Status Asthmaticus

From the Emergency Department to the Intensive Care Unit

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Introduction

Status asthmaticus (SA) is a common medical emergency faced by emergency department and intensive care specialists. Timely evaluation and treatment is required to prevent the morbidity and mortality associated with respiratory failure. SA is a severe asthma exacerbation that proves refractory to standard treatment regimens and represents the most extreme end of the asthma spectrum. Research efforts are aimed at defining the inflammatory characteristics unique to this asthma population. Standard therapy for SA has not changed dramatically in recent years and centers on appropriate oxygen, bronchodilator, and anti-inflammatory administration. A host of adjunct therapies, both old and new, may prove useful in select patients, but further study is required. This article focuses on the epidemiology, pathophysiology, and initial emergency-department (ED) management of adult SA patients. Specifics regarding the severe child asthmatic can be found in other articles in this journal.

The Problem of Status Asthmaticus

Emergency medicine and intensive care physicians manage status asthmaticus (SA) frequently. In 1995, there were an estimated 14 million asthmatics in the US, accounting for 1.5 million emergency department (ED) visits (1). The majority of asthmatics seen in the ED suffer
from mild to moderate exacerbations of their disease; however, all asthmatics are at risk of developing SA and must be attended promptly. SA is defined as a severe asthma exacerbation that does not respond readily to intensive treatment. These patients have limited respiratory reserve and are in imminent danger of respiratory failure and need of assisted ventilation. More descriptive terms for SA include “near-fatal asthma” and “life-threatening asthma,” but a more specific definition that includes physiologic or gas-exchange parameters is lacking. One might assume that SA encompasses the majority of asthmatic patients seen in the ED, yet this is clearly not the case. Of the 1.5 million ED visits by asthmatics in 1995, only one-third required hospital admission (1). In addition, some hospitalized patients are not in SA and do not require intensive care monitoring. In one large tertiary care hospital, for example, only 4% of asthma admissions required intensive care unit (ICU) care over a 10-yr period (2). These facts reflect the notion that many asthmatics inappropriately employ the ED for primary care of their disease and that most asthma exacerbations are largely responsive to medication.

Though death from asthma is relatively uncommon (5600 cases in the US in 1995) (1), SA is a medical emergency that must be diagnosed and treated urgently. It has been suggested that 1–7% of severe asthmatics will die each year (3–5) and perhaps 17% of those who survive a near fatal attack will eventually succumb to their disease (6). Documented mortality rates for patients requiring mechanical ventilation for SA vary widely from 0–37% in series over the last three decades (7–13). In general, morbidity and mortality of hospitalized patients with SA and respiratory failure has decreased significantly and much of the credit is due to timely assessment and treatment by out-of-hospital providers and ED physicians and better ICU care (10,11,13).

**Epidemiology/Demographics**

Several disturbing trends regarding asthma mortalities are evident. The age-adjusted mortality rates are significantly higher for women (2.5 vs 1.9/100,000 population), blacks (3.6 vs 1.2/100,000), and the elderly (14). One popular explanation is that the elderly and minorities do not receive adequate controller therapy for their asthma because of poor access to medical care. One frequently cited example is that 21% of all asthma deaths among young people in the late 1980s occurred in the inner cities of Chicago and New York (15). Although poor primary care of asthma undoubtedly factors into the increase in fatal and near-fatal asthma attacks in certain demographic regions, it does not account fully for the broad trends.
The single largest risk factor for SA is a history of near-fatal asthma (16). One study found a 16-fold increased risk of asthma death for patients with a prior history of SA with respiratory failure (17). Other entities have correlated with presentations for SA, as well. Psychiatric illness, for one, is consistently associated with an increased risk of fatal asthma (18). Similarly, persistent smoking carries a twofold increased risk of death in asthmatics (19). Another oft-reported risk factor for fatal asthma is frequent short-acting $\beta_2$-agonist usage (20,21). In a case-control study, the use of short acting $\beta_2$-agonists conferred a two- to three-fold increased risk per bronchodilator canister per month (20). The belief that improved self-care and appropriate controller therapy can prevent SA and asthma-related death is well-accepted. Asthma is a chronic disease in the vast majority of patients and most hospitalizations, including those requiring ICU care, are preventable.

One opposing argument is that patients with histories of SA and near-fatal asthma have blunted perceptions of dyspnea. In a study of 11 patients with near-fatal asthma compared with mild asthmatics, the former had blunted ventilatory responses to hypoxia and lower Borg dyspnea scores, suggesting that these patients were unable to recognize deterioration in their airway disease (22). This may prove true for select SA patients, but the majority of life-threatening attacks occur in patients with chronic asthma who neglected or misunderstood signs of progressive deterioration.

**Pathophysiology**

SA is a state of profound ventilatory disadvantage. Airway inflammation and increased bronchiolar smooth-muscle tone lead to resistance to expiration and lung hyperinflation. The diaphragm and intercostal muscles contract inefficiently because of the effects of thoracic-cage expansion. Patients in SA have elevated end-expiratory airway pressures and utilize a significant percentage of their energy to breathe. Without correction of the airway obstruction and hyperinflation, patients fatigue and progress to frank respiratory failure.

Asthma is a spectrum of disease governed by a cascade of common inflammatory mediators and research efforts have attempted to delineate specific markers that might differentiate SA from milder forms of asthma. Marked airway thickening and a brisk infiltration of neutrophils into the airways are consistent findings in SA. In cases of fatal asthma, bronchial thickening is routinely 25–300% greater than in normal airways, whereas in nonfatal asthmatics this is less dramatic (23). More recently, Lamblin and colleagues found significantly increased numbers of neutrophils and levels of the neutrophil chemoattractant cytokine,
IL-8, in bronchoalveolar lavage fluid (BALF) in asthmatics requiring mechanical ventilation compared to milder patients (24). In addition, increased matrix metalloproteinases (MMPs), presumably triggered by neutrophil-mediated epithelial-cell injury, were found in the BALF of the severe asthmatics (25). The question of whether SA is driven primarily by a profound neutrophilic response rather than the typical eosinophil and T-lymphocyte inflammatory response has been raised. In a recent study, 34 steroid-dependent asthmatics underwent endobronchial biopsies (26) and two distinct groups were found. Both groups had increased neutrophil infiltration into the airway compared to mild asthmatics, but one subset had no tissue eosinophilia, whereas the other group did. This result suggests that certain severe asthmatics may manifest a neutrophilic inflammatory response while others demonstrate the typical inflammation seen in milder asthmatic forms. Whether the finding of airway neutrophilia without eosinophil involvement places these difficult-to-control asthmatics at increased risk of SA or death is presently unknown.

Further attempts at understanding the pathophysiology of SA have led to further divisions, real or artificial, in the spectrum of severe asthma. One example is based on the time-course of the attack. Most patients presenting to the ED in SA deteriorate over a period of days or weeks, but some clearly present with acute onset bronchospasm without antecedent illness (27). Autopsy findings appear to support this observation as a subset of the fatalities has had clear, mucus-free airways. Presumably, these patients died of profound neurally mediated bronchospasm (i.e., anaphylaxis) or they died of other means. Sur and colleagues separated seven patients that died of severe asthmatic exacerbations into a “sudden-onset” group with symptoms present for less than 1 h and a “slow-onset” group, and found significantly more neutrophil involvement in the submucosa of the former group (28). He postulated, as others have, that a unique inflammatory pathway is triggered in patients with fatal asthma. To date, however, these observations have not led to convincing evidence that might explain fully the pathophysiology of SA. Therapy targeted at certain inflammatory mediators, such as anti-IgE antibody, in SA is not yet recommended, but this clearly represents the future of treatment.

SA leads to hypoxemia via lung hyperinflation and regional ventilation/perfusion alterations (V/Q). Studies of patients presenting to the ED with severe asthma attacks using multiple inert gas-elimination techniques have shown a bimodal blood flow pattern with a significant portion of the cardiac output perfusing poorly ventilated lungs (29,30). Again, a host of inflammatory mediators have been implicated in potentiating this abnormality. Platelet-activating factor (PAF), for one,
appears to be an important culprit. Inhaled PAF has been shown to induce V/Q mismatching and decrease arterial oxygenation in stable asthmatics (31) by eliciting a capillary leak phenomenon (32). Other local and systemic mediators probably act at the alveolar-capillary interface in SA to generate the profound V/Q abnormalities and further research in this area is ongoing.

Abnormalities of carbon-dioxide (CO₂) exchange in SA occur less frequently. CO₂ retention does not usually develop until the FEV₁ is less than 25% of predicted (33) and one large meta-analysis of severe asthmatics found that only 13% had elevated PaCO₂ values > 45 mmHg (34). Failure to eliminate CO₂ likely results from both increased physiologic dead space associated with the profound V/Q abnormalities and alveolar hypoventilation secondary to respiratory fatigue. Although hypoxia is the primary gas-exchange derangement faced in asthmatics presenting to the ED, progressive hypercarbia is the harbinger of impending respiratory failure requiring ventilatory support.

**Clinical Evaluation**

SA is a medical emergency and requires urgent assessment and timely institution of therapy. Patients admitted to the ED in SA are in distress and their focus is on breathing. Many of these patients will be easily recognizable by their tachypnea, wheezing, broken speech, and use of accessory muscles of respiration. Patients with a decreased level of consciousness, shallow respirations, central cyanosis, or other signs of profound fatigue should be considered for immediate intubation. Most patients, however, will present before this extreme and a focused medical history and physical examination should be obtained while treatment is initiated.

In general, the medical history should not differ from that of patients presenting with milder flares of asthma and should focus on the events leading to the present acute decompensation. An acute allergic reaction to a new therapeutic agent, a history of medication non-compliance, or bronchospastic attack following an environmental exposure may help target treatment. In addition, a medical history of prior asthma, including prior episodes of respiratory failure and ICU admissions, helps confirm the diagnosis and alert the practitioner to the attendant risks with a particular patient.

Much of the relevant physical examination of a SA patient can be obtained from the vital signs and by observation. The most severe patients will often be sitting upright, tachypneic, wheezing, and have sternocleidomastoid retractions with respiration. In one study, Brenner and colleagues showed a good correlation between patient position and accessory muscle use and reduction in peak expiratory flow rate (PEFR).
and partial pressure of oxygen (PaO₂) (35). McFadden and colleagues determined that only the presence of sternocleidomastoid retractions correlated with impairment in lung function in 22 patients with acute attacks, whereas the presence of wheezing did not (36). Most consultants discourage the notion that physical-examination findings correlate well with degree of airflow obstruction. In general, physical findings serve as a guide to work of breathing more than an assessment of airflow obstruction (37).

The vital signs of a patient in SA will consistently reveal respiratory rates >30/min and heart rates >120/min (38). Blood pressure can fluctuate depending on the degree of hemodynamic embarrassment secondary to high intrathoracic pressures. In one review, the mean blood pressure in 61 severe asthmatics with hypercapnia was significantly higher than a milder cohort, apparently reflecting the degree of distress and anxiety in the more compromised group (11). The most worrisome patients are hypotensive because of dehydration and marked lung hyperinflation; intubation and initiation of mechanical ventilation in these patients is challenging. Perhaps more useful than systemic blood pressure is a measurement of pulsus paradoxus. High pulsus paradoxus values reflect the wide variations in intrathoracic pressure that occurs with inspiration and expiration in SA. In the aforementioned study by Mountain and Sahn, 61 hypercapnic asthmatics demonstrated an exaggerated pulsus paradoxus of 23 mm Hg compared to 14 mmHg in more mild asthmatics (11). Another study correlated an increased pulsus paradoxus reading with lower FEV₁ values, but this has not been corroborated (39). The presence of an exaggerated pulsus paradoxus reading greater that 15 mmHg is found in approx 25% of asthmatics presenting to the ED (37,40), but this percentage is likely much higher in those with SA (38). It should be remembered that as respiratory failure progresses, a drop in pulsus paradoxus to near normal readings may be seen.

Audible or auscultatory wheezing is a near uniform finding in patients in the ED with life-threatening asthma. The exception is in patients with such diminished air movement—a “quiet chest”—that the findings of airways obstruction are unheard. Loudness or character of wheezing does not correlate well with severity of airway resistance (41) and objective measures are necessary. The remaining focus of the physical examination should center on possible mechanical complications of SA. Pneumomediastinum and pneumothorax may be discovered by a Hamman’s mediastinal crunch, subcutaneous emphysema, asymmetric breath sounds, or deviated trachea.
**Expiratory Flow Assessment**

Every effort should be made in the ED to acquire an objective measure of airflow obstruction by performing a PEFR or a FEV₁ maneuver. The most severely compromised patients will be unable to perform the test properly and this measurement should be deferred initially. Although death has been reported during PEFR testing (42), this is exceedingly rare and clinical deterioration should not be expected. Physicians and patients repeatedly underestimate the severity of airflow obstruction (43) and the PEFR aids in gauging response to treatment in the ED and may help in triage decisions. Several studies consistently found that SA patients have PEFR readings <25% predicted (44) and FEV₁ <20% predicted (45). In one study of 86 patients presenting with acute asthma, a FEV₁ < 1 L (<25% predicted) or a PEFR < 200 L/min (<30% predicted) identified all patients with hypercarbia (PaCO₂ >42 mmHg) or severe hypoxemia (PaO₂ < 60mmHg) (33). Reductions in PEFR to <33% of normal is considered potentially life-threatening (46). One advantage of performing an FEV₁ and full flow-volume loop is in diagnosing upper-airway obstruction, as in vocal-cord dysfunction or a tracheal tumor that may be masked by the presentation of wheezing.

**Arterial Blood-Gas Measurement**

Arterial blood gas (ABG) determinations are not necessary for most asthmatics presenting to the ED. In SA, however, ABGs provide important information in terms of respiratory reserve, metabolic disturbances, and degree of hypoxemia, and assist in management and triage decisions. Respiratory alkalosis is the most common abnormality in mild asthma exacerbations (47), but as PEFR and FEV₁ drop to <30% of predicted, hypercarbia and respiratory acidosis develop (33). In addition, concomitant metabolic acidosis occurs in a significant subset of severe SA patients. Mountain and colleagues found that 28% of 229 acute asthmatics as well as 62% of the hypercarbic subset had a definable metabolic acidosis (47). In another cohort of 12 asthmatics presenting with respiratory distress and an acute lactic acidosis, eight developed a concomitant respiratory acidosis and six required mechanical ventilation (48). The lactate production presumably stems from overload of the thoracic cage muscles as well as tissue hypoxia. Early recognition of metabolic derangements in SA patients aid in triage and treatment decisions, such as possible early ventilatory support. ABGs should be performed early in the ED course of SA patients, but repeat assessments are not usually required.
Chest Radiography

As with ABGs, chest radiographs (CXRs) should not be performed routinely in all asthmatics in the ED. Prior studies revealed that the yield of findings other than hyperinflation or subsegmental atelectasis on CXRs in asthma and chronic obstructive pulmonary-disease exacerbations is <5% (49–52). Complications from barotrauma in SA patients, however, are sufficiently prevalent to justify routine CXRs in this population. In one review of admission CXRs of 54 asthmatics hospitalized after partial response to 12 h of treatment in the ED, 20 (34%) were felt to have major abnormalities that warranted attention (53). Most of these major abnormalities were focal infiltrates that were usually treated with antibiotics, however, only one patient was found to have a pneumothorax. Clearly this does not prove the necessity of CXRs, but in this severely ill population their routine use appears warranted.

Other Studies

Few other studies need be obtained in evaluating patients with SA in the ED. Electrocardiograms in middle-aged patients or those with suspected ischemic heart disease is standard. Screening laboratory chemistries may reveal hypokalemia related to aggressive β₂-agonist usage or abnormalities in sodium and glucose, suggesting concomitant illness. A complete blood count could reveal signs of an acute infectious process, but this will be infrequent. In general, laboratory tests and other investigations should be ordered only if other diagnoses or contributing factors are considered. They are unlikely to change acute management of the SA patient in the ED significantly.

Differential Diagnosis

Most SA patients will be easily recognizable at time of presentation to the ED, but other disease processes should always be considered, particularly in adult patients with no prior history of asthma. Some mimics of severe asthma include pulmonary embolism, foreign-body aspiration, upper-airway obstruction, and cardiogenic pulmonary edema. Patients with vocal-cord dysfunction frequently present to the ED in distress with apparent critical airflow limitation. Similarly, exacerbations of other pre-existing obstructive airway diseases, such as cystic fibrosis (CF), bronchiectasis, and chronic obstructive pulmonary disease (COPD) may mimic SA. Although a clear medical history of congestive heart failure, vocal-cord dysfunction, or aspiration will usually allow the ED physician to appropriately differentiate these disorders from SA, this is not universally true. The astute practitioner must consider many of these diagnoses while initiating treatment for an apparent life-threatening attack of asthma.
Treatment

The treatment of SA patients occurs in parallel with the diagnostic evaluation. As with other medical emergencies, empiric therapy should be instituted almost immediately. Timely intervention is necessary if intubation and mechanical ventilation are to be avoided. The cornerstones of treatment of SA, as with almost all hospitalized asthma patients, are oxygen, bronchodilators, and corticosteroids. A more complete discussion of the asthma therapy is included in the articles entitled “Pharmacologic Treatment of the Adult Hospitalized Asthma Patient” and “Pharmacologic Management of the Hospitalized Pediatric Asthma Patient” in this volume and emphasis in this section will be on therapy that should be instituted in SA patients in the ED.

Oxygen

Modest hypoxemia is common in severe asthma exacerbations, but a PaO2 <55 mmHg is rare (16). Supplemental oxygen should be administered to improve the V/Q mismatch caused by airway plugging and atelectasis and perhaps this therapy may ameliorate some of the symptoms of air hunger. Previous guidelines (46) suggest that oxygen is necessary to balance the V/Q mismatch induced by bronchodilators, and although minor decrements of 3–4 mmHg in PaO2 have been reported after albuterol and ipratropium use, this is rarely clinically significant (54). In the majority of SA patients, FiO2 levels of 30–50% are adequate to correct the hypoxemia and failure to do so should prompt further investigation for pulmonary parenchymal or vascular disease. Although the initial use of 100% O2 has been advocated (46), this is generally not necessary. Infrequently, high-flow oxygen suppresses respiratory drive in select patients with marginal lung function and hypercarbia. A recent study of 37 asthmatics seen in the ED, for example, found that PaCO2 levels increased 5–6 mmHg in the most severe subset after the administration of 100% oxygen (5). Although it is unlikely that this degree of hypercarbia will significantly alter management, physicians should refrain from routinely administering unnecessarily high oxygen concentrations in patients with marginal respiratory reserve.

Helium-oxygen (heliox) mixtures are increasingly used in severe asthmatics in the ED to improve air flow and oxygen delivery to terminal bronchioles. Detailed discussion of the indications and efficacy of heliox therapy is deferred here as this topic is addressed in “When Conventional Asthma Therapies Fail”, later in this volume.

β-agonists

Inhaled β2-agonists remain first-line therapy for all asthma exacerbations, including SA. Albuterol and metaproterenol are most com-
monly used in the US because of their relative early onset of action, intermediate duration of effect, and safety profile. Although these drugs have been mainstays for years, dosing and route of administration are frequently questioned. In addition, the primary or adjunct use of parenteral β-agonists, such as terbutaline and epinephrine, has been studied repeatedly in the ED.

At present, the use of a metered dose inhaler (MDI) with a spacer device delivers a drug to the small airways as effectively as a wet nebulizer. Multiple studies comparing MDI treatments with intermittent or continuous nebulizations found no benefit with either method (56–62). In one example from a recent study, 50 patients randomized to receive two puffs of salbutamol (albuterol) via spacer or the equivalent dose of nebulized salbutamol repeated every 15 min improved equally (60). In another study, 35 patients presenting to a large ED with acute asthma received either 4 puffs of albuterol via MDI with nebulized or inhaled placebo and 2.5 mg nebulized albuterol as initial therapy (61). Improvement in FEV₁ and PEFR was not statistically different between the two groups in the first hour. Cost containment has driven many of these studies and indeed one group reported an impressive savings of more than $250,000/yr by employing MDIs with spacers primarily in their hospitalized, non-ICU patients (59). Contrary to earlier beliefs, nebulization does not improve drug delivery. Approximately 10% of the administered dose reaches constricted bronchioles while the rest is deposited in the oropharynx. Despite their increased cost and poor airway deposition, nebulized β-agonists are routinely prescribed in the ED for SA because of their relative ease of use by distressed patients and busy respiratory-care providers.

Optimal dosing of β₂-agonists in SA patients in the ED is not clearly outlined and patient tolerance and clinical response largely affect prescribing habits. Standard regimens include 2.5 mg nebulized or 4 puffs (90 µg each) via MDI of albuterol repeated 2–3 times/h. Doses as high as 0.4 mg/kg/h were prescribed via continuous nebulizer in one study of seven adult asthmatics (63), but this led to a 16% mean increase in heart rate, high serum-albuterol levels, and drug discontinuation in one patient. Side effects such as tachycardia, palpitations, and tremors are less with the selective β₂-agonists, yet these symptoms limit dosing in certain patients.

Popular in the treatment of SA in years past, parenteral administration of β-agonist agents continues to play a role in the treatment of select adults in the ED with difficult-to-control asthma. Concern regarding the cardiotoxicity of β-agonists given intravenously (IV) or subcutaneously (SC) and their unproven efficacy has persuaded most ED physicians to prescribe inhaled agents initially. Theoretically, IV infusion or SC injection might improve distribution of drug compared to
the inhaled route because of airway plugging and V/Q mismatch, but this is not evident clinically. In one study supporting the use of nebulized β-agonists, 48 asthmatics with acute, hypercarbic attacks treated with nebulized albuterol had statistically higher PEFR while in the ED than those treated with intravenous albuterol (64). In another study of 154 asthmatics seen initially by paramedics, patients were randomized to receive either subcutaneous epinephrine or nebulized metaproterenol or both in the pre-hospital setting (65). No significant difference in improvement in PEFR was noted among the groups. Although most studies support these findings, several do not and deserve mention. In a group of 76 severe adult asthmatics randomized to receive 5 mg salbutamol at 30 min and 2 h via nebulizer or a continuous 4-h salbutamol infusion (12 µg/min) (66), increase in PEFR was more pronounced in the intravenous group. Two patients in the infusion group had to withdraw because of poorly tolerated tachycardia, however. Secondly, in a study of 100 acute asthmatics, Appel and colleagues found that select patients who did not respond adequately to initial aerosolized metaproterenol improved objectively with additional subcutaneous epinephrine injections (67). Lastly, higher PaO₂ levels were reported in a group of 11 asthmatics treated with intravenous terbutaline compared with the inhaled form of this drug, but clinical outcome was unchanged (68). Despite these few exceptions, multiple other investigations have shown no demonstrable clinical difference regardless of the route of administration of β-agonists among asthmatics suffering acute, severe attacks.

Parenteral dosing of β-agonists in adult SA patients is not initially recommended because of their potential systemic toxicity, however, select patients who are unable to cooperate with inhaled drug or who manifest dramatic airway plugging may respond better to either SC or IV therapy. In general, inhaled β-agonist therapy should be administered immediately and dosed repeatedly in SA patients in the ED until admission to the ICU or limiting side effects become evident.

**Anticholinergics**

The role of anticholinergic bronchodilators, namely ipratropium bromide and glycopyrrolate, in the treatment of acute and chronic asthma has been studied extensively (69–79). Anticholinergic bronchodilators are relatively slow-onset (30–60 min) and their efficacy in the acute management of SA is debated. Most studies have shown a measured benefit with the addition of ipratropium bromide to standard β-agonist bronchodilators (69–73,76). One recent study of ipratropium in asthmatics with acute bronchospasm in the ED epitomizes this contention (76). Weber and colleagues randomized 67 asthmatics to continuous nebulization of albuterol vs albuterol and ipratropium (1 mg/
h) during their stay in the ED. Although the combined treatment patients were discharged from the ED 35 min earlier on average, there was no statistical difference in major clinical parameters. Patients in this study, as in most others, had moderate exacerbations (only 31% of patients in Weber’s cohort required hospital admission) and whether these results can be extrapolated to SA is unclear. A recent meta-analysis of 10 studies that randomized combined bronchodilator therapy with ipratropium vs β-agonist therapy alone showed a 100cc improvement in FEV$_1$ or a 22% improvement in PEFR in the combined group (70). Hospitalization rate was also marginally less in the combined group (11 vs 15%). Anticholinergic bronchodilators should not be substituted for β-agonist bronchodilators in the treatment of SA. The adjunct use of ipratropium with albuterol or metaproterenol in the initial management of SA patients in the ED may lead to a modest benefit.

Theophylline

The methylxanthines, aminophylline and theophylline, were once considered standard bronchodilator therapy in the management of SA. In 1980, Rossing and colleagues published a definitive study showing that intravenous aminophylline was an inferior bronchodilator to the β-agonists (80); however, in a follow-up study 1 y later, he reported that combination therapy with β-agonists and aminophylline in patients with severe asthma (FEV$_1$<1 l) was efficacious (81). In the latter study, 89 acute asthmatics were assigned to initial therapy with either three doses of 0.3cc of 1:1000 dilution of SC epinephrine, SC epinephrine, and IV aminophylline (5.6 mg/kg load, 0.9 mg/kg/h infusion) or inhaled isoproterenol and IV aminophylline. The combined treatment groups had better improvement in airflow and earlier discharge from the ED at 2 h compared to the SC epinephrine group. Data since that time has not been as convincing and in a meta-analysis published in 1988, no clear benefit was noted when methylxanthines were added to β-agonists to treat acute bronchospasm (82). Despite a better understanding of the varied effects of theophylline in the past decade, including its role as a potential immunomodulator (83) and respiratory muscle stimulator, no convincing data has surfaced to encourage its use in acute SA. Probably, few asthmatics respond to theophylline when treated appropriately with β-agonists and steroids. The therapeutic window of theophylline is narrow; use should be reserved for those SA patients not responding to standard therapy or for patients known to respond to oral theophylline. When intravenous aminophylline therapy is planned in SA patients in the ED, a loading dose of 6 mg/kg over 30 min followed by an infusion of 0.5 mg/kg/h with measurement of theophylline blood levels is recommended.
**Glucocorticoids**

Glucocorticoids should be given to all SA patients in the ED. Debate has raged over the past three decades as to the efficaciousness, route of delivery, and dosage of steroids in acute exacerbations of asthma, but the preponderance of evidence supports their early use. Why steroids work in the treatment of acute asthma is not completely understood, but centers on their broad anti-inflammatory properties and may relate also to their ability to decrease airway mucous production, decrease capillary leakage, and upregulate airway β-agonist receptors. Because corticosteroids decrease cell-mediated airway inflammation via suppression of gene transcription (84), clinical effects should not be expected in the early hours of asthma management in the ED.

IV steroid dosing remains most popular in SA patients because of its facility of administration and years of clinical experience. Dosing of the two most commonly ordered IV agents, methylprednisolone or hydrocortisone, varies greatly among practitioners. A dose-response relationship has not been firmly established with either drug in acute asthma and the natural tendency is to err towards higher doses than probably necessary. One oft cited study by Haskell in 1983 found that eight SA patients treated with 125 mg of methylprednisolone every 6 h for 3 d improved more quickly compared to patients randomized to the medium dose (40 mg q6h) or low dose (15 mg q6h) groups (85). Larger studies have not supported this finding, however (86–91). Based on the prevailing evidence, initial IV doses of 40–125 mg every 6 h of methylprednisolone (or 0.6–2 g/d of hydrocortisone) have been recommended in previous reviews (16,92,93). Oral prednisone at equivalent doses is also recommended as initial therapy, though this option is less popular because of the potential for reduced absorption in SA patients. Steady reduction in glucocorticoid dose is uniformly recommended after 1–2 d of treatment. More recent trials have focused on the use of inhaled steroids in the ED management of mild asthma attacks, but this option can not yet be recommended as standard therapy for SA (94–97).

**Other Therapies**

The anti-leukotriene drugs, specifically the leukotriene-receptor antagonists, montelukast and zafirlukast, and the 5-lipoxygenase inhibitor, zileuton, are the newest proven asthma therapies in several years. These medications improve airway function by blocking the deleterious inflammatory and bronchoconstrictive actions of specific leukotrienes. Although several studies have shown that airway function improves within several hours of administration (98–100), SA is not considered an appropriate indication for anti-leukotriene drugs at this time. Certain patients in SA, particularly those with known aspirin
sensitive asthma, may benefit from leukotriene-antagonist drugs, but clinical response will not be readily apparent in the ED and these drugs should be employed sparingly. As more experience is gained, leukotriene antagonists may become useful adjuncts to the standard armamentarium for severe asthma exacerbations.

IV magnesium therapy was once common treatment for SA, but its efficacy in numerous studies is unproven and it is no longer routinely prescribed. A recent review, however, identified a subset of severe, acute asthmatics that may benefit from magnesium therapy (101). Rowe performed a meta-analysis on 665 pooled patients and found that IV magnesium therapy improved PEFR and FEV₁, and reduced hospital admission rates in severe asthmatics with initial FEV₁ values <30% predicted. More mild asthmatic patients did not benefit. This data will likely reopen the debate regarding magnesium use in SA patients. Although a definitive recommendation regarding IV magnesium as adjunct therapy in SA patients cannot be supported at this time, there may be a subset of severe patients who benefit from 1–2 g of magnesium.

**Intubation/Assisted Ventilation**

The decision to intubate a SA patient in the ED is often made urgently. A few patients may be close to respiratory arrest at the time of presentation to the ED and require emergent intubation with full sedation, muscle relaxation, and initiation of mechanical ventilatory support. More commonly, though, patients fail to respond appropriately to established treatments and require intubation for progressive respiratory fatigue. Important clinical endpoints that would prompt intubation include decreasing level of consciousness and worsening respiratory and metabolic acidosis; however, no absolute criteria exist to inform ED or ICU staff when to intubate and this remains a clinical judgement.

Documented complications with intubation in hypoxemic, hemodynamically unstable asthmatic patients are significant (38,102–104). Hypotension, arrhythmias, barotrauma, laryngospasm, worsening bronchospasm, aspiration, and seizures will be encountered in the peri-intubation period in SA patients. Intubation can be difficult in these compromised patients, and should be performed by physicians experienced with difficult airway management. While awake, nasotracheal intubations are performed frequently in these tenuous patients, orotracheal artificial airways are preferred. Orotracheal tubes of at least 8.0 mm diameter significantly decrease inspiratory-airway resistance and allow for suctioning of secretions and bronchoscopy. The proper use of sedatives and muscle relaxing agents are important in aiding
Fig. 1. Initial ED evaluation and treatment algorithm for status asthmaticus
intubation and initiating mechanical ventilation in these patients. A full understanding of their onset, duration of actions, and side effects is required. Discussion of these drugs as well as ventilator management is presented in “Mechanical Ventilation in Severe Asthma”, later in this volume.

When respiratory support is required in SA patients, intubation with assisted mechanical ventilation remains the most common option. With the advent and success of noninvasive bi-level ventilation (B:PAP®; expiratory [ePAP] and inspiratory [iPAP] positive airway pressures) in chronic obstructive lung disease patients with respiratory insufficiency, it has been increasingly employed in SA patients in the ED. One study has shown improvement in subjective dyspnea and respiratory rate (105) with noninvasive mask ventilation, and a host of case reports in SA patients describe clinical responses to bimodal ventilation (106,107). Definitive recommendations regarding the use of noninvasive ventilation in SA patients, however, need to be withheld pending further study. Many patients will be unable to cooperate with the tight-fitting mask apparatus because of severe dyspnea, claustrophobia, or decreasing level of consciousness. Noninvasive ventilation should be attempted in few selected patients with SA.

Disposition

Most asthmatic patients requiring hospital admission do not require ICU care. These patients improve partially while in the ED and warrant observation on a ward for a brief time to ensure continued improvement. Concerns about early relapse, multiple ED visits, or prior ICU admissions may separate these asthmatics from those discharged from the ED with similar PEFR and vital signs (108,109). In contrast, SA patients who fail to respond readily to aggressive bronchodilator and steroid therapy while observed in the ED require increased monitoring and observation. Absolute criteria for triaging SA patients are lacking, but ED physicians and critical-care physicians should opt to transfer these tenuous asthmatics to the ICU. Clearly, worrisome patients with a worsening respiratory or metabolic acidosis should be immediately transferred to an intensive care setting. Established guidelines have suggested also that patients with PEFR <200 L/min, a pulsus paradoxus >15 mmHg, use of accessory muscles of respiration, or a <10% improvement in PEFR while in the ED be monitored in an ICU (16,110). Data supporting these recommendations are scant, however, and in-hospital triage depends on the clinical judgement of the treating physicians. Triage of SA patients requires clear communication between the treating ED and ICU physicians and the uncommon patient that is transferred initially to a ward bed should receive timely attention by nursing, respiratory-care, and consultation staff.
Conclusions

SA patients represent the most critical and challenging of all asthmatics. SA is a medical emergency that requires timely evaluation and initiation of therapy by pre-hospital and ED staff. Morbidity and mortality of patients who progress to respiratory failure requiring intubation and ventilator support remains significant. Debate whether SA represents a separate pathophysiologic entity in the spectrum of asthma is likely to continue until further understanding of this disease is gained. Until that time, therapy in the ED will center on β-agonists, bronchodilators, parenteral steroids, consideration of adjunctive treatments, and critical airway skills in those requiring assisted ventilation. Appropriate coordinated care between the ED and the ICU team is important to prevent unnecessary errors in the triage or lapses in care. Though SA patients are critically ill, well-orchestrated care can be wholly satisfying for the patient and the treating team of physicians, nurses, and respiratory therapists.

References

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