Curr Emerg Hosp Med Rep (2015) 3:144–153
DOI 10.1007/s40138-015-0081-y

ASTHMA (G. VOLTURO, SECTION EDITOR)

Management of Status Asthmaticus

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Published online: 27 June 2015

Abstract Status asthmaticus (SA) is a severe and life-threatening asthma exacerbation that requires aggressive treatment. First-line treatment entails continuous treatment of nebulized short-acting β-receptor agonists and intravenous (IV) steroid administration. This review article focuses on the current literature supporting the use of these medications as well as other treatment modalities such as inhaled anticholinergics, parenteral β-agonists, IV magnesium, and IV ketamine. We also explore the utility methylxanthines, volatile anesthetics, nitric oxide, antibiotics, IV fluids, and mucolytics in treating SA. Finally, we explore the data pertaining to the use of Heliox, non-invasive positive pressure ventilation, and bronchoscopy, and discuss ventilator management for patients with SA requiring intubation.

Keywords Asthma · Status asthmaticus · Management · Severe asthma · Treatment

This article is part of the Topical Collection on *Asthma*.

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Introduction

Of the 22.2 million people with asthma in the United States, 1.8 million per year suffer an exacerbation requiring emergency department (ED) treatment, and 497,000 require hospitalization of which about 4,000 will die (0.8 %) [1]. Status Asthmaticus, also known as *severe acute asthma*, is an acute exacerbation of asthma which is recalcitrant to standard therapy [2] and carries a mortality of approximately 10 % [3].

Patients in SA have a spectrum of illness severity. End-tidal CO_2 ($EtCO_2$) monitoring failed to predict severity of illness in children [4] but extremely high or low measurements correlated with need for intubation, non-invasive positive pressure ventilation (NIPPV), ICU admission, and death in adults [5•]. Radiographic imaging of the chest rarely contributes actionable data [6]. Spontaneous pneumothorax may occur in up to 0.6 % of children with asthma exacerbation [7] and bedside ultrasonography has superior sensitivity (80 %) when compared to chest X-ray [8, 9•, 10, 11]. Arterial or venous blood gas analysis may be used to assess the degree of respiratory acidosis and carbon dioxide retention by evaluating pH and pCO_2; however, they should not replace clinical judgement.

This review focuses specifically on the management of status asthmaticus and assumes that standard resuscitative measures have been employed.

Management

First-Line Medical Therapy

The primary goal of the ED management is to ensure adequate oxygenation and ventilation; thus, oxygen should

be administered to all patients in status asthmaticus to keep their SpO_2 above 92 % [12]. Unlike COPD, oxygen administration does not decrease respiratory drive in patients with asthma [13].

Inhaled Short-Acting β-Receptor Agonists (SABA)

Inhaled short-acting β-receptor agonists (SABA) are the mainstay of therapy for SA in combination with steroids [14••, 15]. When a drug such as albuterol binds to the β2-receptor, an increase in cyclic AMP and activation of protein kinase A results in smooth muscle relaxation and bronchodilation [16]. Nebulized albuterol is superior to metered-dose inhaler (MDI) for patients in SA [17], and continuous therapy is superior to intermittent dosing [18] with no significant increase in adverse events [19, 20]. These findings were echoed by a Cochrane review for treatment of asthma exacerbation [15]. Furthermore, there is no benefit of administration of levalbuterol, an isomer of albuterol, when compared to racemic albuterol (RCT $n = 81$) [21]. Typical dosing ranges from 2.5 to 20 mg/h. The National Institute of Health (NIH) recommendation is up to 15 mg/h [14••], but doses as high as 150 mg/h have been shown to be safe and efficacious [22••]. In addition, nebulized racemic epinephrine is non-inferior to albuterol in a metanalysis of 6 studies [23]. There are also case reports of patients improving with racemic epinephrine who failed albuterol therapy [24].

Administration of β2-receptor agonists can lead to intrapulmonary shunting and transient hypoxemia which should be anticipated [25]. Other Adverse events of albuterol include elevated myocardial markers [26] and diastolic hypotension [27]. Ischemic EKG changes (ST depression) occur in approximately 8 % of patients [27]. All patients recovered uneventfully. Reversible Takotsubo cardiomyopathy has been reported in patients with SA treated with β-agonists [28, 29].

Hypokalemia due to intracellular potassium shifts as a consequence of cAMP-dependent activation of Na^+/K^+ ATPase [30] occurs in about 15 % pediatric SA patients treated with high-dose continuous albuterol and 35 % of adults with NIH-dose albuterol [3]. However, arrhythmias beyond sinus tachycardia and PVCs are rare [22]. At the NIH-dose of continuous albuterol, serum potassium changes by about −0.5 mEq/L after 2 h, only 2.5 % of patients fall below 3 mEq/L [31]. Potassium repletion should be reserved for symptomatic patients as a reverse shift will occur with discontinuation of β-agonist therapy.

Lastly, inhaled β-agonists have been shown to induce acidosis with hyperlactatemia in some patients despite absence of hypoxia or significant respiratory muscle work [32–34]. This effect is believed to be due to β-agonist-enhanced production of pyruvate by inhibition of the pyruvate dehydrogenase [35].

Anticholinergics

Ipratropium is a derivative of atropine that cannot cross the blood brain barrier. It blocks acetylcholine from muscarinic receptors on bronchial smooth muscle, thereby reducing intracellular cyclic GMP concentrations and easing bronchoconstriction [12]. Nebulization of 0.25–0.5 mg every 20 min upon presentation has been shown to reduce the need for admission for asthma exacerbation [12, 36], but data for status asthmaticus are lacking. As the half-life of ipratropium and its metabolites is 3.6 h [37], administration is recommended once every 6 h once admitted [12], and Ipratropium is not currently recommended by the National Heart, Lung, and Blood Institute asthma guidelines [14••].

Adverse effects of ipratropium include unilateral pupillary mydriasis from corneal exposure to mist which could be misinterpreted as a sign of neurologic catastrophe [38]. No significant systemic effects have been reported [12].

Steroids

The efficacy of corticosteroids for status asthmaticus has been well established [39, 40]. This class of drugs reduces airway inflammation by suppression of cytokines, mucous production, and mast cell degranulation [41]. Unlike inhaled β2-agonists, the effect of corticosteroids is significantly delayed, with the onset at 1–3 h and a peak effect at 4–8 h [42]. The route of administration does not appear to affect outcome in status asthmaticus [43, 44]; however, the patient's age and ventilatory status may necessitate intravenous administration. The most common agents used are methylprednisolone, hydrocortisone, and dexamethasone. All agents have similar efficacy [45].

Side effects of steroids are relatively benign and include hyperglycemia, psychosis, and hypertension [12]. Yet in the cases of status asthmaticus, several cases of acute myopathy and rhabdomyolysis have been reported [46–50]. This appears to occur mostly when steroids are combined with neuromuscular blocking agents [49]. It is therefore recommended to avoid paralytic agents for ventilatory compliance [12].

Second-Line Medical Therapy

Parenteral β-Agonists

Several parenteral β-agonists are available for the treatment of status asthmaticus. Parenteral administration

provides the theoretic benefit of reaching airways too constricted to receive nebulized medication [51].

Terbutaline is a β2-agonist often administered to children in SA, but efficacy data are lacking. No benefits have been found in children with SA in terms of improvement, length of stay (LOS), or cost [51]. However, one prospective study on 20 pediatric patients showed that administration of an intravenous terbutaline drip by protocol reduced ICU and hospital length of stay (Fig. 1) [52]. Adverse events of terbutaline, including ST depression, are well documented [53].

A 2012 Cochrane Review analyzed 109 studies but found only a single randomized controlled trial that supported the use of intravenous β-agonists in SA, demonstrating that IV albuterol increased recovery and decreased LOS in children with SA [54•].

Epinephrine can be given via nebulizer, intravenously, or by subcutaneous routes. There are conflicting data on the safety of IV epinephrine. In one study, 30.5 % of patients suffered minor adverse events, whereas 3.6 % had major events such as SVT, ischemic EKG changes, or hypotension [55]. This was not seen in other studies [56]. Subcutaneous epinephrine appears to be safer. A literature review of adults having received subcutaneous epinephrine prehospital for either asthma or anaphylaxis only found 3 case reports of adverse events [57].

Overall, the data are lacking to support the routine use of parenteral terbutaline or epinephrine in management of SA; however, both can be considered as options to consider for refractory SA, in an attempt to prevent intubation and mechanical ventilation. The use of other parenteral β-agonists such as isoproterenol has fallen out of favor due to associated cardiotoxicity [58, 59].

Magnesium Sulfate

Magnesium ions antagonize calcium, thereby reducing smooth muscle contractility and calcium-mediated release of acetylcholine from parasympathetic synapses [60]. Data on the efficacy of intravenous magnesium are ambivalent [61]. A multicenter RCT ($n = 1{,}109$ adults FEV1 <50 %) comparing IV magnesium sulfate, nebulized magnesium sulfate, and standard therapy alone, in asthma (not SA) failed to demonstrate any clinically significant benefit [62••]. Although IV magnesium sulfate appears to have limited benefits in asthma exacerbation, other studies have demonstrated that patients with status asthmaticus do benefit [63, 64]

No significant side effects were reported, even with a high-dose protocol in children with SA [65]. Bronchodilation is achieved with serum magnesium levels of 4–6 mg/dL, which is about half the toxic serum level [61]. Given the benign side effect profile and the potential benefit, intravenous magnesium sulfate is recommended by the National Asthma Education and Prevention Program (NAEPP) guidelines for status asthmaticus [14••].

Nebulized magnesium sulfate has been shown to be ineffective in multiple RCTs for patients with asthma exacerbations [62••]. However, as is the case with

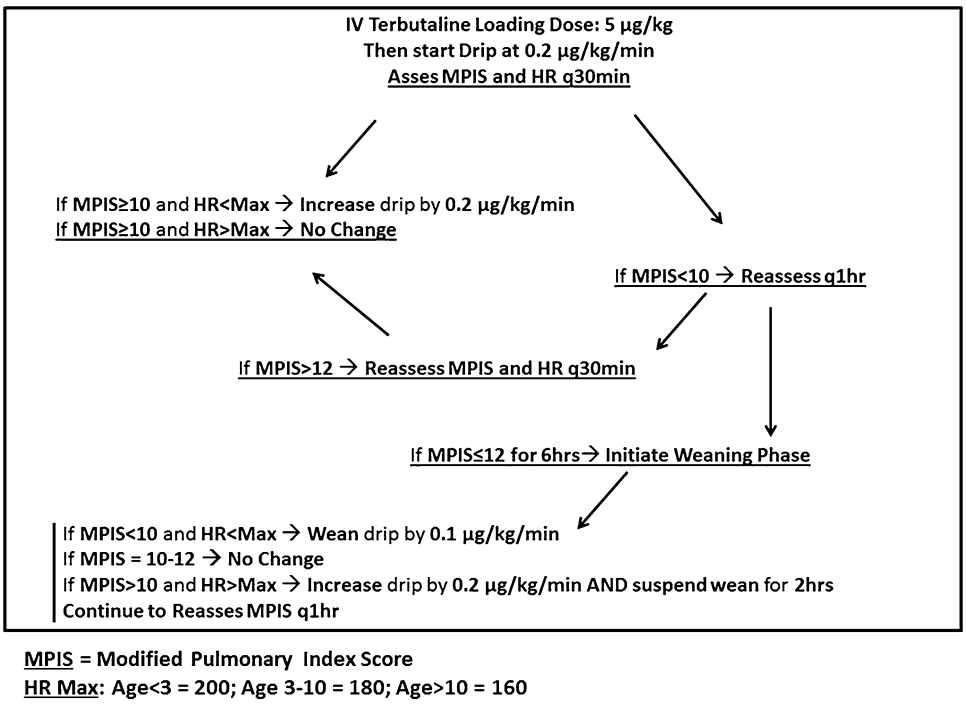

Fig. 1 Protocol used to Titrate IV terbutaline drip [52]

intravenous magnesium sulfate, patients in status asthmaticus may benefit from nebulization [66].

Methylxanthines

Methylxanthines inhibit phosphodiesterases, and thereby increase intracellular cAMP concentrations. Furthermore, they block adenosine receptors and release catecholamines, resulting in bronchodilation [67].

Aminophylline plays no role in the treatment of mild-to-moderate asthma exacerbations [68•] but is still commonly used in pediatric ICUs for patients in SA [69]. A 2005 Cochrane Review found that children >2 years of age in SA experience improved lung function with aminophylline, but did not affect any other outcomes [70]. One study showed that children who had received aminophylline had a *longer* length of stay in the pediatric ICU [71•].

The therapeutic range for aminophylline (10–20 mcg/mL) overlaps with its toxic range (>15 mcg/mL) [12]. Nausea and vomiting are seen in about a third of patients, and may cause deleterious effects for patient on non-invasive positive pressure ventilation [72, 73]. In addition, several arrhythmias and seizures have been described after administration of methylxanthines [74, 75].

While aminophylline has minor therapeutic benefits in children with SA, the significant side effects need to be carefully weighed by the treating physician. Currently, the NAEPP guidelines do not recommend the use methylxanthines [14••].

Third-Line Medical Therapy

Ketamine

In addition to its sedative and analgesic properties, ketamine is an effective bronchodilator [76, 77]. Ketamine functions as a noncompetitive antagonist of glutamate *N*-methyl-D-aspartate (NMDA) receptors [78]. Its mechanism of bronchodilation is complex and is thought to be a combination of several mechanisms. These include prevention of catecholamine reuptake, prevention of calcium influx into airway smooth muscle, and inhibition of vagal bronchoconstriction [79–81].

Multiple case reports have shown that ketamine is an immediate and effective treatment for otherwise refractory SA in combination with standard therapy [82–85]. It may also prevent the need for mechanical ventilation [85]. However, in one randomized control trial, ketamine did not produce significant bronchodilation compared to standard therapy, but patients receiving ketamine expressed more significant relief with their treatment [86]. Ketamine is usually administered as a bolus of 0.5–1 mg/kg followed by a continuous infusion at a rate of 0.5–2 mg/kg/h. In some case, infusions with doses as low as 0.15 mg/kg/h were used [80].

The use of ketamine in SA is controversial due to its side effects which include dysphoria, laryngospasm, and increased bronchial secretions. Laryngospasm occurs in approximately 0.7 % of patients and appears to be more common after intramuscular administration compared to intravenous administration [87]. Despite the controversy, ketamine is an option to consider in patients with refractory SA, heading toward intubation and mechanical ventilation.

Volatile Anesthetics

Halogenated ethers such as isoflurane [88–93] and halothane [94] have been used successfully in children and adults in SA with significant hypercarbia. It is hypothesized that isoflurane inhibits RhoA, an important mediator of calcium-independent smooth muscle contraction [95]. Isoflurane concentrations of 0.75 % failed to improve FEV1 in mild asthmatics [96], but a concentration of 1 % was efficacious in a 13-year old with SA [91]. Halothane appears to be efficacious at 2 % [94]. Improved inspiratory pressures were noted after initiation of volatile anesthetics [97]. While improvement can be noted within 30 min [94], therapy is often required for several days [91, 94]. Isoflurane is preferred over halothane due to its lower lipid solubility and subsequent lower cumulative toxicity [98]. Desflurane should be avoided as it can worsen lung mechanics [99].

The most common adverse event with halogenated ethers is fluid-responsive hypotension in 77 % of children [93]. Intravenous β-agonists should be weaned quickly to reduce the risk of arrhythmia and myocardial damage once volatile anesthetics become effective [93]. There is a theoretical concern of fluoride toxicity with prolonged isoflurane therapy, but no clinically significant fluoride toxicity has been reported despite continuous use for more than 200 h [91, 100]. Significant barriers to this therapy are the logistics of having equipment and personnel available in the ICU that are normally only available in the operating suite [93].

Nitric Oxide

Nitric oxide (NO) inhibits T-type calcium channels in smooth muscle [101]. Inhalation of NO has been used successfully in status asthmaticus at a concentration from 15 to 80 ppm [102, 103]. In one case series, patients experienced a decrease in $PaCO_2$ of over 20 % with NO with no significant hypotension or methemoglobinemia [103].

Antibiotics

Of the many triggers for asthma exacerbations that may progress to SA, infectious causes are common [104]. While most infections are viral in nature, one retrospective study found that 42 % of children with SA had recent Mycoplasma pneumoniae infections. Despite this, treatment with macrolide antibiotics did not change clinical parameters [104]. A Cochrane Review (2001) failed to demonstrate benefit of empiric antibiotics in asthma (not SA) [105], and the NAEPP guidelines do not endorse antibiotic administration [14••].

Intravenous Fluids

Limited data exist on the utility of volume resuscitation in SA. Patients may be slightly dehydrated from decreased intake and increased insensible losses. Patients in SA may develop hypotension as a consequence of their treatment or from auto-PEEP (discussed below) for which fluid resuscitation is inappropriate [106, 107]. The NAEPP guidelines do not endorse aggressive fluid resuscitation [14••].

Mucolytics

In asthma and SA, a triad of bronchospasm, inflammation, and increased mucous secretions occur [12]. As mentioned above, ketamine also increases mucorrhea. Several case reports of mucolytic administration such as rhDNase and *N*-acetylcysteine in combination with bronchoscopy in intubated SA patients showed benefit [108]. However, in patients with SA who are not yet intubated as well as patients with moderate to severe asthma exacerbations, nebulized rhDNase showed no clinical benefit over placebo [109••]. Currently, treatment with mucolytics is not recommended by the NAEPP [14••].

Additional Therapies

Heliox

Heliox is a mixture of helium, an inert gas with no adverse effects, with oxygen in rations of 70 % to 30 %, respectively. Heliox is less dense and less turbulent than oxygen alone and this property is thought to allow for more laminar flow of oxygen to alveoli distal to regions of profound bronchospasm. This can serve as a temporizing measure until conventional therapies take effect. Most of the data examining the utility of Heliox in SA are anecdotal from case reports and there have been conflicting data. In one prospective study, Heliox 70/30 showed improvement in peak expiratory flow rates and subjective dyspnea [110], while a different prospective study showed no difference in various clinical outcomes (LOS or clinical asthma scores) with Heliox compared to air/oxygen alone [111]. Nevertheless, using Heliox as a bridge therapy until conventional therapy is in full effect should be considered in patients in status asthmaticus who are heading toward respiratory failure and intubation with mechanical ventilation.

Non-Invasive Positive Pressure Ventilation (NIPPV)

In patients with SA and hypercarbia heading toward respiratory failure, the use of NIPPV, such as Bilevel Positive Airway Pressure (BiPAP) and Continuous Positive Airway pressure (CPAP), has been explored as a temporizing measurement to prevent intubation and mechanical ventilation. While A 2012 Cochrane review concluded that there are insufficient data to support the use of NIPPV [112•], one prospective observational study concluded that NIPPV can be safely used and is clinically effective in patients with SA and hypercarbia whose clinical status fails to improve with optimum medical management [113]. They concluded that patients on NIPPV had a reduction in respiratory distress, measured by a reduction of respiratory rate, work of breathing, and subjective dyspnea. They also stated that gas exchange rapidly improved and that the technique was well tolerated with only 1 out of 17 patients requiring sedation to tolerate the mask. Furthermore, two other prospective trials on children with SA concluded that NIPPV can improve subjective and objective measures of respiratory dysfunction such as respiratory rate, Modified Pulmonary Index Score, and the need for adjunctive therapy [114, 115••]. Overall, while there are insufficient data to recommend the use of NIPPV in SA, we suggest considering it as a temporizing measure in selected patients who can tolerate it to prevent intubation and mechanical ventilation which increases morbidity.

Intubation and Mechanical Ventilation

Intubation and mechanical ventilation in patients with SA is associated with increased morbidity [4] and a mortality that ranges from 10 to 20 % [116]. Indications for intubating patients in SA include respiratory failure, altered mental status, physical exhaustion due to increased work of breathing, and persistent hypoxia or respiratory acidosis despite initial medical therapy. Anecdotally, if a qualitative colorimetric carbon dioxide device is used to confirm intubation, there may be a delay in seeing color change due to profound bronchospasm. For rapid sequence intubation, options include ketamine, propofol, and etomidate for sedation with succinylcholine as a paralytic agent. Ketamine and propofol have advantage of inducing bronchodilation [116]. The recommended dose of ketamine is 1–1.5 mg/kg IV.

Mechanical ventilation in patients with asthma can lead to hypotension and barotrauma from hyperinflation

Table 1 Medical and adjunctive therapies used to treat status asthmaticus

First-line	
Albuterol	Continuous nebulized albuterol with a recommended dose of up to 15 mg/h
Ipratropium	Nebulized ipratropium at a dose of 0.5 mg every 6 h is help for acute asthma exacerbations, but there are limited data for its use in SA
IV Methylprednisolone	1st dose at 2 mg/kg, with a maximum of 125 mg, then 0.5–1 mg/kg every 6 h, usually 60–80 mg IV q6 h
Second-line	
Terbutaline	Adult: 0.25 mg SC q15–30 min × 2 doses PRN
	Age 6–12: 0.005–0.01 mg/kg SC q15–30 min × 2 doses PRN
Epinephrine (1:1,000)	Adult: 0.3–0.5 mg SC/IM q20 min × 3 doses PRN
	Pediatric: 0.01 mg/kg SC/IM q20 min × 3 doses PRN
Magnesium sulfate	Bronchodilation is achieved with serum magnesium levels of 4–6 mg/dL. Initial dosing:
	Adult: 2 g IV
	Pediatric: 25–50 mg/kg IV
Other therapies	
Ketamine	Limited data in SA; however, consider IV bolus of 0.5–1 mg/kg followed by a continuous IV infusion at a rate of 0.5–2 mg/kg/h
Isoflurane	Limited data in SA; however, consider 1 % inhaled isoflurane in severe refractory SA
Nitric oxide (NO)	Inhalation of NO has been used successfully in status asthmaticus at a concentration from 15 to 80 ppm
Heliox 70/30	Improves laminar flow and delivery of oxygen and nebulized medications distal bronchioles and alveoli, but has no therapeutic properties of its own
NIPPV	BiPAP or CPAP
Mechanical ventilation	Reduces RR and TV and/or adjust I:E ratio such that expiration is prolonged to prevent auto-PEEP and lung hyperinflation

secondary to breath stacking [116]. Auto-PEEP is caused by decreased expiratory flow due to bronchospasm, leading to increased end-expiratory lung volumes and hyperinflation. This can lead to complications such as tension pneumothorax and hypotension. Hypotension is often due to increase positive pressure in the thorax leading to decrease venous return and decrease cardiac output. This can be treated with crystalloid IV fluid boluses and a short trial of apnea by disconnecting the ventilator and applying external pressure on the chest to reduce lung volumes [116]. This should be for no more than 60 s.

Adjusting the ventilator settings is critical in preventing complications associated with mechanically ventilating a patient with asthma, with the goal being to optimize oxygenation and ventilation and control hyperinflation and auto-PEEP [116]. This can be achieved by reducing the respiratory rate or tidal volume or to adjust the inspiratory: expiratory ratio such that inspiration is short and expiration is prolonged. Reducing the respiratory rate has the greatest effect, and auto-PEEP and plateau pressures on the ventilator should be monitored [116]. However, doing so may lead to hypercapnia. Nevertheless, some hypercapnia (a pCO_2 of up to 80 mmHg and pH as low as 7.15) is preferred to hyperinflation, a term referred to as permissive hypercapnia [116].

Bronchoscopy

Patients with SA who are intubated may benefit from bronchoscopy and removal of mucous plugs. This is achieved by decreasing turbulent airflow and disruption of medication delivery by removal of the mucous plug. Although there is no solid evidence of any benefit, there have been case reports published describing this phenomenon [117].

Management of SA in Pregnancy

Pregnant patients with SA are in general managed in the same manner as non-pregnant patients. Nebulized albuterol is considered a Category C medication, having not been studied in pregnancy. However, it is generally considered safe to administer in pregnant patients [118].

Systemic corticosteroids, such as intravenous methylprednisolone, are also Category C; however, there are some conflicting case reports that suggest that they may cause increase birth defects as well as an increase incidence of pre-term labor, preeclampsia, and low birth weight [118]. Nevertheless, they remain the mainstay of therapy in treating SA, and their use in pregnancy is recommended for severe asthma exacerbations and SA [118]. In pregnant

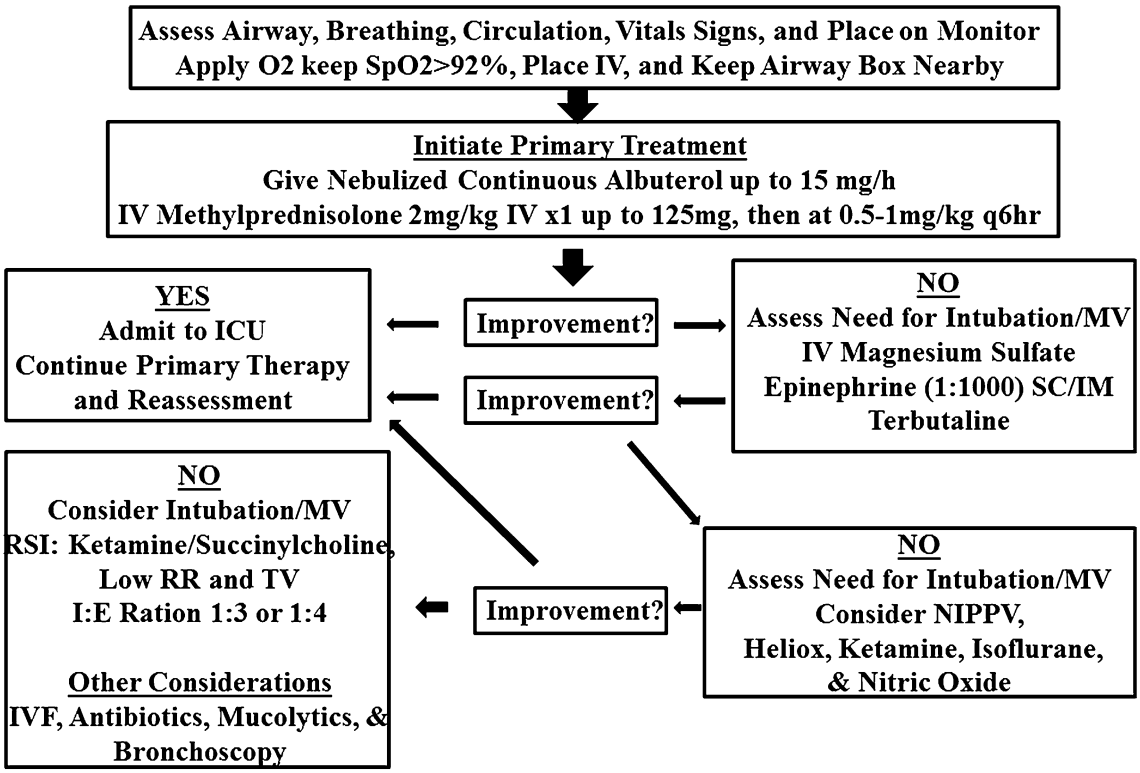

Fig. 2 Suggested algorithm for management of status asthmaticus

patients with SA who are intubated and undergoing mechanical ventilation, opiates such as fentanyl should be used for sedation [118]. Benzodiazepines are Category D and should be avoided [118].

Conclusions

Status Asthmaticus is condition that can affect all age groups and requires aggressive treatment. Optimizing oxygenation and ventilation are the primary goals of therapy. This is primarily achieved by reversing bronchoconstriction and reducing the secondary inflammatory response associated with asthma. Table 1 summarizes the medical and adjunctive therapies used to treat SA. Figure 2 is our proposed algorithm in managing SA.

In summary, the mainstay of therapy is nebulized continuous albuterol as well as systemic corticosteroids and nebulized ipratropium. In status asthmaticus, however, the use of second- and third-line medical therapies as well as adjunctive therapies should be considered in non-responding patients. All patients with SA should be admitted initially to an ICU setting. Adults and pediatric populations should be treated with the same approach.

Although there is no compelling to support regular use, in patients failing medical and adjunctive therapy for SA, if available, approaches such as extracorporeal membrane oxygenation (ECMO) and mechanical external chest compression (MECC) can be considered; however, it is beyond the scope of this article to discuss these modalities.

Compliance with Ethics Guidelines

Conflict of Interest The authors declare that they have no conflicts of interests.

Human and Animal Rights and Informed Consent This article contains no studies with human or animal subjects performed by the author.

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