obstruction, it is conceivable that some distal airways may still be directly exposed to high proximal pres-

ures and thus be at risk for barotrauma.¹⁸³ Therefore, an attempt should be made to adjust the ventilatory pattern to keep peak inspiratory pressure < 40 cm H₂O. Evidence¹⁸⁶ suggests an advantage of pressure-support ventilation (PSV) over assist-control modes (such as PRVC) in asthmatic children receiving mechanical ventilation. This technique is discussed under "Subsequent Ventilator Management."

The use of positive end-expiratory pressure (PEEP) in the asthmatic patient receiving mechanical ventilation remains controversial. Many authors^{178,187} recommend against using PEEP because of concern for causing more air trapping (*ie*, auto-PEEP and hypotension). However, low-level PEEP may positively affect the anatomic location of dynamic airway collapse in asthma,^{188,189} and may decrease trigger work in spontaneously breathing patients receiving ventilation.^{190,191} Externally applied PEEP in the asthmatic child receiving ventilation should be set to a level below auto-PEEP, as determined with the end-expiratory hold method,¹⁹² in order to decrease trigger work but to not impede expiratory airflow.¹⁹³

Sedation and Paralysis: The hypercapnic child receiving mechanical ventilation will require heavy sedation to avoid tachypnea and ventilator dyssynchrony. A continuous infusion of midazolam or lorazepam can be adjusted to achieve deep sedation. Morphine should be avoided because of its potential to release histamine. The dissociative anesthetic ketamine is frequently chosen in asthmatic patients receiving mechanical ventilation because of its bronchodilator activity (see below).

Neuromuscular blockade should be reserved for those patients in whom adequate ventilation cannot be achieved at acceptable inspiratory pressures. Avoidance of neuromuscular blockade may possibly decrease the incidence of neurologic complications seen in asthmatic patients receiving mechanical ventilation. Prolonged severe muscular weakness has been reported in adults and children receiving mechanical ventilation, steroids, and neuromuscular blockade for severe asthma.^{194–196} This acute myopathy frequently has a component of rhabdomyolysis with marked increase in serum creatine kinase levels,¹⁹⁷ but creatine kinase levels may remain normal despite severe weakness.¹⁹⁸ Muscle biopsy specimens usually show myonecrosis. Recovery is complete but may be prolonged. Although neuromuscular blocking agents have been strongly implicated, the exact etiology for this disorder remains unclear. Meanwhile, limiting the duration and depth of neuromuscular blockade in asthmatic patients seems advisable.¹⁹⁴

Subsequent Ventilator Management: Deliberate hypoventilation as described above will lead to hypercarbia. Even extreme hypercarbia is usually well tolerated in children in the absence of increased intracranial pressure,¹⁹⁹ and we usually accept a pH of > 7.10, as long as oxygenation is adequate (transcutaneous oxygen saturation > 90% in fraction of inspired oxygen < 0.6). The adequacy of expiratory time can be assessed by listening for termination of wheezing before the onset of the next breath (although severe asthmatic patients may wheeze for ≥ 10 s), by observing a return to baseline on the flow-time wave,¹⁰² or by observing a plateau on the capnography waveform.¹⁰² Initially these goals will be difficult to achieve, but as airflow obstruction improves, flow-time and capnography tracings will begin to normalize, and decreasing peak and plateau inspiratory pressures will indicate improving respiratory dynamics.

A transition to spontaneous breathing requires switching the ventilator modes: PC and PRVC are assist-control modes, *ie*, any breath triggered by the patient above the set rate will be delivered at preset pressure or volume. In the agitated or dyspneic child, this can lead to worsening hyperinflation. Therefore, once sedation and paralysis are withdrawn to allow spontaneous respiration, the ventilator should be set to synchronized intermittent ventilation with pressure support (PS), or to PS only. PS allows patients to determine their own respiratory pattern (rate, inspiratory time, and tidal volume) and decreases patient-ventilator dyssynchrony,¹⁸⁶ and it decreases work of breathing by partially or fully unloading respiratory muscles.²⁰⁰

PS ventilation can also be used immediately after intubation, while the asthmatic child requires full or near-full respiratory support. Wetzel¹⁸⁶ reported a case series of four asthmatic children who experienced a rapid improvement in gas exchange, inspiratory pressures, and respiratory pattern when switched from PC ventilation to high-level PS (22 to 37 cm H₂O). He argued that PS will not only reduce inspiratory work, but will also allow the patient to actively assist exhalation and therefore decrease hyperinflation.¹⁸⁶ PS has also been successfully used in adult asthmatic patients.²⁰¹

Inhalational Anesthetics

Inhalational anesthetic agents have been used for > 5 decades in the treatment of refractory status asthmaticus.²⁰² The exact mechanism of the bronchodilatory effect of these agents in asthma remains unclear.¹⁷⁰ Halothane¹⁷⁴ and isoflurane^{170,203–206} have been successfully administered in children receiving mechanical ventilation with life-threatening

asthma unresponsive to conventional therapy. In the available reports, halothane concentrations ranged from 0.5 to 1.5%,²⁰⁷ and isoflurane concentrations between 0.5% and 2%.²⁰³ Further reports^{208,209} exist in the literature on asthma in adults, including the use of enflurane.

Proper and safe administration of inhalational anesthetics in the pediatric ICU requires either an anesthesia machine or a custom-fitted ventilator (such as the Siemens 900C; Siemens-Elema AB; Solna, Sweden²⁰³) with scavenging system and continuous analysis of inspiratory and expiratory vapor concentrations. An anesthesiologist must be involved in this aspect of patient management.

Significant adverse effects to inhalational anesthetics need to be anticipated. Halothane may have a negative inotropic effect by direct myocardial suppression, and may induce arrhythmias, especially in the presence of hypoxia, acidosis, and hypercarbia, and when used together with β -agonists or aminophylline. Isoflurane is not known to have negative inotropic effects, but can cause hypotension due to vasodilatation.¹⁷⁰ Isoflurane is not arrhythmogenic. Inhalational anesthetics may aggravate intrapulmonary shunting due to abolition of the hypoxic pulmonary vasoconstriction.¹⁷⁴ Prolonged use of some inhalational anesthetics may cause fluoride accumulation resulting in nephrotoxicity and nephrogenic diabetes insipidus. Less than 1% of isoflurane undergoes biotransformation resulting in inorganic fluoride, and even prolonged administration of isoflurane to children²⁰³ and adults²¹⁰ did not result in nephrotoxicity. However, renal function should be followed closely in any patient receiving inhalational anesthetics. As there appears to be no difference in bronchodilatory effect between halothane and isoflurane, isoflurane may be the safer agent for use in children with life-threatening asthma.

Ketamine

Ketamine is a dissociative anesthetic agent with strong analgesic action. It also mediates bronchodilatation by a mechanism not yet well understood. Ketamine acts in a sympathomimetic fashion by inhibiting neuronal norepinephrine reuptake,²¹¹ and also appears to be blocking airway N-methyl-D-aspartate receptors linked to the mediation of increased airway tone.²¹²

Because of its anesthetic and bronchodilatory properties, ketamine has been used in children with severe asthma receiving mechanical ventilation.^{213–215} An IV bolus of 2 mg/kg is usually followed by a continuous infusion of 0.5 to 2 mg/kg/h,²¹⁴ but higher doses have been used for asthmatic children.²¹⁵ Ketamine may be very useful as an induction agent for

intubation,²¹⁶ as it may diminish the bronchoconstrictor response to insertion of the endotracheal tube.

Unwanted effects of ketamine include increase of bronchial secretions (atropine or glycopyrrolate should be co-administered), as well as postanesthesia emergence reaction in older children. The latter can be ameliorated by concurrent benzodiazepine administration. Due to its indirect sympathomimetic effect, ketamine usually causes a hyperdynamic cardiovascular response, but may have a direct cardiodepressant effect in critically ill, "catecholamine-depleted" patients.²¹⁷ As ketamine increases cerebral blood flow through cerebral vasodilatation,²¹⁸ this drug should be used with caution in patients who have other risk factors for intracranial hypertension, such as having suffered hypoxic-ischemic arrest or having severe hypercarbia.

Extracorporeal Life Support

Extracorporeal life support (ECLS) has occasionally been reported^{219–222} as last resort in refractory status asthmaticus. ECLS remains an experimental, expensive, and invasive therapy in asthma. As ventilation strategies aimed at avoiding hyperinflation and barotrauma are becoming more accepted, the use of ECLS will rarely be indicated.²²³

Bronchoscopy and Bronchial Lavage

Airflow limitation in asthma is caused by a combination of bronchospasm, inflammation, and mucous plugging. Conventional therapy targets bronchospasm and inflammation. Development of marked mucous plugging may be a contributing factor to a small number of patients whose conditions are deteriorating despite maximal therapy.²²⁴ Asthmatic children with massive bronchial casts or "plastic bronchitis" have been described.^{40,225,226} Combined bronchoscopy and bronchial lavage in patients receiving mechanical ventilation has been used in desperately ill asthmatic adults^{224,227–229} and children.²³⁰ Bronchial lavage with bicarbonate solution²²⁵ and recombinant human deoxyribonuclease²³¹ have been performed successfully in moribund asthmatic children despite maximal therapy. Severe mucous plugging should be considered in the asthmatic patient receiving mechanical ventilation whose condition is deteriorating despite maximal anti-inflammatory and bronchodilatory therapy.

SUMMARY

Severe asthma in children is increasing in prevalence and mortality. Even in the very-sick-appearing asthmatic child, an aggressive treatment trial of

β -agonists, anticholinergics, and corticosteroids is warranted. Intubation and mechanical ventilation carry a significant risk of worsening bronchospasm and hyperinflation, barotrauma, and cardiovascular depression. It should be delayed as long as possible, but mechanical ventilation is indicated for respiratory failure or a rapid decrease in level of consciousness. Recent advances in mechanical ventilation include deliberate hypoventilation with low tidal volume, high inspiratory flow, and long expiratory time, and possibly the early institution of PSV. Other, more unusual therapeutic modalities include magnesium, ketamine, inhaled anesthetic agents, and heliox.

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