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The Management of Status Asthmaticus in Infants and Children

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Acute asthma in childhood is a common problem. It is estimated that approximately 2%–9% of the pediatric population suffers from asthma as an underlying illness.[1-3] A variable proportion of these children are treated for acute exacerbations of their illness in medical settings daily. There are many different, acceptable methods for the treatment of acute asthma in children.[4-7] The purpose of this review of childhood status asthmaticus is to summarize current knowledge about the pathophysiology, to present a rational treatment framework, and to provide the clinician with detailed recommendations for an approach to the effective treatment of this disorder.

For the purpose of this review, we shall define "status asthmaticus" as acute severe wheezing that is not significantly reversed by the administration of a series of subcutaneous injections of epinephrine or terbutaline, inhaled beta-adrenergic agents, or a combination of these treatments. The authors admit that this is a relatively broad definition, but feel that it limits "status asthmaticus" to those patients who have received emergency treatment of their asthma without experiencing adequate resolution.

Major advances have been made in the treatment of acute and chronic asthma of childhood over the last two decades. The mortality of childhood asthma in the United States remains low, with an estimate of 0.8 per 100,000 population[8]; yet one of the more disconcerting aspects of acute asthma is the potential for rapid deterioration, leading to acute respiratory failure before the patient can receive effective medical care. This rapid course is more frequently seen in young children.[9-12] Therefore, status asthmaticus must be recognized as a potentially life-threatening illness and must be treated vigorously. Such treatment should take place in a hospital seting, where close monitoring of clinical status and advanced therapeutic management by skilled, experienced pediatric support personnel are available.

Pathophysiology

There have been numerous reviews of the pathophysiology of asthma. Several have focused on cellular events leading to bronchospasm[13-17]; others have

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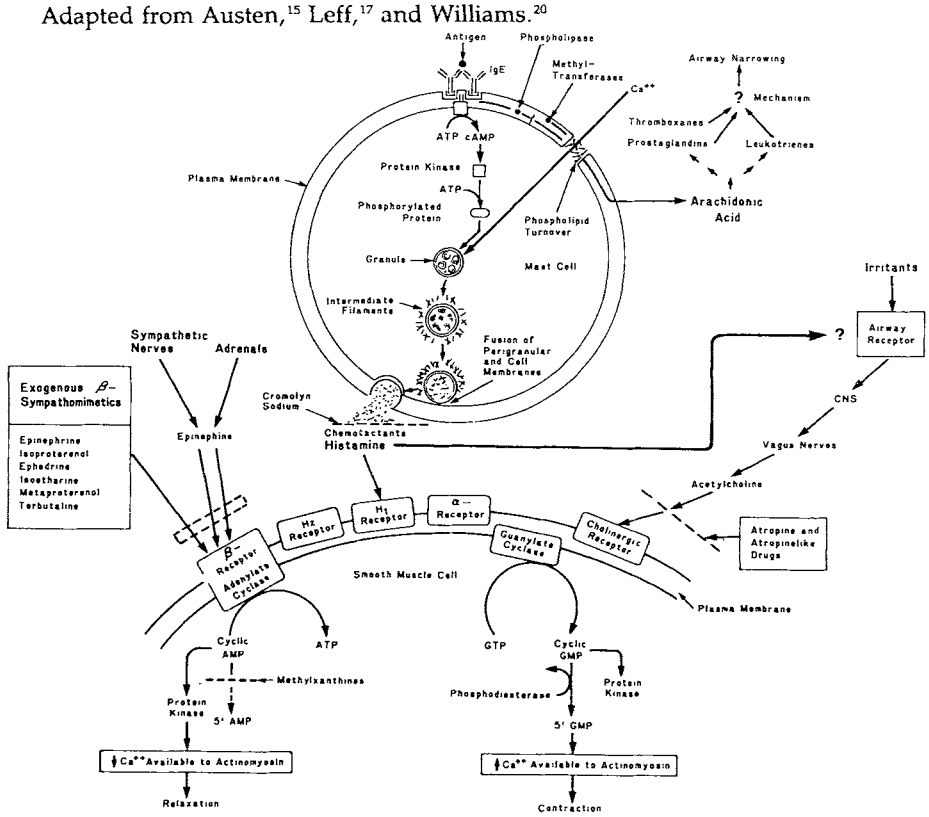
discussed the physiologic results of cellular changes.[3,4,18,19–21] The basic underlying "event" in asthma is airway narrowing or obstruction. This results from a combination of the contraction of airway smooth muscle, airway mucosal edema with cellular infiltration, and inspissation of airway secretions and cellular debris. In children with acute asthma, these occur as a result of the underlying cellular mechanisms of the illness. Although bronchial smooth muscle contraction is best understood and will serve as the basis for discussion, the reader is reminded that the other forms of airway obstruction also play major roles in the pathophysiology of acute asthma.

Cellular mechanisms are shown in Figure 1. The basic mechanism most commonly invoked is the release of specific mediators from tissue mast cells.[14–18] This can be secondary to nonspecific factors or to the binding of allergen-specific IgE to tissue mast cells. Reexposure of the "primed" mast cell to the appropriate allergen leads to a perturbation in the mast cell membrane and, ultimately, exocytosis of cytoplasmic granules containing preformed mediators, such as histamine, and a variety of chemotactic factors. The perturbation in the mast cell membrane also leads to a release of arachidonic acid, an influx of calcium, and a change in intracellular cyclic adenosine monophosphate (AMP) levels. Arachidonic acid may be oxidatively metabolized to prostaglandins and thromboxanes via the cyclooxygenase pathway, or to leuko-

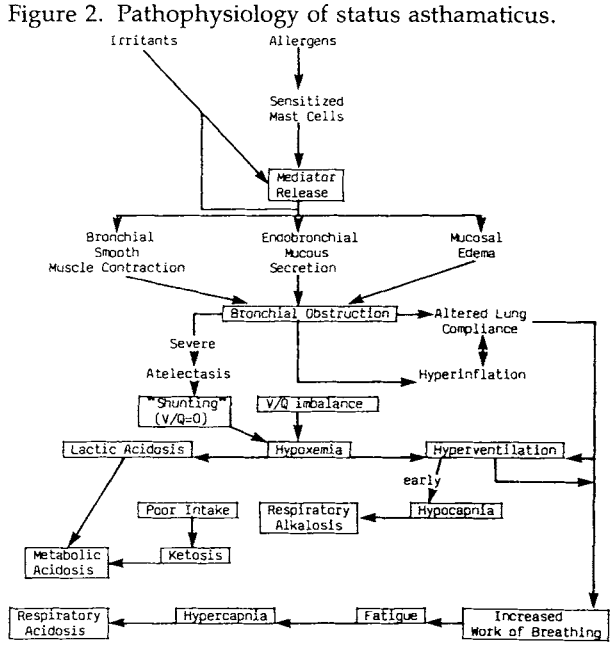
Figure 1. Cellular mechanisms involved in mast cell-mediator release and bronchial smooth muscle contraction.
Adapted from Austen,[15] Leff,[17] and Williams.[20]



trienes via the lipoxygenase pathway. Leukotrienes C4, D4, and E4 have been implicated as the "slow-reacting substance of anaphylaxis" (SRS-A). The bronchial smooth muscle cell carries receptors for mediators such as histamine as well as cholinergic, alpha, and beta-2 agonists. These various receptors regulate the intracellular milieu, with a resultant contraction or relaxation of smooth muscle actomyosin. This state of contraction of actomyosin is felt to be related to intracellular cyclic nucleotides and the availability of calcium. Histamine receptors in bronchial smooth muscle cells have recently been implicated in smooth muscle contraction.[22,23] β_2-receptors are involved in bronchial smooth muscle relaxation. Limited studies suggest a defect in or deficiency of β-receptors in asthmatic subjects[24] and experimental animals.[25] Alpha-receptors may play a role in bronchoconstriction, and an increase in α-receptors in asthmatic subjects has been reported.[26,27] Recent experimental evidence suggests that these receptors are of the α-2 subtype and that their activation involves a postreceptor mechanism rather than a direct mediation of membrane depolarization.[28] Irritant receptors in the lung and the parasympathetic nervous system also play a major role in bronchial hyperreactivity.[13,29,30] The localization of prostaglandin receptors is not clear, although recent data suggest that leukotrienes may exert their bronchoconstrictive effects either at a site anatomically removed from the site of histamine action *or* by altering the sensitivity of other receptors to other mediators.[31,32]

Several changes in lung function occur during status asthmaticus (Fig. 2). In addition to airway obstruction, there is reduced lung compliance,[33] hyperinflation changes in lung volumes,[33–35] and impaired respiratory muscle function.[35,36] Because of nonuniform obstructive changes throughout the lung, ventilation/perfusion inequality ($\dot{V}/Q$ mismatching) occurs.[37] This results in a widened alveolar-arterial gradient and, in the majority of patients with acute asthma, some degree of hypoxemia. Initially, the child's rapid respiratory rate

Figure 2. Pathophysiology of status asthamaticus.



will maintain a normal or supernormal alveolar ventilation, leading to a respiratory alkalosis.[37–40] As airway narrowing worsens and respiratory muscles fatigue, alveolar ventilation may decrease, with ensuing respiratory acidosis. The severely ill asthmatic child will often have poor oral intake and increased insensible water loss, with the development of ketosis.[38] Hypoxemia and an increased lactate production by anaerobic metabolism in overworked respiratory muscles may lead to lactic acidosis.[35,41,42] This in turn decreases the effectiveness of cardiac contractility and respiratory muscle function, which can lead to cardiac arrhythmias, hypoperfusion, hypoxemia, acidosis, and death.

Initial Assessment of the Acutely Ill Asthmatic Child

History

When confronted by an acutely ill, wheezing infant or child and his or her anxious parents, the clinician would do well to take a *directed* history. The history should concentrate on the circumstances of the acute attack being treated, recent medications (dosages and times of administration), and brief histories of past attacks and hospitalizations.

Acute asthma is a medical emergency and carries with it the risk of respiratory failure. Because of this, the history taking should occupy a matter of a few minutes, during which time the physical exam is carried out and therapy initiated.

Physical Examination

The physical examination of the acutely ill child with asthma must be rapid, with attention directed to certain specific areas. Vital signs must include the patient's weight, temperature, respiratory rate, cardiac rate and rhythm, and blood pressure. The pulsus paradoxus has shown some predictive value in terms of asthma severity and therapeutic success.[43–45] It should be obtained in patients who are old enough to cooperate. The pulsus paradoxus is an accentuation of the normal variation in cardiac output during the respiratory cycle[46] and is increased in several pathologic states, including asthma.[43] The physical examination of the asthmatic child may include the rapid assessment of the ears (to rule out otitis media), nose and sinuses (to assess for sinusitis and flaring of the alae nasi), and throat. The neck should be palpated for the presence of subcutaneous emphysema, an indicator of pneumomediastinum, which is a complication of asthma.

The key to the rapid assessment of the acutely wheezing child is the careful examination of the chest. The chest configuration should be noted, paying attention to the degree of hyperinflation, pectus deformity, and symmetry of expansion. The use of accessory muscles of respiration must be noted, as their use correlates with severity of airway obstruction.[47] The chest can be quickly percussed as a further guide to hyperinflation; areas of dullness may indicate consolidation or atelectasis. Finally, the lungs should be auscultated,

preferably with a differential stethoscope, which permits evaluation of differential aeration, wheezing, or timing of air entry. An appreciation of the degree of wheezing, the amount of expiratory prolongation (the inspiratory:expiratory ratio), the presence of adventitious sounds, as well as an overall assessment of the adequacy of air exchange should be the goals of chest auscultation.

The cardiac evaluation should include palpation of the chest for right ventricular heave and auscultation to assess the pulmonic component of the second heart sound. Overt cor pulmonale in acute childhood asthma, however, is unusual.[48] The abdomen should be palpated for hepatomegaly as another sign of hyperinflation. Extremities should be assessed for nail bed cyanosis. The neurologic exam should focus on the mental status of the child: altered mental states, including confusion, restlessnes, irritability, and coma, may be signs of respiratory failure.

Laboratory Data

Several laboratory tests may prove helpful in the management of children with status asthmaticus, but therapy must not await their completion. For practical purposes, a portable, upright chest x-ray can document atelectasis, consolidation, pneumomediastinum, or pneumothorax. Atelectasis may require specific therapy, such as chest physiotherapy or, possibly, bronchoscopy if the patient's condition deteriorates. Consolidation may indicate the need for bacterial culture and initiation of antibiotic therapy. Pneumomediastinum or pneumothorax must be recognized if mechanical ventilation is imminent. To send an acutely wheezing child with possible impending respiratory failure to a radiology department is unwarranted. Bacterial cultures, except as noted above, are generally not helpful; most episodes of acute asthma associated with an infection are secondary to viral, rather than bacterial, etiologies.[49]

A complete blood count is not especially helpful, particularly if subcutaneous epinephrine has been recently administered. Serum electrolytes, blood urea nitrogen (BUN) determination, and urinalysis are necessary and will be discussed in the section on hydration. A blood theophylline level is mandatory in patients who have recently received this drug; this will be discussed further in the section on theophylline. An arterial blood gas may be very useful and will be discussed in the sections on oxygen, intravenous isoproterenol, and mechanical ventilation.

The combination of physical findings and laboratory data are useful in establishing clinical scoring of patients.[45,50,51] Various scoring systems have been advocated, and examples of two, one used by Downes and his coworkers and a second used by one of the authors (G.K.), are shown in Table 1. The importance of clinical scoring may be both *prognostic,* to delineate patients who require hospitalization or are at risk for development of respiratory failure, and *directive,* to establish patients who meet criteria for specific interventions, including intravenous isoproterenol or mechanical ventilation. Clinical scoring systems need further development and modification, as they have potential value for assessing treatment outcomes in a comparative fashion.

Table 1. Examples of Clinical Asthma Scoring Systems

Clinical asthma score used by Downes[50]					
Score	Cyanosis (or PaO_2 in torr)	Inspiratory breath sounds	Use of accessory muscles	Expiratory wheezing	Cerebral function
0	None (70–100)	Normal	None	None	Normal
1	In air (≤70 in air)	Unequal	Moderate	Moderate	Depressed or agitated
2	In 40% O_2 (≤70 in 40% O_2)	Decreased to absent	Maximal	Marked	Coma

Impending respiratory failure: score ≥5, $PaCO_2$ ≥55 torr.
Acute respiratory failure: score ≥7, $PaCO_2$ ≥65 torr.

Clinical asthma score used by Kurland[99a]					
Score	Respiratory rate	"Wheezing"	Inspiratory/ expiratory ratio	Accessory muscle use	Pulsys paradoxus[b] (mm Hg)
0	<30	None	5:2	None	<10
1	31–45	End-expiratory only	5:3–5:4	Trace	10–20
2	46–60	Expiratory	5:5	Intercostal	20–30
3	>60	Inspiratory and expiratory	<5:5	Intercostal and suprasternal	>30

[a]Modified from Pierson et al[51] and Fischl et al.[45]
[b]When easily obtainable.

General Medical Management

Nursing Care

It is difficult to overstate the importance of skilled pediatric nursing care in the management of children with status asthmaticus. The need for close monitoring of objective data, such as respiratory rate, heart rate and rhythm, and urine output, are mandatory in guiding therapeutic decisions. Less tangible, but useful, subjective impressions of clinical progression result from experience. Further, the ability to medical personnel to establish rapport with an acutely ill child will facilitate the acceptance of therapy, including the wearing of nasal prong or mask oxygen, the inhalation of beta-adrenergic agents, and the allowance of blood drawing. Although most children with status asthmaticus can effectively be treated on pediatric wards, the minority with very severe asthma who may be at risk for respiratory failure should be cared for in a pediatric intensive care unit.

Oxygen Therapy

Children with status asthmaticus invariably are hypoxemic to some degree, primarily due to alterations in ventilation/perfusion secondary to the uneven distribution of ventilation caused by variable airway obstruction.[37,38,52,53] In one study, the arterial oxygen (PaO_2) in children with acute asthma was

reduced to an average of 60 torr.[38] Evaluation of the oxyhemoglobin dissociation curve shows that below this level, small decreases of PaO_2 are associated with large decreases in saturated hemoglobin and oxygen content. In addition, hypoxemia may be further transiently aggravated by aerosolized bronchodilators in asthmatic patients because of changes in the distribution of pulmonary arterial flow to relatively poorly ventilated regions of the lung.[54] Lack of recognition or adequate treatment of hypoxemia is felt to be the major cause of significant sequellae of status asthmaticus, including sudden death, cardiac arrest, and hypoxic brain damage.

Accordingly, oxygen should be an initial treatment cornerstone in any child with status asthmaticus. Subsequent adjustments of inspired O_2 should be guided by clinical status and blood gas determinations. Clinic evaluation of gas exchange is often unreliable, and although measures of airflow obstruction may be useful as a screen,[55] inability to perform such tests in small children and lack of sufficient data limit techniques other than the direct measurement of arterial blood gases. The majority of patients will have normalized PaO_2 by an inspired oxygen concentration of about 30%–50%.

The theoretical possibilities of respiratory depression, creation of atelectasis, or other potential detrimental effects of oxygen in the treatment of acute childhood asthma are as yet undetermined. On the other hand, children with chronic asthma may be especially endangered by lack of prompt treatment with oxygen during acute severe episodes. There is evidence that the ventilatory response to hypoxia in the presence of hypercarbia is impaired in these children, although this is controversial.[56,57] In addition, because of the known cardiac toxicity of the methylxanthine derivatives and adrenergic agents commonly used in asthma, appropriate oxygen treatment may lessen the potential for myocardial dysrhythmias.[58,59]

Hydration

Because of tachypnea during severe asthma, the insensible loss of water is generally high. Vomiting is often a problem, as is inadequate oral intake. Hypovolemia has been reported in some adults with status asthmaticus.[60] In such instances, it is mandatory to reverse shock with the rapid infusion of volume expanders, such as 5% albumin, normal saline, or fresh-frozen plasma.

Until recently, the rapid administration of intravenous fluids to patients with status asthmaticus was accepted as a safe adjunct to therapy in all cases. It has generally been held that such therapy is useful in the mobilization of secretions, although this is not well documented. However, the rapid rehydration of some patients may lead to an increased likelihood for the development of pulmonary edema. A markedly negative intrapleural pressure, increased right ventricular afterload, and decreased interstitial pressure favor the accumulation of interstitial pulmonary fluid. As pointed out by Stalcup and Mellins,[61] all of these factors may be present during acute severe asthma.

It is recommended that all patients with acute severe asthma requiring hospitalization have their BUN concentration and urine specific gravity determined. If necessary, rehydration should be initiated; a rate of 1.25–1.50 times the usual maintenance rate is then commonly required. The infusion

should be slowed to a maintenance rate when the urine specific gravity and BUN are normal and the urine output is at least 1–2 ml/kg/hr. There is no single "best" intravenous fluid to rehydrate the patient in status asthmaticus. For routine use, the authors suggest 5% dextrose/0.2% NaCl with added KCL; the determination of serum electrolytes will guide fluid management.

An unusual complication of status asthmaticus,[62,63] as well as low-dose intravenous isoproterenol,[64] which may be required for therapy of unresponsive asthma, is the inappropriate secretion of antidiuretic hormone (SIADH). This should be considered in patients having hyponatremia and decreased urine output. Simultaneously derived serum and urine electrolytes and osmolality will be essential in establishing the diagnosis. The treatment for SIADH is fluid restriction, rather than the increased fluids outlined above.

Sodium Bicarbonate

Metabolic acidosis secondary to ketosis is common in severe status asthmaticus[38] (Fig. 2). The use of intravenous sodium bicarbonate in acute asthma has been an area of some controversy. Bronchial smooth muscle may show more responsiveness to bronchodilators, such as theophylline and beta-adrenergic agents, when the arterial pH is greater than 7.3.[65] Furthermore, treatment of metabolic acidosis may provide some "blunting" of the acidosis of respiratory failure.[4] This may allow time to initiate definitive treatment for respiratory failure and may decrease the likelihood of cardiac arrhythmias.[66] The administration of sodium bicarbonate has been recently advocated as a therapeutic maneuver in adult asthmatics requiring mechanical ventilation.[67] In this report, bicarbonate was used to maintain a relatively normal pH, while allowing an elevated $PaCO_2$ during ventilation, thereby decreasing the risk of barotrauma.

In all cases, the knowledge of arterial blood gases is mandatory for determining the necessity of bicarbonate therapy. The authors recommend that when the arterial pH is less than 7.2, sodium bicarbonate administration should be considered in the following dosage:

$$NaHCO_3 \text{ (meq)} = \text{(Base deficit)} \times \text{Body weight (kg)} \times 0.3$$

Pharmacologic Management of Status Asthmaticus

The current understanding of the basic cellular mechanisms of the allergic reaction has evolved in parallel with the improvements in pharmacologic management for patients suffering from allergic emergencies. The development of the "β_2-selective" adrenergic agents, the advances in the measurement of blood theophylline levels, the appreciation of the pharmacokinetics of theophylline, and the utilization of corticosteroids have all contributed to the improved management of acute asthma. Because several of the medications are additive or synergistic, the authors advocate their joint use. Table 2 outlines our initial medical management of these patients.

Table 2. Summary of Basic Management of Status Asthmaticus in Childhood

Directed history and physical examination
Laboratory Evaluation (as indicated)
Theophylline level (Fig. 3)
Arterial blood gas
Serum electrolytes with BUN
Complete blood count
Urinalysis with specific gravity
Chest x-ray
Pulmonary function tests of airflow (e.g., FEV_1, FVC, PEFR)
Bacterial cultures
Initial treatment:
Humidified oxygen, 30%–50%
Intravenous fluids based on state of hydration, serum chemistries, ability to take oral fluids
Intravenous theophylline (Fig. 3 and Table 3)
Intravenous corticosteroid options:
Methylprednisolone sodium succinate: 1–2 mg/kg initial bolus, then 1 mg/kg every 4–6 hr, or 2 mg/kg/24 hr continuously; *or*
Hydrocortisone sodium succinate: 5–7 mg/kg every 4–6 hr, or 2 mg/kg/hr for 12 hr then 1 mg/kg/hr, or 2 mg/kg initial bolus then 0.5 mg/kg/hr; *or*
Dexamethasone phosphate: 0.25/mg/kg every 8–12 hr, 0.25 mg/kg initial bolus then 0.3 mg/kg/24 hr continuously
Aerosolized beta-adrenergic agent suggested dosage options:
Metaproterenol 5% solution: 0.1–0.3cc (based on size of the child) diluted in 2–3 cc saline, up to every 30 min for 2 hr then every hour for 4 hr, then every 2–4 hr; *or*
Isoetharine 1% solution: 0.25–0.5 cc (based on size of the child), diluted in 2–3 cc saline, every 1–4 hr; *or*
Isoproterenol, 1 : 200 : 0.1–0.5 cc (based on size of the child) diluted in 2–3 cc saline, every 1–4 hr.

Adrenergic Agonists

For over half a century, epinephrine (adrenaline) has been a standard therapeutic agent for the treatment of acute asthma.[68,69] Only in the last 35 years has the pharmacology of adrenergic agents been elucidated, and only relatively recently have agents with more selective bronchodilator effects been available. The work of Ahlquist[70] and Lands and their associates[71] has led to an increased understanding of these agents and has permitted their division into α- and β-agonists. The former have stimulatory (contractile) effects on smooth muscle in the vascular and bronchial systems; the β-agonists have cardiac inotropic and chronotropic effects and relax smooth muscle, including smooth muscle in the tracheobronchial tree. The further subdivision of β-agonists into β_1 (affecting cardiac rate and contractility) and β_2 (causing bronchodilation) has spurred the development of the "β_2-specific" agents presently available.[71,72] To an increasing extent, these agents are replacing epinephrine as the primary drug of choice for the outpatient treatment of acute asthma.[74–76] Beta-adrenergic agents have been the subject of several recent reviews.[69,72,73,77] Most studies have demonstrated that the more selective agents cause effective

bronchodilation without many of the undesired side effects seen with epinephrine, which has both α- and β-adrenergic effects.

The mechanism of action of β_2-adrenergic agents is through the interaction with a cell membrane receptor linked to adenylate cyclase. Increased intracellular cyclic AMP levels, as a result of increased adenylate cyclase activity, leads to decreased mast cell degranulation and to bronchial smooth muscle relaxation.[15,17,72,77]

The inhalational use of β-adrenergic agents in the treatment of status asthmaticus remains the subject of some debate. Aerosolization of a β_2-adrenergic agonist solution has been shown to be effective in the treatment of acute asthma in children who are capable of cooperating with the technique.[74,78–80] The topic of aerosol generation has been the subject of extensive reviews[81]; the objective of administration is to generate droplets small enough (< 6 μm) to reach the airways rather than to impinge upon the mucosa of the nasopharynx.[82] The use of concomitant oral β_2-agents has been argued on the basis that the sites of action of oral and inhaled medications may be additive.[83]

The use of inhaled β_2-agents in young patients who are not cooperative is more debatable, especially when pressurized nebulizers are used.[84] The question as to whether inhaled β-adrenergic agents are effective bronchodilators in children less than 20 months of age has been studied with varying results using albuterol.[85,86] Response in this age group is difficult to document because of the lack of easily reproducible pulmonary function tests for small children and the lack of cooperation with aerosol administration by these patients. Therapeutic recommendations regarding inhaled β_2-adrenergic agents in young children vary. The authors join with others[85,87] in recommending that such agents be given a therapeutic trial in young children with asthma.

The dosage and choice of inhaled β_2-adrenergic agents are difficult to state as absolutes. As McFadden has pointed out,[72] while in vitro data may be useful for determining the potency of β_2-adrenergics, in vivo (clinical) data are less clear cut. Isoproterenol, the former mainstay of inhaled adrenergics, has both β_1 and β_2 effects and is an excellent bronchodilator. The more selective β_2-agents, such as isoetharine, metaproterenol, terbutaline, fenoterol, albuterol, and carbuterol, have fewer undersirable β_1 effects, but are not necessarily more potent bronchodilators on a molar basis when compared with isoproterenol.[73] An additional major benefit of the newer agents is their longer duration of action, with the possible exception of isoetharine.

The authors currently administer inhaled β_2-adrenergic agents to all children with status asthmaticus except those receiving intravenous isoproterenol. Like Garra and co-workers,[78] we have utilized metaproterenol, 0.2–0.3 ml of 5% solution in 2.5–3.0 ml of normal saline, by aerosol administration up to every 30 min for 2 hr, then hourly for 4 hr without deleterious side effects. Less frequent administration of metaproterenol, or isoetharine, eg, every 2–6 hr, may be adequate adrenergic therapy in many patients.

Methylxanthines

Methylxanthines have a long and controversial history in the treatment of acute asthma. Theophylline is the most important and useful form and has been the subject of several extensive reviews.[88–90]

Chemically, theophylline is 1,3-dimethylxanthine and is related to caffeine (1,3,7-trimethylxanthine). Several salts of theophylline have been formulated, ostensibly to improve gastrointestinal absorption or to increase the solubility for use in intravenous solutions. Both of these "reasons" for the manufacture of such salts are, in fact, not valid. Theophylline solutions are completely and rapidly absorbed from the gastrointestinal tract.[91] The intravenous use of solutions of theophylline rather than one of its salts is currently possible.

Theophylline relaxes smooth muscle in the bronchial tree. Until recently, it was assumed that theophylline renders this effect by inhibiting phosphodiesterase (PDE), thereby increasing intracellular cAMP levels. However, the concentration of theophylline inhibiting PDE in vitro is toxic in vivo.[82] Other proposed mechanisms for theophylline's effect on bronchomotor tone have included the antagonism of bronchoconstricting prostaglandins,[93] altered binding of cAMP to a cAMP-binding protein,[94] and changes in the intracellular calcium concentration.[95] Although theophylline does not inhibit IgE-mediated skin test reactivity,[96] it does decrease the airway response to inhaled allergens.[97]

The therapeutic index of theophylline is relatively narrow, and severe side effects include life-threatening cardiac arrhythmias and seizures.[89] The availability of rapid, sensitive, and specific assays for theophylline have permitted clinicians to utilize theophylline preparations more safely and effectively. The pharmacokinetics of theophylline are better understood, although individualization of therapy is important.[88–90,98–100]

Several systems of intravenous theophylline administration have been described for the treatment of status asthmaticus. Until recently, a "bolus" method, using periodic intravenous doses of aminophylline, has been the method of choice. However, this results in nonuniform serum theophylline levels, resulting in variable bronchodilation[98] and the possibility of acute toxicity associated with each administered dose.

The continuous intravenous infusion of theophylline for the treatment of acute severe asthma is a reasonable, safe procedure if serum theophylline levels are available.[88,89,101,102] Theophylline or aminophylline is administered as single "loading" dose (bolus) followed by a continuous infusion to maintain the serum theophylline level in the therapeutic range (10–20 μg/ml). Theophylline clearance is affected by various factors. Those especially important in childhood include the younger age group, macrolide antibiotics (eg, erythromycin), and acute febrile viral respiratory illness. All of these result in decreased clearance (ie, longer half-life).[89] Because of these factors and interpatient clearance variability, the close monitoring of serum theophylline levels is mandatory. Table 3 shows suggested guidelines for initial intravenous infusion rates based on patient age.

There are several suggested schedules for serum theophylline determinations when continuous intravenous infusions are used.[83,102,103] Several investigators have devised programs for computers or hand-held calculators to predict steady-state theophylline levels to guide therapy.[103–105] Our experience suggests that this can lead to the accurate prediction of steady-state serum levels during the infusion.[106]

Our current treatment protocol for intravenous theophylline is represented by Figure 3 and Table 3. For each patient, recent theophylline administration

Table 3. Theophylline: Suggested Initial Dosage[a] for Maintenance Intravenous Infusion[89]

Patient age	Theophylline[b] infusion rate (mg/kg[c]/hr)
Infants: 6–52 weeks	[Age (wk) × 0.008] + 0.21
1–9 years	0.8
9–12 years	0.7
12–16 years (nonsmoker)	0.7[d]
12–16 years (smoker)	0.5[d]

[a]See also Figure 3. The infusion dosage should be modified and/or levels followed more closely in the presence of factors affecting clearance. See text and reference 83.
[b]Theophylline (mg) = Aminophylline (mg) × 0.80.
[c]In obese patients, use lean body weight to calculate dosage.
[d]Not to exceed 900 mg/24 hr. Serum theophylline levels must be followed to evaluate need for increased dosage.

is determined. If no theophylline has been taken, the patient receives an intravenous theophylline loading dose (bolus) of 4–6 mg/kg lean body weight over 30 min. This assumes a volume of distribution of approximately 0.48 L/kg.[89,99,100,106] If oral theophylline has been taken, a "stat" theophylline level is drawn; the bolus to be determined may be decreased, based on the dosage history, medication compliance, and past theophylline levels.

The solution for infusion is 1.6 mg/cc theophylline in 5% dextrose (Travenol Laboratories). The use of pure theophylline is preferred, as anaphylactic reactions to the ethylenediamine salt (aminophylline) have been reported.[89] This solution is "piggy-backed" into the rehydrating intravenous solution. As soon as the loading dose has been administered, the theophylline infusion is slowed to deliver the selected rate. This technique allows for instantaneous adjustments of either the rehydrating solution or the theophylline infusion.

The prebolus level is used to further adjust the loading dose, as outlined in Figure 3. If the level is subtherapeutic and the clinician has decreased the loading dose significantly, a repeat bolus is given. If there is an increased risk of toxicity by the combination of this level and the loading dose, or if signs of toxicity are present, the infusion is interrupted. Theophylline levels are then followed until the infusion can be safely reinstituted.

A theophylline level is obtained after about 6 hr of continuous intravenous infusion, and a projected steady-state level is calculated.[103–106] If this level and the projected steady-state level are in the therapeutic range, another determination is obtained in 12–24 hr. If 6-hr and projected levels are not in the therapeutic range, the infusion is modified.

Our approach recognizes the need for clinical judgment. When suspicion is raised about the patient's theophylline level, another determination is warranted. Furthermore, this approach relies on the availability of two important services: a computer program[104] and rapid laboratory determination of theophylline levels.

Corticosteroids

Corticosteroids have been a mainstay in the treatment of asthma since 1950,[107] and their use in the treatment of asthma has been the subject of recent reviews.[108,109]

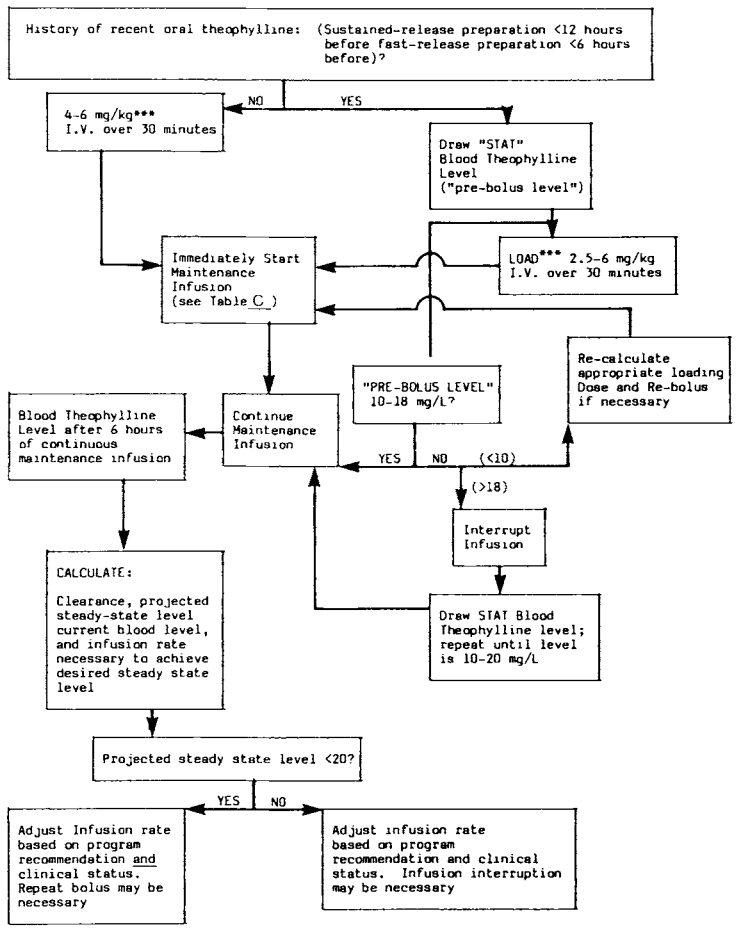


Figure 3. Theophylline: Decision making during treatment of status asthmaticus. All doses are given as theophylline: theophylline (mg) = aminophylline (mg) × 0.8. Decision making utilizes *projected* values from programmable calculator.[94] Clinical judgment of need for theophylline levels, based on patient's condition, should always take precedence. ***Use lean body weight for calculating loading dose. ****Adjustment of loading dose when there is a history of recent theophylline dose is based on the history of recent dosage(s) and preparation(s), compliance, and previous theophylline levels, if possible.

The mechanism(s) of action of corticosteroids in asthma is still not fully understood. The antiinflammatory effects of corticosteroids have been reviewed by Claman[110,111] and relate to their interference with leukocyte distribution and function. Antigen processing, inflammatory factor release, and the effects of such factors are modified by corticosteroids. A further important effect of corticosteroids is their apparent potentiation of the β-adrenergic receptor.[112]

Corticosteroid activity is mediated through specific proteins, which are generated by the action of intracellular steroid–receptor complexes. Potentially beneficial effects of corticosteroids are thus often not seen until hours after their administration.[113] Because of the risk of clinical deterioration in acute asthma, the prompt consideration of corticosteroid usage is therefore advised.

Although the clinical efficacy of corticosteroids in acute childhood asthma has been asserted, there have been few rigorous, well controlled, double-blind studies affirming this claim. The study by Pierson and co-workers[51] demonstrated that a loading dose followed by a continuous intravenous infusion of betamethasone, dexamethasone, or hydrocortisone, in addition to a regimen of intravenous aminophylline and inhaled β-adrenergic agents, resulted in an improvement of hypoxemia, when compared to the same regimen without steroids. However, their study did not demonstrate a statistically significant improvement in spirometric measurements or in a clinical asthma score in the steroid-treated group.

Similarly, Kattan et al[114] were unable to demonstrate a beneficial effect of intravenous hydrocortisone on spirometric measurements or clinical asthma score. Their study, however, did not examine its effect on PaO_2.

Shapiro and co-workers[115] have recently demonstrated that a short, rapidly tapering course of oral methylprednisolone accelerates resolution of moderately severe acute exacerbations of asthma. Their study examined expiratory flow rates in outpatients and documented significant improvement by 7 days of therapy. They also demonstrated no significant suppression of adrenal function by this mode of treatment.

Studies of the efficacy of corticosteroids in adults with status asthmaticus are also conflicting. Recently, Fanta et al[116] studied adults with status asthmaticus refractory to 8 hr of inhaled isoproterenol, injected terbutaline, and intravenous aminophylline. Hydrocortisone as an intravenous bolus (2 mg/kg) followed by a continuous infusion (0.5 mg/kg/hr) was added to the regimen of the treatment group, with normal saline given to the control group. Unlike the study of Pierson et al,[51] this study showed no difference in PaO_2 between treatment and control groups. On the other hand, respiratory mechanics significantly improved in the treatment group, but remained unchanged or deteriorated in the control group.

Luksza,[117] reporting a nonrandomized study of acute asthma in adults, recently questioned the need for corticosteroids. In response, Grant[118] pointed out several shortcomings of Luksza's study and his conclusion. Grant agreed that corticosteroids have never been proven by controlled clinical trial to actually save lives of individuals with status asthmaticus. However, he states that studies showing significant harm of short corticosteroid courses are also lacking. Grant therefore feels it is untenable to ". . . condemn a form of treatment which, in certain circumstances *may* be life-saving, but, even if it's not, can do no harm if administered for short periods."[118] Based on a review of the published reports indicating lack of significant deleterious side effects and the promise of beneficial clinical effects, the authors feel that the use of corticosteroid therapy in childhood status asthmaticus is warranted.

There is a wide range of steroid preparations, dosages, and dosing frequencies described in the literature. Collins and co-workers[119] suggested that hydrocortisone hemisuccinate be given in order to achieve plasma 11-hydroxycorticosteroid levels of 150 μg/dl, which is higher than the physiologic response to stress. Whether this level is adequate to diminish the inflammatory effects seen in acute severe asthma is not clear. Harfi et al[120] compared high-dose (300 mg/m²/6 hr) with low-dose (30 mg/m²/6 hr) intravenous meth-

ylprednisolone in children with status asthmaticus. They found no significant difference in outcome and concluded that there was no advantage of the high-dose regimen.

A universally accepted, potent, safe, and rapidly acting corticosteroid regimen for childhood status asthmaticus remains undetermined. The Section on Allergy and Immunology of the American Academy of Pediatrics recently recommended that children with status asthmaticus be treated with an intravenous loading dose of hydrocortisone hemisuccinate, dexamethasone phosphate, or betamethasone phosphate equivalent to 1–2 mg/kg of prednisone, followed by administration of the equivalent dosage during the following 24 hr either by continuous infusion or with divided doses every 4–6 hr.[121] There are no studies that specifically support this recommendation, although it is reasonable and does not lead to side effects. Currently, the authors use methylprednisolone intravenously in a dose of 1 mg/kg every 6 hr. This dosage has the advantage of being easy to remember and has few side effects when given over a short period (7–10 days).[122]

The clinician is frequently faced with an acutely ill asthmatic child who has required long-term corticosteroid therapy in the past. Because of the possibility of hypothalamic-pituitary-adrenal axis suppression in such patients,[122] it is imperative that the clinician provide adequate corticosteroids to prevent acute adrenal insufficiency.

Isoproterenol by Continuous Intravenous Infusion

In cases of impending respiratory failure secondary to childhood status asthmaticus, several authors have advocated the use of the continuous intravenous infusion of isoproterenol (CIIS) as an alternative to mechanical ventilation, which has considerable complications.[4,123–125] Advantages of intravenous isoproterenol include its potency, rapidity of onset, and fast metabolism (half-life of 2.5–5 min in children).[123,126]

Initially ascribed to Harwood and Talner,[123] the technique has been strongly supported and critically studied by Downes et al.[4,123] They have recommended its use in children with status asthmaticus and in those who develop impending respiratory failure despite therapy with intravenous aminophylline and corticosteroids. They define impending/acute respiratory failure as a clinical score $\geq$ 55 torr or $PaCO_2$ rapidly rising between 45 and 55 torr (Table 1). They have treated over 100 such patients, with success (defined as a sustained reduction of $PaCO_2$ and an improvement in the clinical score) in over 90% of the cases. Even in patients with preinfusion $PaCO_2$ of more than 65 torr ("acute respiratory failure"), the rate of treatment failure was only 14%.[4] Thus, Downes and others have shown that CIIS is an effective treatment of impending/acute respiratory failure in status asthmaticus in children.

Major complications of CIIS include cardiac arrhythmias, particularly ventricular tachycardia,[123,124] and bronchorrhea.[124] Generally, these complications respond to discontinuing or slowing the infusion. In addition, the possibility of beta-adrenergic blockade has been raised, because at least one of the metabolites of isoproterenol, 3-0-methylisoproterenol, is a weak beta-adrenergic blocker with a longer half-life than isoproterenol.[126] Therefore, CIIS should

be tapered slowly to prevent possible beta blockade and rebound bronchospasm.[126]

Another potentially life-threatening risk of CIIS is myocardial injury. In animal models, parenteral isoproterenol is capable of producing myocardial necrosis, especially in those having concomitant hypokalemia, steroid dependency, or obesity.[127] Reports of myocardial ischemia[128] and myocardial necrosis[129] in patients receiving CIIS for treatment of severe asthma should provide ample warning to clinicians utilizing this form of therapy.

A summary of the technique, as modified by the authors, is shown in Table 4. Inhaled beta-adrenergic agents are discontinued. Downes suggests that theophylline be discontinued because the potential cardiac toxicity with arrhythmias may be additive with the use of both drugs together.[4] The authors know of no study in humans to support this claim, although increased cardiotoxicity by the combination of massive doses of isoproterenol and aminophylline has been demonstrated in animals.[130–133] Nicklas and co-workers[134] pointed out that the clinical relevance of such animal studies is unclear. They emphasized the need for further investigation of possible synergistic cardiotoxicity of methylxanthines and beta-adrenergic agents (including isoproterenol) and for the careful cardiac monitoring of patients receiving both drugs.

Table 4. Intravenous Isoproterenol in Childhood Status Asthmaticus with Impending Respiratory Failure*

Preparation
Arterial catheter placement
Separate indwelling intravenous access for isoproterenol
Continuous EKG monitor
Discontinue aerosolized beta-agonists
Notify arterial blood gas laboratory of need for frequent determinations
Baseline laboratory: Arterial blood gas, EKG, theophylline level, cardiac enzymes
Isoproterenol infusion
Initial isoproterenol titration
Use standard ampule: 0.2 mg/ml
Isoproterenol dilution: Patient's weight (kg) × 0.15 = isoproterenol added to 100 ml of D5W. (e.g., for a 20-kg child, 20 × 0.15 = 3 mg added to 100 D5W)
Initial dose: 0.5 ,cg/kg/min = 2 ml/hr of above dilution
Measure arterial blood gases 15–20 min after initiation and after each dosage change
Increase isoproterenol by a factor of 2 every 15–20 min up to a level of 0.8 mcg/kg/min. Increments thereafter are by 0.2–0.4 mcg/kg/min.
Increase isoproterenol until one of the following:
$PaCO_2$ decreases to <55 torr *or* decreases by at least 10% of prefusion $PaCO_2$ (Further dosage increase may be required to achieve or maintain normocapnia)
Tachyardia >200/min: decrease infusion rate
Cardiac dysrhythmia: discontinue infusion
Maximum isoproterenol dosage is unknown. (Downes suggests a maximum of 6 mcg/kg/min[4])
Measure cardiac enzymes and theophylline level every 12–24 hr, EKG every 24 hr
After $PaCO_2$ improves, *continue* isoproterenol infusion at least 12–24 hr, then *taper* over 24–36 hr. Average duration of infusion required is 2 days

Herman et al[135] reported on 37 asthmatics over a 2-year period who were treated with intravenous isoproterenol and aminophylline corticosteroids. Cardiotoxicity was not encountered, although one patient had a nodal arrhythmia associated with Wolff-Parkinson-White defect. The authors noted a mean effective isoproterenol dosage of 0.2 (range 0.075–0.625) μg/kg/min; the response time after starting isoproterenol was 1.3 hr. The authors postulated that potential synergistic effects of theophylline and isoproterenol may be beneficial, permitting a lower, less toxic, dosage of isoproterenol.

Presently, we continue intravenous theophylline when CIIS is used. Blood theophylline levels are closely monitored, as intravenous isoproterenol may increase theophylline clearance.[136,137]

All patients receiving CIIS must have a secure intravenous access that is reserved for isoproterenol. An indwelling arterial line is required for continuous blood pressure monitoring and for frequent determination of arterial blood gases. Before starting CIIS, the authors recommend that all patients have a 12-lead EKG and blood drawn for cardiac enzyme activity (eg, CPK-MB) and theophylline level. Preferably, patients receiving CIIS should have PaO_2 of 80–100[129] and be continouously monitored for heart rate and cardiac arrhythmias.

Because precision in delivery of isoproterenol is essential in CIIS, an infusion pump is required. After an arterial blood gas is determined, isoproterenol is diluted in a solution of 5% dextrose and administered at an initial rate to provide 0.05 μg/kg/min. If neither clinical response nor adverse effects are seen in 15–20 min (see below), the rate of the infusion is doubled to give 0.1 μg/kg/min. The dose is progressively doubled every 15–20 min to 0.8 μg/kg/min if the infusion is tolerated and improvement is not seen. Above the dose of 0.8 μg/kg/min, the dose is increased by 0.2–0.4 μg/kg/min every 15–20 min until a clinical response is seen or toxicity supervenes. The maximum recommended dose is 6.0 μg/kg/min.[4] In Downes' series, the average dose required for initial improvement was 0.3 μg/kg/min.[4]

A clinical response is defined as a decrease in the $PaCO_2$ to less than 55 torr, or by 10% from its preinfusion level.[4] Blood gas determinations are made after 10–15 min of each dose of isoproterenol; the decision to change the dose is made based on changes in the $PaCO_2$, as described above.

Two other criteria are used to determine the highest allowable dose of isoproterenol in any individual patient. These are tachycardia, with a maximum of 180–200/min suggested, or the presence of a cardiac dysrhythmia, at which time the infusion must be promptly decreased or terminated. Usually, patients receiving CIIS have simultaneous improvement in respiratory status, with a decrease in $PaCO_2$ and an abrupt increase in heart rate. The heart rate will then often mildly decrease and stabilize.[4,123,124]

Once clinical improvement is noted, the dose of isoproterenol usually must be increased to achieve normocapnia by an average of 0.7 μg/kg/min.[4] Clinical experience indicates that once normocapnia is achieved, the dose of isoproterenol should be unchanged for at least 12 hr. After this period of time, the dose should be gradually tapered over at least 24 hr, while closely monitoring clinical status. Rebound bronchospasm during tapering of the isoproterenol dosage has been described[124] and may necessitate an increase in the infusion

rate. After a dose of 0.1 μg/kg/min has been reached, the infusion may be discontinued. The average duration of infusion is approximately 2 days. Reinstitution of inhaled beta-adrenergic agents is then recommended, along with the continuation of the previously discussed forms of therapy.

While a patient recieves CIIS, the authors recommend that serum theophylline and cardiac enzyme levels, along with 12-lead EKGs, be closely monitored. It is also important that patients receiving CIIS have their cardiac status followed closely for 24–48 hr after discontinuing isoproterenol.[129]

Mechanical Ventilation

Prior to the description of CIIS, respiratory failure associated with status asthmaticus necessitated treatment with mechanical ventilation. This technique, however, is not without morbidity or mortality[4,12,124,138,139]; complications may include the results of barotrauma, such as pneumomediastinum and pneumothorax, and postextubation subglottic stenosis. There are, however, instances in which mechanical ventilation is indicated. In severe respiratory failure, immediate steps must be taken to restore ventilation and gas exchange. This implies immediate resuscitation by intubation and mechanical ventilation. Likewise, patients who are treated with CIIS and do not improve despite maximal isoproterenol dosage *or* who develop untoward side effects during the infusion before improvement is seen, require mechanical ventilation.

Downes et al have established methods for mechanical ventilation of children in status asthmaticus progressing to respiratory failure.[4,139] The following is based on their technique. Intravenous access should be established as quickly as possible, both for fluid replacement (when necessary) and for the administration of medications. Because the patient with severe hypercarbia and hypoxemia may be combative or irritable, intubation may be difficult. Therefore, intubation should be performed by the member of the medical team who is most skilled in the technique. It may be safer to manually ventilate the patient with a bag and mask while awaiting an anesthesiologist or intensivist, if they are readily available. To avoid aspiration of gastric contents during intubation, the stomach should be emptied with a nasogastric tube.

Premedication recommended to facilitate intubation includes intravenous atropine (10–20 μg/kg) to prevent bradycardia, ketamine (2 mg/kg) for sedation, and succinylcholine (4 mg/kg) for neuromuscular blockade. Orotracheal intubation should be carried out; if prolonged intubation proves necessary, elective nasotracheal intubation may be carried out in 12–24 hr. Because the pressure required for ventilation of patients in severe status asthmaticus is often high, an adequate tracheal seal is necessary. Less turbulent flow and resistance is achieved by using the largest bore endotracheal tube possible. For patients under the age of 8–10 years, an uncuffed endotracheal tube is generally necessary. For older patients, an endotracheal tube with a large volume low-pressure cuff is preferable.

A chest x-ray to document tube placement and to detect pneumomediastinum or pneumothorax must be obtained. If pneumothorax is present, closed

chest thoracostomy tube drainage is mandatory. Continuous cardiac monitoring to detect abnormal heart rate and rhythm and an indwelling arterial catheter are essential. A bladder catheter to document an adequate urine flow (at least 1–2 ml/kg/hr) is also needed.

Clinical experience has shown that a volume-preset ventilator is a more useful mode of ventilation in treating respiratory failure secondary to status asthmaticus. An initial tidal volume of 15–20 ml/kg should be delivered to the patient after adjustment for internal compliance of the ventilator. Because positive end-expiratory pressure (PEEP) may add to the expiratory airflow obstruction, it is not recommended. Also, a prolonged expiratory phase (inspiratory:expiratory ratio of 1:1.5 or greater) will allow improved ventilation. The rate of ventilation should be relatively slow (50% of the normal rate for age) to provide a less turbulent inspiratory flow as well as an adequate expiratory time per cycle. Initially, humidified 100% oxygen is recommended. Arterial blood gases must be used to monitor gas exchange and to direct changes in ventilator settings. Maintaining the PaO_2 between 80 and 100 will provide adequate hemoglobin saturation. Higher levels are unnecessary for tissue oxygen delivery, and excessive inspired oxygen concentrations carry risks such as atelectasis and pulmonary oxygen toxicity.

Neuromuscular blockade with intravenous pancuronium bromide (0.1 mg/kg) allows coordination of the patient with the ventilator. This reduces the maximal pressure required to deliver the set volume, thus decreasing the risk of barotrauma. The dose may be repeated as frequently as every hour or given as a continuous infusion at a rate of 0.1 mg/kg/hr. Intravenous diazepam (0.2–0.3 mg/kg every 1–3 hr) may be given to provide sedation and amnesia. Morphine sulfate (0.1 mg/kg) may be used, although it has a theoretic disadvantage of nonspecific histamine release.[140]

Tracheobronchial toilet with chest physiotherapy and deep suctioning are necessary for the removal of secretions and prevention of atelectasis. If available, a side port valve allows suctioning while ventilation continues, thus reducing the risk of hypoxemia. If atelectasis secondary to mucous plugging occurs and is unresponsive to routine suctioning, flexible fiberoptic bronchoscopy, preferably through a side port valve, may be necessary.[141–143]

Mechanical ventilation generally must be continued 12–24 hr in children with status asthmaticus. CIIS may be given during mechanical ventilation, although the same regimen must be followed, and CIIS tapered or discontinued if life-threatening arrhythmias supervene. Downes does not advise a trial of spontaneous breathing with assisted or intermittent mandatory ventilation (IMV) prior to discontinuing mechanical ventilation because of poor coordination of asthmatic children with the ventilator.[4] Some children, however, will tolerate a tapering IMV rate while breathing spontaneously and can be weaned in this fashion.

Before attempting to discontinue mechanical ventilation, Downes states that the following criteria should be met:

1. The presence of a sustained bronchomotor response to intravenous isoproterenol or subcutaneous epinephrine, with a decrease in either wheezing or peak airway pressure for 1 hr or more.

2. Chest x-ray demonstrating a decrease in hyperaeration, without atelectasis or air leak.
3. $PaCO_2$ less than 45 torr, with a minute ventilation of less than 150% of predicted normal.
4. PaO_2 greater than 200 torr in 50% oxygen.

When these criteria are met the patient is usually ready for rapid reversal of neuromuscular blockade. Chest physiotherapy and thorough tracheobronchial suctioning should be done prior to extubation. The patient is then given intravenous atropine (20 μg/kg) and neostigmine (70 μg/kg), which should lead to vigorous spontaneous respirations. Once these are established, the patient should be allowed to ventilate spontaneously through a "T-Piece" adaptor while receiving sufficient humidified oxygen. In the absence of significant atelectasis, fatigue, or deteriorating arterial blood gases, the endotracheal tube can be removed in 2–6 hr and the patient given mask or hood oxygen. Extubation should take place under controlled circumstances, and close monitoring should be continued.

Complications

Complications during status asthmaticus include both those intrinsic to the pathogenic mechanisms of the disease and those related to therapy. The latter have been discussed in the pertinent sections of therapy, such as tachyarrhythmias secondary to intravenous isoproterenol. Status asthmaticus may progress to severe hypoxemia and acidosis, resulting in cardiorespiratory failure, hypoxic brain damage, and death. These conditions may also potentiate the myocardial toxicity possible with the therapeutic intervention of adrenergic agents and theophylline.[58,59,128,129]

Eggleston et al[144] reported that up to approximately 25% of children admitted for asthma have chest radiographic abnormalities other than hyperinflation or peribronchial thickening. The most frequent finding was perihilar infiltrates (20%). Atelectasis (10%), especially of the right middle lobe, and pneumomediastinum (15%) were also common, and pneumothorax was rare. Pulmonary infiltrates were more frequently noted in younger children, whereas pneumomediastinum was more likely to occur in older children. In many instances, these chest radiographic findings were felt to be important in guiding therapy. Brooks et al[145] found a similar incidence of radiographic abnormalities. Subsegmental atelectasis (19%), however, was the most common abnormality other than hyperinflation or peribronchial cuffing. This was followed by possible pneumonia or pneumomediastinum (6%) and segmental atelectasis (4%). The authors found a poor correlation between the clinical assessment and the radiographic findings. Radiographic abnormalities rarely (3/128 cases) led to treatment alterations. Thus, the authors took a more circumspect position regarding the value of chest radiographs in acute asthma.

In the series of Brooks et al, none of the suspected pneumonias was shown to be bacterial. Shapiro et al have previously found that broad-spectrum antibiotics were nonbeneficial in children in status asthmaticus without signs of bacterial infection.[146] McIntosh et al similarly found a lack of association of

pathogenic bacteria in acute asthma.[49] On the other hand, surreptitious bacterial sinusitis has been implicated in some patients with chronic, difficult to control asthma.[147]

Mucous plugging, resulting in significant obstruction that is refractory to conventional therapy, is a complication that has not been subjected to carefully controlled study. There are several reports[141–143] in adults suggesting that bronchopulmonary lavage might be of some benefit in selected patients.

Fluid therapy in acute asthmatics must be carefully assessed because of the potential for pulmonary edema or the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The mechanism for the former is felt to be due to the markedly negative inspiratory intrapleural pressures generated in severe asthma, resulting in interstitial edema.[61] Elevated plasma antidiuretic hormone has been noted in patients during status asthmaticus and is felt to be due to stimulation of atrial volume receptors secondary to decreased pulmonary blood flow.[62] The clinical syndrome of SIADH has been noted in one adult with status asthmaticus.[63]

In addition to pulmonary edema, the markedly negative pleural pressures generated during status asthmaticus, along with increased right heart transmural pressure, was believed to account for electrocardiographic evidence of P pulmonale by Gelb et al.[148] In their study, 25/51 adult patients in whom the initial $PaCO_2$ was $\geq$ 45 torr and the initial pH was $\leq$ 7.39 had transient P pulmonale.

A rare poliomyelitis-like illness with permanent residual weakness occurring during the recovery from acute asthma in previously immunized children was initially described by Hopkins and Shield in 1974.[149] In this syndrome, lower motor neuron paralysis without sensory deprivation occurs in usually one extremity only. It appears from 4 to 11 days after the onset of acute asthma and has a rapid progression. Clinical findings may include meningeal signs and muscle pain or tenderness. Cerebrospinal lymphocytic pleocytosis and elevated protein are sometimes seen. The etiology remains speculative, with no clear viral agent implicated in this unusual complication of status asthmaticus.[150,151]

Treatment Projections

The treatment of status asthmaticus has dramatically improved in the past two decades. As knowledge is advanced in the pharmacology of presently availbale medications, safer and more efficacious drugs will be formulated. In addition, new unique therapeutic agents may follow the increased understanding of the basic mechanism(s) of airway obstruction.

Albuterol (salbutamol) is a recently FDA-approved β_2-adrenergic agonist for oral and hand-held pressurized aerosol usage. It is considered by many to be the treatment of choice for acute reversible airways obstruction.[72] It may replace intravenous isoproterenol in those cases of acute severe asthma requiring parenteral adrenergic therapy. It has greater selectivity and is more effective as a bronchodilator than isoproterenol at a comparative dose, resulting in cardiac stimulation.[85,152] However, the optimal role of intravenous versus aerosolized albuterol remains controversial.[85,153–155] Terbutaline is a

comparable[72] agent available for adults in tablet and injectable forms. A recent study in children indicates that a subcutaneous 12 μg/kg dose produced bronchodilation comparable to 10 μg/kg of epinephrine with fewer adverse effects, although previous results have varied.[76,156] Other newer adrenergic stimulants include fenoterol, pirbuterol, carbuterol, clenbuterol, bitolterol, and others that have been recently reviewed.[72,73,157]

The importance of the parasympathetic nervous system in regulation of airway caliber has been discussed previously. The inhalation of smoke from burning stramonium (stinkweed) or belladonna (deadly nightshade) leaves had been utilized for asthma after its discovery in India. More recently, the alkaloids scopolamine and atropine have been used for bronchodilation.[158] In an attempt to increase antimuscarinic receptor selectivity, aerosolized atropine has been tried. Anticholinergic side effects, such as dry mouth, tachycardia, mydriasis, and urinary retention, are reduced by this technique. A dose–response study of atropine in children has shown that a dose of 0.05–0.1 mg/kg is an effective bronchodilator.[159] Aerosolized atropine has been shown to be an effective therapeutic adjunct in acute asthma in adults.[160]

Ipratroprium bromide (Sch 1000) (availability pending in the United States), a quaternary ammonium derivative of atropine, has received recent interest because of its greater bronchial selectivity without central stimulation or other significant side effects when compared with atropine. Bronchodilation occurs within minutes after inhalation, although peak action is relatively delayed (1.5–2 hr), with a duration of action of about 4–6 hr.[161] It has been shown to be efficacious in children with chronic asthma.[162] In addition, it has been shown to be effective in acute asthma in adults and has additive effects with aerosolized albuterol.[163] Several studies have indicated that there are increased bronchodilation effects without additional side effects when used with theophylline or adrenergic medications.[161,164,165] In addition, there is evidence that children under 18 months of age with reactive airways disease respond poorly to β_2-agonists or xanthine derivatives,[86,166] whereas ipratropium may be beneficial in this age group.[167,168] The role of antimuscarinic agents in childhood status asthmaticus remains to be further defined, but appears to be quite promising.

Other potential agents on the horizon may include calcium channel blocking agents. This is due to the postulated central role of calcium within the target organs of airway smooth muscle and mucous glands, as well as within pathogenic mechanisms, including mast cell mediator release and vagus nerve impulse transmission.[169,170]

Other researchers have focused on the other pathogenic mechanisms of asthma in the search for useful medications. Alpha-adrenergic antagonists have been shown thus far to have limited effect.[171,172] The leukotrienes LTC4 and LTD4 have been shown to be very potent bronchoconstrictors and probably are major mediators of reversible airway disease. However, inhibitors of the oxidative metabolism of arachidonic acid currently remain speculative for clinical investigation.[15,173,174] Antihistamine therapy, primarily with clemastine, has shown some laboratory promise but no clinical utility thus far.[175,176] Meanwhile, newer methylaxnthines, corticosteroids, and cromolyn sodium derivatives have thus far shown no greater promise than the currently available

agents.[157] Nonetheless, because of the potential cardiovascular side effects of currently available agents and other shortcomings, striving for the "ideal bronchodilator" is warranted.[177]

Role of Prevention

Finally, the authors wish to emphasize that status asthmaticus is a serious, life-threatening event in the course of a complex disease and is often preventable or more easily controlled. It is important to understand exacerbating as well as complicating factors. Early disease recognition by child, parents, and clinicians and appropriate management cannot be overstated. Recent data implicate the physiologic impact of acute episodes of asthma in persistent pulmonary obstruction.[178–180] These observations have important connotations in the management of asthma and in preventing deterioration and perhaps a state of irreversible airway obstruction.

Kravis et al[181] have noted several characteristics of chronic asthmatic children that place them at high risk for sudden death. These include: (1) early, severe onset of wheezing, particularly in the first year of life, (2) frequent prolonged, severe episodes, (3) steroidal dependence, (4) excessive usage of adrenergic aerosols, (5) medication noncompliance, (6) persistent physical stigmata, including chest deformities and growth delay as well as persistent auscultatory findings, (7) persistent radiographic findings, and (8) pulmonary function abnormalities. The authors cited the need for early and appropriate corticosteroid management as well as constant medical supervision and surveillance for other underlying disease or a complication. Similarly, other authors have also indicated the need for early administration of systemic corticosteroids as well as maximal bronchodilator therapy in the treatment of young chronically severe asthmatics who are especially vulnerable to life-threatening acute episodes.[182,183] Of sobering note is the fact that many of the childhood asthma deaths in the published series occurred outside a medical setting. Thus, family education and close medical management is vital in high-risk asthmatics.

Infants and young children with acute severe wheezing pose a particular problem when compared to adults. Not only is the speed of onset of symptoms often faster,[9–12] but several differences in pathophysiologic mechanisms predispose them to greater symptom severity and potential respiratory failure. Tabachnik and Levison[184] have summarized the differences as increased peripheral airway resistance, decreased elastic recoil pressure and early airway closure, deficient collateral channels of ventilation, an unstable rib cage, and a mechanically disadvantaged diaphragm. In addition, there is relatively less bronchial smooth muscle and a greater number of mucous glands in the bronchial mucosa. These multiple differences may result in an increased likelihood of atelectasis, decreased pulmonary reserve, and diminished response to bronchodilators.[185] Indeed, beta-adrenergic agents and theophylline appear to have limited efficacy in many patients less than 12–18 months of age,[86,184,186] though therapeutic trials are certainly warranted. As mentioned previously, parasympatholytics may prove to be especially efficacious in this age group.[187,188]

In addition to appropriate recognition and understanding of acute asthma by the clinician and family, complicance with complex medical regimens is important in the amelioration of severe disease. An intervention program has been described in which nurse-educators utilize techniques for teaching self-management skills to asthmatic children and their families.[189] This program, structured in-patient programs with similar aims,[190] and other comprehensive programs[191,192] appear to reduce the frequency and severity of attacks. They attempt to address the complex issues of family dynamics, coping skills, understanding, and self-confidence. Though beyond the scope of this review, due consideration must be given to the importance and appreciation of psychologic factors involved in the optimal management of childhood asthma.[192–194] By providing a comprehensive approach, prevention can become, not a phrase, but rather a reality in the effective treatment of status asthmaticus in childhood.

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