4 Management of Status Asthmaticus in Critically Ill Children

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Introduction

Asthma remains as one of the most common chronic, noncommunicable diseases in childhood, generally associated with variable respiratory symptoms from variable limitations in airflow. Asthma manifests as the consequence of complex genetic and environmental interactions, presenting with extreme heterogeneity in the clinical signs and symptoms, their frequency and severity, as well as significant heterogeneity in the types and extent of airway inflammation and airway remodeling over time. Historically, the prevalence of asthma in children (and adults) has been under recognized. Our understanding has improved in the last 40 years through survey-based prevalence studies that estimate asthma affects as many as 334 million people worldwide [1, 2]. With the current global prevalence estimated at 4.85%, asthma remains the 14th leading cause of years lived with disability (YLDs) [1]. The Global Asthma Network formed in 2012 plans to continuously monitor the global burden of asthma to better understand how it is changing, improve diagnosis, and reduce risk factors for its occurrence [3].

Asthma prevalence has generally remained the highest in developed countries (e.g., 21% in Australia) and lowest in developing countries (e.g., 0.2% in China) [4], although its prevalence is increasing in developing countries as they modernize and may be substantially underestimated in some resource-poor countries. Children show greater variability in asthma symptoms, in early childhood ranging from 2.8% in Indonesia to 37.6% in Costa Rica, and in early adolescence, ranging from 3.4% in Albania to 31.2% in Isle of Man [2, 5]. The CDC reported increases in the prevalence of asthma among US children from 5.8% in 2003 to 9.6% in 2007, currently affecting more than seven million US children [6]. Asthma prevalence is much higher in boys than in girls, but it changes around puberty such that prevalence is almost 20% higher in adult women than in men [7]. This pattern is likely related to gender differences in airway development – male children have smaller airways relative to lung size as compared to female children, while adolescent females have smaller airways relative to lung size as compared to adolescent males. Therefore, remission in childhood asthma is more likely among boys than in girls, except in patients with severe asthma or those with sensitization to fur [8]. Gender differences in obesity, cigarette smoking, or environmental exposures may also increase the prevalence of asthma [9].

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Asthma exacerbations not only produce frequent symptoms and increase medical resource utilization but are also associated with substantial disability, impaired quality of life, and avoidable deaths in children. Surveys from the International Study of Asthma and Allergies in Childhood (ISAAC) found positive correlations between the prevalence of wheezing in childhood (6–7 years of age) with national mortality rates ($r = 0.32$, $p < 0.05$) and hospital admission rates ($r = 0.73$, $p = 0.003$) among 13–14-year-old children, whereas *severe* wheezing at 6–7 years of age had stronger correlations with mortality at 13–14 years ($r = 0.42$, $p < 0.025$) [10]. Given the strong positive correlations between asthma symptom prevalence, hospital admissions, and mortality, it is not surprising that status asthmaticus is a leading source of critical illness in children and the most common medical emergency [6]. While evaluating these patients, clinicians must maintain a high index of suspicion and greater vigilance, since 13% of patients with near-fatal asthma present with their first-ever attack of status asthmaticus [11]. Among those with a previous history of asthma, 63% had no prior hospital admissions for asthma in the year preceding their presentation with near-fatal status asthmaticus, and 86% had no prior admissions to the pediatric intensive care unit (PICU) [11].

Pathophysiology: A Brief Précis

The National Institutes of Health (NIH) define asthma as a chronic inflammatory disorder of airways in which many cells including mast cells and eosinophils contribute to symptoms associated with variable airflow obstruction that is reversible either spontaneously or with medications [12]. Although the detailed immunology of asthma is beyond the scope of this chapter, clinicians must recognize that eosinophilic asthma may include patients with allergic and non-allergic eosinophilic inflammation, whereas non-eosinophilic asthma may include patients with paucigranulocytic and neutrophilic inflammation. Some patients may also present with a mixed granulocytic inflammation, carrying features of eosinophilic asthma and non-eosinophilic asthma (see recent reviews [13, 14]).

The key pathophysiologic feature of status asthmaticus is inflammation of small airways leading to increased airway resistance and dramatically extending the time required for full exhalation. Residual air remains "trapped" in alveoli at the time of the next inhalation, thus alveolar volumes may increase progressively with each breath and lead to increased end-alveolar and intrathoracic pressures. Consequently, the end-expiratory alveolar pressures are often two- to threefold higher than normal, increasing the required changes in pressure to reach the negative alveolar pressures necessary to generate airflow by the patient [15, 16]. For example, continuous positive airway pressure (CPAP) functionally normalizes this gradient and has been shown to reduce the respiratory load in the spontaneously breathing asthma patient [15]. Although changes in the respiratory system mainly reduce dynamic lung compliance due to increased airway resistance [17, 18], atelectasis develops around the overdistended alveoli to reduce static lung compliance as well. Greater resistance to airflow increases work of breathing, presenting initially as increased distress and expiratory effort. Later, worsening lung hyperinflation limits full diaphragmatic relaxation, thus reducing the efficiency of diaphragmatic function and calling into play the use of accessory respiratory muscles with increased work of breathing during inhalation and exhalation [19, 20].

The progressively increasing lung volumes seen in status asthmaticus can also affect cardiac ventricular function. Alveolar hyperinflation-associated airway obstruction, increasing micro-atelectasis, hypoxia-induced pulmonary vasoconstriction in atelectatic areas, β-agonist and/or dehydration-induced metabolic acidosis, and respiratory acidosis from impending respiratory failure all contribute to increases in right ventricular afterload. Moreover, spontaneously breathing patients during an asthma exacerbation can have peak inspiratory pressures as extreme as -35 cm H_2O [21]. This negative intrathoracic

pressure directly accentuates left ventricular afterload, with increasing likelihood of pulmonary edema and worsening gas exchange [22]. *Pulsus paradoxus* is a physiological manifestation of the exaggerated variation in systolic blood pressure associated with high intrathoracic pressures during inspiration [23, 24]. Therapy with β_2-agonists increases heart rate, contributing to progressively diminished ventricular filling time and consequently lower cardiac output. Switching from negative pressure ventilation to positive-pressure ventilation in patients who require intubation is likely to result in acute hypotension secondary to decreased venous return [22]. In addition, many of the sedative agents used for intubation also have vasodilatory and myocardial depressant effects, particularly among children, further affecting cardiac output and increasing the risks of cardiac arrest during or immediately after tracheal intubation.

Clinical Assessment

Patients suffering from status asthmaticus require rapid and frequent assessments, watching for signs of respiratory distress or impending respiratory failure. A focused approach both for positive and negative findings on the physical exam will ensure that children are treated with the required escalation of care as necessary. The level of alertness is particularly important in their neurological assessment, since lethargy may be due to fatigue or due to hypercarbia, and this observation may be confused with their natural sleep cycle during nighttime hours. Children who are lethargic due to fatigue or hypercarbia very likely have impending respiratory failure and warrant close attention in the PICU.

Children may also exhibit profoundly increased work of breathing as demonstrated with retractions or paradoxical thoracoabdominal breathing. A prompt evaluation of the patients' general appearance, airway patency, effectiveness of respiratory effort (including both inhalation and exhalation), adventitious breath sounds, and adequacy of circulation form the foundations of their clinical assessment. The most vital aspect of clinical assessment in asthmatic patients is serial physical exams by bedside clinicians at least hourly or every couple of hours to appreciate changes in their clinical trajectory.

Presenting symptoms usually include a history of cough, increased respiratory rate, increased work of breathing and disordered breathing patterns. Auscultation of the chest will demonstrate turbulent airflow with diffuse wheezing and a prolonged expiratory phase due to air trapping by their hyper-reactive small bronchial airways. Children with mild-to-moderate status asthmaticus present with wheezing during the expiratory phase only, those with moderate-to-severe status asthmaticus manifest wheezing during both inhalation and exhalation phases, and patients with critical status asthmaticus may present with a "silent chest" since wheezing is only appreciated if there is adequate airflow in the small bronchi [24]. All patients with status asthmaticus must be monitored closely in a pediatric ICU, with serial physical exams being supplemented with continuous cardiorespiratory monitoring and intermittent arterial blood gas sampling.

Diagnostic Evaluation

The evaluation of children with status asthmaticus is mostly based on clinical findings, biplanar chest radiographs, an arterial blood gas to evaluate gas exchange, a complete hemogram to exclude eosinophilia or other abnormalities, tests to exclude viral or atypical pneumonitis, and a basic metabolic profile to rule out dehydration or β_2-agonist-induced hypokalemia. More advanced testing is rarely required but may be indicated to exclude parasitic, toxic, or environmental triggers for status asthmaticus. Bedside asthma scores may facilitate communication between members of the pediatric ICU team, though most clinical asthma scores lack sufficient validation and are limited by the subjective evaluation of the variables comprising these scores [25, 26].

Fiberoptic Bronchoscopy

Bronchoscopy may be indicated to rule out foreign body aspiration and bilateral bronchomalacia or diffuse bacterial bronchitis, but the vast majority of patients can be managed without bronchoscopy. The risks versus benefits of bronchoscopy must be weighed carefully because instrumenting hyper-reactive and inflamed airways may lead to significant clinical deterioration, life-threatening hypoxemia, and cardiac arrest. In a single-center case series of 44 ventilated asthmatic patients, bronchoscopies revealed thick mucus plugs, secretions, and bronchial casts. Saline lavage of obstructive airways was well tolerated with demonstrable improvements in pulmonary compliance, reduced duration of mechanical ventilation, but no differences in the PICU length of stay [27]. Occasionally, fiberoptic bronchoscopy can be used to instill human recombinant DNase or other mucolytic agents into plugged airways, but this practice is not routine at most centers [28].

Xenon Ventilation Computed Tomography

Recent studies have examined the usefulness of xenon ventilation computed tomography in asthmatic patients [29]. This technique is a relatively new method to evaluate pulmonary functions and ventilation defects in asthmatic patients by examining alteration in xenon trapping following administration of methacholine and salbutamol [30]. Although this testing may potentially unmask airway abnormalities contributing to ventilation-perfusion mismatch, its application to pediatric patients with status asthmaticus remains controversial. The potential usage of xenon is considered relatively benign since it is nonreactive in the body and disposed of from the lungs without any systemic effects in critically ill patients [29, 31].

Exhaled Nitric Oxide

Inhaled nitric oxide is not indicated for the treatment of status asthmaticus [32], but measurements of exhaled nitric oxide may estimate the extent of inflammatory airways in asthmatic patients. An increase in exhaled nitric oxide is known to accompany eosinophilic inflammation [32]. Although measured concentrations of exhaled nitric oxide may help gage the pathophysiologic trajectory of patients with status asthmaticus, the accuracy and prognostic value of this investigational test has not been established in clinical studies as of yet [33]. Exhaled nitric oxide is increased in steroid-naïve asthmatic subjects during status asthmaticus, although this returns to baseline after appropriate anti-inflammatory treatment is administered [33]. Additional studies are needed before testing for exhaled nitric oxide demonstrates its effectiveness to bedside clinicians.

Case Scenario

An 11-year-old female with a history of moderate-to-severe asthma presents to a local emergency department with wheezing progressing to severe respiratory distress over the previous 24 h. Her respiratory rate is 40 breaths per min, her heart rate is 125 breaths per minute, and her oxygen saturation as determined by pulse oximetry is 96%. She receives three consecutive albuterol nebulization treatments (2.5 mg each), one nebulization treatment with ipratropium bromide (500mcg), and one dose of intravenous methylprednisolone (1 mg/kg). One hour later, she is assessed by a pediatric intern, who notes that her vital signs and her respiratory effort have not improved, and persistent prolonged expiration and wheezing are apparent on auscultation of her chest. After this assessment, the pediatric intern asked her attending physician what the next best step in the management would be.

Pharmacological Management

In a study including 13,552 children critically ill with asthma, marked clinical variability in pharmacological management and mechanical support was noted (21% were treated in Collaborative Pediatric Critical Care Research Network (CPCCRN) PICUs, 79% were treated in non-CPCCRN PICUs). Wide variations occurred in the frequency of medication use in CPCCRN centers – ipratropium bromide 41–84% patients, terbutaline 11–74% patients, magnesium 23–64% patients, and methylxanthines 0–46% patients – implying a lack of consensus with regard to the pharmacological management of children with status asthmaticus [34]. We present the following sections recognizing that different clinicians may choose different elements from this menu based on the clinical features of specific patients, local institutional practices, resource availability, and personal preference. We have also summarized a suggested algorithmic approach to the management of status asthmaticus in Fig. 4.1.

Inhaled β-Adrenergic Agonists

β-Agonists cause smooth muscle relaxation by activating the β_2-adrenergic receptor and increasing cyclic adenosine monophosphate (cAMP) concentrations in smooth muscle cells, which inhibits the release of calcium ion from intracellular stores and reduces the membrane calcium entry and its intracellular sequestration [35].

Albuterol is a racemic mixture of R-albuterol and S-albuterol. The R-enantiomer is pharmacologically active, and the S-enantiomer is inactive. Levalbuterol is the pure R-enantiomer available as a preservative-free solution. In comparative trials, the use of equivalent doses of levalbuterol was not superior to albuterol [36]. Albuterol remains the drug of choice for treatment of status asthmaticus. Depending on different variables, approximately 10–20% of the albuterol dose will reach the lungs. The National Asthma Expert Panel recommends nebulized albuterol doses for asthma exacerbations in children younger than 12 years of 0.15 mg/kg (minimum dose 2.5 mg)

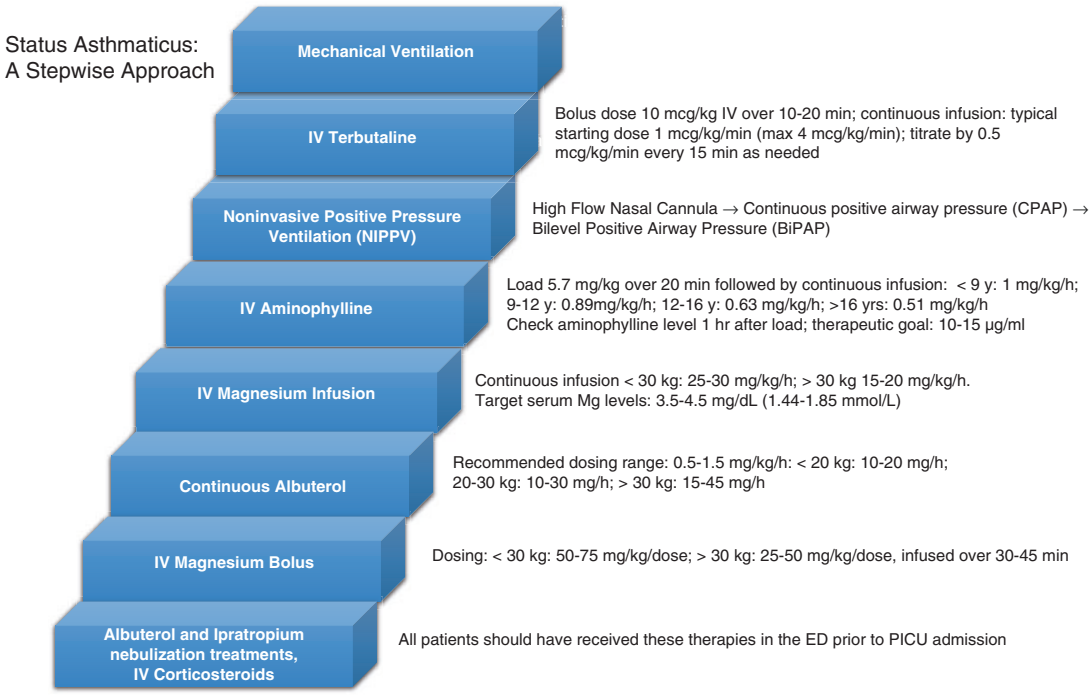

Fig. 4.1 An algorithmic approach to status asthmaticus

every 20 min for three doses, followed by 0.15–0.3 mg/kg (maximum 10 mg) every 1–4 h.

For patients not showing clinical improvement, continuous albuterol nebulization at 0.15–0.5 mg/kg/h is recommended. Larger doses, up to 30 mg/h, can be used for critical or near-fatal asthma. Existing evidence supports the use of continuous albuterol nebulization in pediatric patients with status asthmaticus and impending respiratory failure, leading to faster clinical improvement and decreased duration of hospital stay when compared with intermittent albuterol nebulization and decreased hospitalization rate when continuous albuterol regimen is used in the emergency department. Additionally, continuous albuterol treatment at these doses is safe and well tolerated [37]. Reported doses of albuterol used in pediatric patients often exceed the expert panel recommendations [38]. Data on the effectiveness and safety of these higher doses compared to traditional recommended doses are sorely needed.

Anticholinergic Agents

The parasympathetic nervous system contributes to airway resistance via acetylcholine-mediated airway smooth muscle contraction; regulation of mucus secretion, ciliary beat frequency, and mucus clearance via mucosal glands and epithelial cells; vasodilation by smooth muscle relaxation in blood vessels; and modulation of inflammation [39]. There are five subtypes of muscarinic receptors (M1-M5), which belong to the larger group of G protein-coupled receptors. Acetylcholine stimulates these receptors. M3-receptors located on the airway smooth muscle mediate bronchoconstriction, and M3-receptors located on the submucosal cells regulate glandular secretion. M2 muscarinic receptors are also on the bronchial smooth muscle, which indirectly cause smooth muscle contraction by reducing β-adrenoceptor-mediated relaxation through inhibition of adenylate cyclase. Blockade of both M2 and M3-receptors on airway smooth muscle should therefore inhibit bronchoconstriction.

On the other hand, parasympathetic nerves supplying the lungs also have muscarinic receptors. M2-receptors on postganglionic parasympathetic nerves limit acetylcholine release by a negative feedback mechanism. Thus, blocking the M2-receptors on parasympathetic nerves with muscarinic antagonist will increase acetylcholine release and potentiate vagally induced bronchoconstriction. Parasympathetic neuronal M2-receptors are susceptible to viral infections and exposure to ozone (which decreases their function) and are less functional in patients with asthma. The mechanism for this latter reduction in neuronal M2-receptor functions in multifactorial and involves the downregulation of receptor expression and blockade by endogenous antagonists [40]. Anticholinergic drugs block M2 and M3 muscarinic receptors on the airway smooth muscle, glands, and nerves with similar affinity, thereby impairing smooth muscle contraction and decreasing airway secretions while simultaneously augmenting acetylcholine release, supporting the rationale to develop selective M3-receptors medications [41].

Ipratropium bromide is a synthetic quaternary ammonium derivative with an isopropyl group at the N-carbon atom of atropine that limits its systemic absorption. Inhaled ipratropium targets the muscarinic receptors in the bronchial airways without the systemic effects of atropine, such as tachycardia. The low oral absorption of ipratropium is beneficial, since up to 90% of an aerosolized dose may be swallowed. Ipratropium is a nonselective muscarinic receptor inhibitor, which produces bronchodilation by the inhibition of acetylcholine-mediated bronchospasm without affecting the mucociliary clearance. Ipratropium has no impact on intraocular pressure or pupillary size even when up to four times the recommended dose is used; nevertheless, it can produce prolonged pupillary dilatation when sprayed accidently into the eyes [42]. The half-life of ipratropium is 3–4 h, the onset of action is 15 min, peak effects occur at 1–2 h after administration, and duration of action is 4–6 h.

Early administration of three or more repeated doses of inhaled ipratropium with β_2-agonists has been shown to decrease the rate of hospital

admission for pediatric and adult patients with moderate-to-severe status asthmaticus by 30% [43]. Improvements in spirometry and clinical scores have also occurred with the use of multi-dose protocols, without increasing side effects [43]. A double-blind, randomized study in adults with severe asthma found that those receiving ipratropium for 36 h or longer were discharged home earlier than those that receiving ipratropium for 12 h [44]. In another study, patients using fenoterol/ipratropium versus fenoterol or ipratropium alone were found to have greater bronchodilator effects in children with acute asthma [45].

Intermittent ipratropium therapy is recommended in hospitalized patients with acute asthma because of its high safety profile and documented beneficial impact [46]. The effect of ipratropium is dose-dependent, with the recommended dose range from 250 to 500 mcg [47]. In one case report, a 13-year-old patient with status asthmaticus refractory to β_2-agonist treatments showed improvement after starting continuous ipratropium at 1000 mcg per hour [48]. Despite this report, however, continuous ipratropium therapy has not been systematically investigated.

Anti-inflammatory Drugs

Corticosteroids are a cornerstone for both acute and long-term asthma management, as airway edema and inflammation are the most prominent pathological features of the disease. Indeed, use of systemic corticosteroids to treat status asthmaticus is not controversial and will therefore be discussed briefly. Methylprednisolone, dexamethasone, prednisone, and hydrocortisone are the traditional corticosteroids used for critically ill patients, but they differ in glucocorticoid potency, duration of onset, and mode of administration. For patients with mild-to-moderate asthma exacerbations, oral prednisone is the most common therapy prescribed. Oral dexamethasone has also been used to treat patients with asthma in the acute care setting. Dexamethasone is a long-acting corticosteroid that has traditionally been used for children with croup. In one study of patients 2–18 years of age who presented to the emergency department with mild-to-moderate acute asthma exacerbations, Qureshi et al. evaluated the efficacy of oral prednisone versus oral dexamethasone [49]. Compared to oral prednisone, oral dexamethasone did show similar efficacy with improved compliance and fewer side effects when compared with oral prednisolone [49]. The authors hypothesized that the improved compliance was observed because dexamethasone is more palatable than oral prednisone with shorter prescription duration. Hydrocortisone, a short-acting corticosteroid with relatively less anti-inflammatory potency than the other corticosteroids, is not commonly used for acute asthma exacerbations.

Corticosteroids that are highly potent with a fast onset are the most desirable for patients with status asthmaticus. Systemic corticosteroids are preferred and have also been shown to be superior to inhaled corticosteroids for status asthmaticus, with reduced need for hospitalization [50]. Intravenous methylprednisolone is the most commonly recommended due to its potent glucocorticoid effects and limited mineralocorticoid effects [51]. Patients presenting with status asthmaticus should receive intravenous methylprednisolone 2 mg/kg (maximum dose 80 mg) early in the course of their management, as its onset of action occurs approximately 4 h after administration. There are no significant added benefits from systemic corticosteroids at doses above 80 mg/day or 2 mg/kg/day with regards to pulmonary function, rate of hospital admission, or hospital length of stay [23].

Magnesium

Magnesium sulfate acts in the airway by blocking voltage-sensitive calcium channels, inhibiting calcium uptake and calcium-myosin interactions, thus producing smooth muscle relaxation [52]. Magnesium also stabilizes T-cells and inhibits mast cell degranulation, consequently decreasing histamine release and inflammatory mediators. Other mechanisms of action include inhibition of acetylcholine release by the cholinergic motor

terminals and stimulation of nitric oxide and prostacyclin production. When intravenous magnesium sulfate is added to β_2-agonists and systemic corticosteroids, it improves pulmonary function in children and adults and reduces hospital admissions by 30% in children and in a lesser degree in adults [53].

Magnesium has a rapid onset of action and its duration of action is limited by renal clearance. As serum magnesium concentrations increase, renal excretion of magnesium increases linearly, potential hindering achievement of goal serum concentrations. Specifically, serum magnesium concentrations of up to 4 mg/dL are thought to be required for airway smooth muscle relaxation. In a cohort study of children with status asthmaticus, using continuous magnesium infusions at 40 mg/kg/h for 4 h after a loading dose of 50–75 mg/kg was safe and attained magnesium levels of 4.4 mg/dL at the end of the infusion [54]. Pediatric patients receiving magnesium sulfate in this study improved clinically, with reductions in tachycardia and tachypnea. The optimal dose of magnesium sulfate is currently unclear, with recommended dose ranges of 25–100 mg/kg to a maximal dose of 2,000 mg, independent of weight. In obese patients, magnesium dose should be based on their ideal body weight. We recommend an initial bolus dose of 50–75 mg/kg for children weighing <30 kg and 25–50 mg/kg for those weighing >30 kg, infused over a period of 30–45 minutes to improve acute respiratory symptoms and avoid hypotension. In cases of life-threatening status asthmaticus refractory to standard treatment, a continuous infusion of 25–30 mg/kg/h for children <30 kg and 15–20 mg/kg/h for children weighing >30 kg, up to a maximum dose of 40 mg/kg/h can be added. Titration to the desired clinical effect should be based on target serum magnesium concentrations of 3.5–4.5 mg/dL and tolerability [55]. On the other hand, there is limited evidence that intravenous magnesium is beneficial in asthma exacerbations of less severity (i.e., moderate-to-severe asthma presentations) [56].

Nebulized inhaled magnesium sulfate has also been trialed as a therapeutic agent for asthma exacerbations. In a systematic review study including adult and pediatric patients, inhaled magnesium has shown some clinical benefit in patients with acute severe asthma attacks with no apparent serious adverse effects [57]. In another study containing adult asthma patients, treatment with nebulized magnesium sulfate improved pulmonary functions and reduced hospital admissions in adults by 37% [53]. In contrast, a study of pediatric patients with moderate-to-severe asthma using 800 mg of nebulized magnesium failed to reduce their time to discharge [58]. Similarly, a recent Cochrane review reported minimal clinical improvement and no reduction in hospital admissions when nebulized magnesium was used concomitantly with β_2-agonists and ipratropium therapy [59].

In conclusion, intravenous magnesium sulfate should be used in children, especially those with life-threatening critical asthma and those not responding to initial treatments, with low risk for severe adverse effects. Nebulized inhaled magnesium therapy, however, cannot currently be recommended.

Methylxanthine Drugs

The most commonly used methylxanthine in acute asthma exacerbation is theophylline. Theophylline brings relief to asthmatic patients due to its direct bronchodilator effect [23]. Parenteral form of theophylline is aminophylline, which is a 2:1 complex of theophylline and ethylenediamine (aminophylline is converted to theophylline systemically, such that 1 mg aminophylline = 0.8 mg theophylline). Aminophylline is FDA approved as an adjunctive treatment for acute asthma exacerbations in all age groups, including children older than 1 year.

Theophylline pharmacokinetics are age-dependent, which affects its pediatric dosing recommendations. The elimination half-life of theophylline gradually decreases during the first year of life from ~ 24 h in term neonates to between 2 and 10 h (mean 4 hs) in children 1 to 9 years old and between 3 and 16 h (mean 8 h) in

adults [60]. Theophylline's primary actions are dose-dependent, as lower serum concentrations result in anti-inflammatory and immunomodulatory effects, whereas higher serum concentrations show greater bronchodilator effects [61]. Due to potential toxicity, serum theophylline concentrations should be followed at least every 12 h, and repeated bolus doses or infusion rates should be adjusted based on the target steady-state serum concentrations, with a traditional goal range of 10–15 μ/mL. Obese patients should have their ideal body weight used for dosage calculation [23]. Theophylline dosing is summarized in Fig. 4.1.

In a prospective, randomized, controlled trial by Ream et al. published in 2001, 47 children admitted to a pediatric ICU with status asthmaticus receiving traditional β-agonist, anticholinergic, and corticosteroid therapy were randomized to receive IV theophylline or placebo [62]. Twenty-three patients who received theophylline were compared with 24 controls, with cohorts having similar clinical asthma scores (i.e., Wood-Downes score [63]) prior to study enrollment. Faster recovery times (defined by clinical asthma scores ≤ 3) were noted in both non-intubated and intubated patients receiving theophylline as compared to controls – 19 ± 3 h versus 31 ± 5 h for non-intubated patients and 66 ± 10 h versus 191 ± 33 h for intubated patients. Four years later, Wheeler and coworkers examined the effects of intravenous theophylline and terbutaline in a randomized controlled trial in 36 patients with status asthmaticus receiving traditional β-agonist and corticosteroid therapy [64]. More specifically, they randomized patients to receive adjunctive therapy with intravenous theophylline plus placebo, intravenous terbutaline plus placebo, or intravenous theophylline plus terbutaline. The authors observed no differences in clinical asthma score over time, length of pediatric intensive care unit stay, or incidence of adverse events between the three groups, with the exception of a higher incidence of nausea in children who received both theophylline and terbutaline. Importantly, in a cost analysis that included the cost of both drugs and the cost of theophylline levels, median hospital cost was significantly less in patients who received only theophylline: $280 US dollars compared to ~$4000 in each of the other two cohorts.

Prior to these two small but important trials, several studies were published suggesting lack of benefit from theophylline therapy for patients with acute asthma exacerbations. Most of the patients in these studies however were not critically ill [65–68]. Recently, a meta-analysis of 52 study arms from 42 trials involving theophylline, some of which included adults and others included children, involving intravenous theophylline concluded that, when given with bronchodilators and corticosteroids, theophylline can be helpful and represents a cost-effective and safe choice for patients with status asthmaticus [69]. We recommend initiation of intravenous aminophylline in patients who are not improving or worsening despite inhaled β-agonists, systemic corticosteroids, ipratropium bromide, and intravenous magnesium.

As previously concluded by Mahemuti et al. given the low cost of theophylline, and its similar efficacy and rate of side effects compared with other drugs, we suggest that theophylline, when given with bronchodilators and corticosteroids, is a cost-effective and safe choice for acute asthma exacerbations [69].

Intravenous Albuterol

One study examined the advantage of combining intravenous albuterol (salbutamol) to inhaled albuterol in children during the initial management of severe acute asthma in the emergency department. Children receiving a single dose of 15 μg/kg intravenous albuterol over 10 min with inhaled albuterol had a shorter recovery time and earlier discharge compared with a group of children who received inhaled albuterol alone. The intravenous albuterol cohort had increased incidence of tremors, but no other notable side effects [70]. These data support the use of a single-dose intravenous albuterol in addition to inhaled albuterol in the emergency department in children with severe asthma.

Intravenous Terbutaline

Use of intravenous albuterol in contemporary pediatric ICU is rare. Rather, terbutaline is typically used as an intravenous β-agonist for children with status asthmaticus who are failing traditional therapy. Terbutaline can be given as a subcutaneous dose of 10 mcg/kg, with a maximum dose of 250 mcg, and can be repeated every 20 min for a total of 3 doses. The recommended intravenous loading dose is 10 mcg/kg over 10–20 min, followed by continuous infusions of 0.1–10 mcg/kg/min. The usual starting dose is 1 mcg/kg/min, with an average maximum dose of ~4 mcg/kg/min [71]. Frequently reported side effects are tachycardia, arrhythmias, diastolic hypotension, tremors, and hypokalemia (which results from upregulation of sodium-potassium pumps on cell membranes, resulting in shifting of potassium from extracellular to intracellular space [71]).

The postulated failure of inhaled albuterol to enter through constricted airways led to the recommendation for intravenous β_2-adrenergic agonists in children with severe asthma exacerbation. Regardless of this rationale, there is little evidence showing clear benefits to support the use of intravenous β_2-agonists as a substitute for or in addition to inhaled β_2-agonists. One retrospective study found that early administration of intravenous terbutaline in the emergency department might decrease acute respiratory failure and the need for mechanical respiratory support in pediatric patients [72]. On the other hand, a prospective, randomized, double-blind, placebo-controlled trial in pediatric patients with status asthmaticus found no differences between patients randomized to receiving terbutaline and those receiving placebo infusions in clinical asthma severity scores, need for continuous nebulized albuterol, or length of stay in the PICU. Additionally, more patients who had received terbutaline had elevated serum troponin levels at 12 and 24 h, suggesting possible cardiotoxicity, compared to those who received placebo [73]. Three different meta-analyses have also failed to show a clinical advantage with intravenousβ_2-agonists compared to other therapies for status asthmaticus [74–76]. Based on these data and the aforementioned work by Wheeler and colleagues [64], there is not sufficient evidence supporting routine use of intravenous β_2-agonists. On the other hand, because of the conflicting nature of the available data and the sound physiologic rationale for its use, we consider a trial of terbutaline in patient's refractory to standard therapy and at risk for progressing to fulminant respiratory failure and mechanical ventilation to be reasonable.

Anesthetic and Other Gases

Helium

Helium-oxygen (heliox) is a gaseous mixture commonly utilized for patients with airway obstruction because of its lower density as compared to oxygen alone or room air [77]. The lower density of inhaled gas improves flow through high-resistance airways by reducing the degree of turbulent flow. As gas flow becomes less turbulent in the affected airways, the flow velocity is reduced, and the flow pattern may transition from turbulent to more laminar. Additionally, heliox can improve removal of carbon dioxide (CO_2), as CO_2 will diffuse into heliox four times as rapidly than in oxygen or room air [24]. The reduction in turbulent airflow may also aid with the delivery of aerosolized medications into distal lung segments [24]. Heliox is most commonly applied as a mixture of at least 70% helium (i.e., 70% helium/30% oxygen, 75% helium/25% oxygen, etc.), with mixtures containing lower concentrations of helium being relatively ineffective at improving airflow.

Heliox has been recommended by some as a means of avoiding endotracheal intubation in patients with status asthmaticus [78–80]. Several pediatric studies examining the use of heliox for acute asthma exacerbations or status asthmaticus however have failed to demonstrate consistent benefits, including its use as a carrier for albuterol nebulization [81–84]. At most, heliox may improve clinical asthma scores, but it has not been associated with a reduced rate of

hospitalization or other important clinical outcomes [78, 85]. Its role in mechanically ventilated asthmatics is also likely limited. In a very recent prospective study of 13 adults with severe asthma or chronic obstructive pulmonary disease exacerbations requiring mechanical ventilation, use of heliox led to only modest reductions in peak inspiratory pressure and partial pressure of CO_2 measurements and had little effect indices of dynamic hyperinflation (e.g., plateau pressure and total positive end-expiratory pressure) [86].

Use of heliox therapy is costly, has limited utility in patients with hypoxemia, and can be technically difficult to provide, especially in mechanically ventilated patients [87]. Many ventilators are not equipped to deliver heliox safely [88], and for mechanical ventilators that are capable of administering heliox, delivery of the appropriate fractional oxygen component, volume measurements, and valve functioning can also be adversely affected [87]. Routine use of heliox for patients with status asthmaticus can therefore not be recommended, and its use in mechanically ventilated patients should be avoided. On the other hand, it may be useful in select patients, such as children with status asthmaticus without significant hypoxemia, though clinicians should be prepared for endotracheal intubation and intervene quickly if no improvement or clinical worsening is noted.

Isoflurane

Inhaled isoflurane, a gaseous anesthetic, has been used outside of the operating room in some centers for status asthmatics and other conditions. Isoflurane is a potent bronchodilator and particularly attractive as a therapy for status asthmaticus due to its rapid onset and absence of cumulative toxicity [89]. Trained anesthesiologists have used inhaled anesthetics successfully in pediatric patients with life-threatening asthma exacerbation with favorable outcomes [89–93]. Unfortunately, its use is technically challenging in many facilities because of limited air scavenging systems. Cost, variability in physician and nursing credentialing and comfort with this class of drugs, and the logistical issues of administering an inhaled anesthetic gas for long periods of time outside of the operating room setting have also prevented widespread use. If the capabilities to administer inhaled isoflurane are available, close monitoring including invasive arterial pressure measurement is mandatory, as observational studies have described frequent side effects, the most common of which is hypotension requiring vasoactive infusions (77%) [74]. Other reported side effects include arrhythmias, neurologic abnormalities, accumulation of inorganic fluoride, tolerance during therapy, and abstinence syndrome after discontinuation [89, 94, 95].

Respiratory Support

Oxygen Therapy

The goals of treatment as outlined by the National Asthma Education and Prevention Program (NAEPP) are to treat significant hypoxemia, reverse the airflow obstruction, and reduce the likelihood of future episodes [96]. Oxygen should undoubtedly be applied to treat hypoxemia, but high inspired oxygen concentrations are infrequently required for patients with status asthmatics. Thus, the need for higher inspired oxygen concentrations should raise concern for other respiratory insults, most important and life-threatening of which are pneumothoraces [97, 98].

High-Flow Nasal Cannula (HFNC)

High-flow nasal cannula is often used to prevent respiratory failure by generating positive airway pressure [99], particularly in patients with status asthmaticus [100]. HFNC can also serve as a delivery method for albuterol nebulization or metered-dose inhaler (MDI) therapy and leads to rapid improvements in blood gas and clinical parameters within 24 h [101]. Preliminary outcome studies reported that HFNC in status asthmaticus resulted in equal to greater efficacy of bronchodilator therapy, reduced work of

breathing, less tachycardia, and shorter ED times in children with status asthmaticus [101, 102]. Despite low-grade evidence specific to this population supporting this modality, HFNC as a safe and effective method of respiratory support for patients with acute asthma exacerbations is widely accepted and thus not controversial.

Noninvasive Positive-Pressure Ventilation (NIPPV)

For patients with acute asthma exacerbations, NIPPV aims to prevent collapse of airways during exhalation, reduce microatelectasis, and unload respiratory muscle work, thereby preventing respiratory fatigue. NIPPV has been reported to be feasible and clinically effective in improving symptoms in pediatric ICU patients with status asthmaticus when compared to standard therapy [103]. In a randomized crossover trial (N = 20), NIPPV for 2 h decreased work of breathing, respiratory rate, accessory muscle use, and dyspnea as compared with standard therapy [19]. Another randomized pilot study (N = 20) found that adding NIPPV to standard care reduced their clinical asthma scores, oxygen requirement, and respiratory rate compared to standard care alone [104].

Support for the use of NIPPV in acute asthma exacerbations has also been noted in two large registry studies. In a study from the PHIS database containing 13,552 PICU patients, use of NIPPV occurred 3–5% of children with asthma, and sites that used noninvasive ventilation more often appeared to have reduced rates of endotracheal intubation and mechanical ventilation [34]. Similarly, a study from the VPS database noted NIPPV use in 6% asthmatic patients, and PICU length of stay was lower in high-utilization centers [105]. These reports suggest the potential for NIPPV to become an important part of the management of status asthmaticus in pediatric patients. With more study, standardization and optimization of this mode of respiratory support in management pathways for this patient population should be prioritized. Currently, we support the use of NIPPV in children with status asthmaticus as a stop-gap measure to prevent worsening respiratory failure and avoid the potential complications of endotracheal intubation and mechanical ventilation [106, 107].

Tracheal Intubation

Observational studies report that 10–14% of children admitted to the PICU for asthma require invasive mechanical ventilation [34, 108, 109]. There is no standard protocol for when to intubate a child in status asthmaticus. In one study of 51 episodes of status asthmaticus, 41% were intubated for respiratory acidosis, 37% for clinical fatigue, and 22% for cardiopulmonary arrest [98]. While arterial or venous blood gas data can be helpful in deciding when to intubate an asthmatic, Newth and colleagues found that only 48% of patients with fatal or near-fatal status asthmaticus in a multicenter cohort from the CPCCRN (n = 260) collaborative had blood gas data prior to intubation, with an average partial pressure of carbon dioxide (pCO_2) of 52 mmHg [11]. Clinical intuition therefore seems to be the major driving force leading to intubation of children with status asthmaticus and respiratory failure. Specific indicators for intubation include exhaustion and fatigue despite maximal therapy, worsening mental status, refractory hypoxemia, increasing hypercapnia, hemodynamic instability, impending coma or apnea, increasing metabolic acidosis, or upper airway compromise. Importantly, practice varies widely across centers too, particularly between children's hospitals and community centers [97]. Children managed at community hospitals were 3.3 times more likely to be intubated despite similar severity of illness and with many children routinely not receiving standard asthma therapies like corticosteroids [110, 111].

The decision to intubate should not be taken lightly as severe asthmatics are at high risk for severe morbidity and mortality during intubation. Worsening status asthmaticus is characterized by dynamic alveolar hyperinflation with associated diffuse microatelectasis and pulmonary hyper-

tension, relative hypovolemia from dehydration, β-agonist-induced metabolic acidosis, hypercarbia from respiratory muscle fatigue, reduced left ventricular filling from tachycardia, and increased left ventricular afterload from negative inspiratory intrathoracic pressures [21]. Additional concerns include instrumenting the hyper-reactive airway for intubation, which accentuates respiratory obstruction; analgesic sedative drugs used for intubation, which can cause systemic vasodilation and reduce myocardial contractility; transitioning to positive-pressure ventilation, which further reduces venous return; and the risk of barotrauma associated with mechanical ventilation and hyperinflated lungs [112].

Prior to intubation, efforts must be made to maximize management of status asthmaticus using bronchodilators, intravenous corticosteroids, magnesium, aminophylline, judicious correction of hypovolemia with intravenous fluids, and, if possible, a trial of noninvasive ventilation [97, 113–117]. Ketamine is the first choice for pre-intubation sedation because of its potentially advantageous bronchodilator and hemodynamic effects [118–121], but the use of adjunctive short-acting sedatives like midazolam, propofol, or dexmedetomidine can also be helpful. Strategies for achieving sedation and analgesia must take into account their systemic vasodilatory, respiratory depressant, myocardial contractility, and other side effects [122]. Advanced airway skills are essential, and neuromuscular blockade is desirable to minimize the number of attempts required for successful intubation [123].

Following intubation, chest rise and auscultation of breath sounds may be difficult to elicit in the setting of severe airway obstruction. For this reason, in-line end-tidal CO_2 monitoring is essential to the verify correct placement of the endotracheal tube [124–127]. Manual ventilation following intubation must limit the tidal volumes and respiratory rates used, to avoid accentuating barotrauma and allowing complete exhalation between breaths. Attempts to normalize pH by correcting hypercapnia are unnecessary and potentially harmful [128]. Correction of hypoxemia and permissive hypercapnia (i.e., pH 7.2–7.3) are reasonable goals. Close bedside observation of all intubated asthmatic patients is required for the first few hours after initiating mechanical ventilation, since the risk of life-threatening complications and unanticipated hemodynamic effects is highest in that period.

Mechanical Ventilation

Although there are no absolute criteria for mechanical ventilation, clinicians should consider stepwise escalation in support from inhaled therapies to intravenous therapies and noninvasive mechanical support and, ultimately, culminating in invasive mechanical ventilation for refractory or rapidly progressive respiratory failure. Mechanical ventilation, either noninvasive or invasive, is generally designed to overcome the dramatically increased work of breathing inherent to status asthmaticus. Most clinicians agree that a low respiratory rate, long expiratory time ventilator strategy is optimal to permit CO_2 clearance. The amount of positive end-expiratory pressure (PEEP) to set on the ventilator, on the other hand, is controversial [129–133]. After initiation of mechanical ventilation, total $PEEP_{tot}$ should be measured using an expiratory pause maneuver [134]. $PEEP_{tot}$ represents the sum of the PEEP set by the ventilator and the PEEP generated by air trapping, typically referred to as auto-PEEP. While some clinicians support measuring auto-PEEP to regulate the ventilator PEEP in order to actually reduce alveolar hyperinflation and also recruit areas of atelectasis [133], others do not support this concept and recommend using minimal PEEP [112, 124]. The controversy surrounding the practice of higher PEEP settings in status asthmaticus is primarily due to reports of paradoxical responses that lead to undesirable increases in FRC in some patients with status asthmaticus [129–131]. Interpretation of the data generated from these studies however has varied, and a consensus on optimal PEEP strategy for status asthmaticus has yet to be reached [132]. We recommend careful titration of ventilator PEEP close to the $PEEP_{tot}$, which attempts to maintain airway patency during expiration. Patients must be monitored closely, and ventilator

PEEP should be carefully weaned as clinical condition improves.

The optimal mode of ventilation for status asthmaticus is also not clear [6]. Regardless of mode of ventilation, goals while on mechanical ventilation should include minimizing dynamic hyperinflation and air trapping, reduction in atelectasis, and implementation of permissive hypercapnia to avoid ventilator-induced lung injury and air-leak complications [119]. Lung protective strategies from close monitoring of the converse dependent variables can be used with either volume-targeted or pressure-targeted modes. For instance, when using a volume-targeted mode, inspiratory plateau pressures measured via inspiratory pause maneuvers while the patient is neuromuscularly blocked must be measured regularly, as high inspiratory plateau pressures (>30 mH_2O) can cause life-threatening pneumothoraces [135]. For patients on pressure-targeted modes of mechanical ventilation, tidal volumes must be followed closely and set inspiratory pressures reduced as airway resistance improves. We most commonly utilize pressure-regulated volume control ventilation for patients with status asthmaticus, which has the theoretical advantages of offering the high initial inspiratory flow associated with pressure-targeted modes and the ability to set and limit tidal volumes associated with volume-targeted modes of ventilation.

Case Scenario Resolution

After receiving three consecutive albuterol nebulization treatments (2.5 mg each), one nebulization treatment with ipratropium bromide (500mcg), and one dose of intravenous methylprednisolone (1 mg/kg) in the emergency department without improvement, continuous inhaled albuterol therapy is initiated at 20 mg/hr (~0.5 mg/hr), and she is admitted to the pediatric intensive care unit for continuous monitoring, hourly vital signs and hourly clinical respiratory scores (CRS). Upon arrival at the unit, her physical exam continued to be concerning, with a prolonged expiratory phase with wheezing appreciated in all lung fields and suprasternal and subcostal retractions. She had difficulty in taking in full sentences. Vital signs were remarkable for heart rate 155 beats/min, respiratory rate 50 breaths per minute, and blood pressure 90/45 mmHg.

Intravenous magnesium of 25 mg/kg is administered over 30 minutes, and a magnesium infusion is started at 15 mg/kg/hr. Continuous inhaled albuterol, inhaled ipratropium bromide every 8 h, and intravenous methylprednisolone 1 mg/kg every 6 h also continue to be administered after arrival to the PICU. One hour later, after reassessment and no change in CRS, an intravenous theophylline bolus of 5.7 mg/kg/hr is administered, and an infusion is initiated at 0.89 mg/kg/hr. Noninvasive positive airway pressure is also applied.

Over the next 12 h, she slowly improves and is transitioned to high-flow nasal cannula. A recommended stepwise algorithm for the management of status asthmaticus is included in Fig. 4.1.

Take-Home Messages

- All patients with status asthmaticus should be immediately placed on continuous cardiorespiratory monitoring with serial clinical assessments to determine the need for admission to the intensive care unit.
- Inhaled β-agonist therapy and intravenous corticosteroid therapy are the mainstays of treatment for status asthmaticus.
- Intermittent nebulization of ipratropium bromide is also recommended as a first-line therapy for pediatric patients admitted with status asthmaticus.
- Intravenous magnesium sulfate and aminophylline represent relatively low

cost and safe "second-tier" therapies for patients with refractory status asthmaticus.

- Routine use of intravenous terbutaline or heliox gas mixture cannot be recommended, but these therapies may have a role in preventing intubation and mechanical ventilation in select patients.
- Compelling but not conclusive evidence exists to support the use of noninvasive positive pressure for children with status asthmaticus.

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