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Abstract: Following a peak in asthma mortality in the late 1980s and early 1990s, we have been fortunate to see a substantial decrease in asthma deaths in recent years. Although most asthma deaths occur outside the hospital, near-fatal events are commonplace, with anywhere from 2–20% of patients with acute asthma admitted to intensive care, and 2–4% intubated for respiratory failure. Standard therapies for acute severe and near-fatal asthma include administration of systemic corticosteroids, and frequent or continuous inhaled beta agonists. Controversy remains regarding the optimal therapy of those who fail to respond to these initial treatments, those who remain at risk of acute respiratory failure, and patients requiring mechanical ventilation. There remain significant gaps in our knowledge regarding relative benefits of intravenous *versus* oral corticosteroids, intermittent *versus* continuous beta agonists, and the role of various adjunctive treatments including intravenous magnesium, systemic beta agonists, aminophylline, and helium-oxygen mixtures. Using models and radiolabeled aerosols, there is a greater understanding regarding effective administration of inhaled beta-agonists in ventilated patients. There is limited available evidence for treatment of near-fatal asthma, a fact reflected by the significant variability in asthma critical care practice. Much of the data guiding treatment in this setting has been generalized from studies of acute asthma in the ED and from general populations of hospitalized patients with acute asthma. This review will focus on pharmacologic approaches to life-threatening asthma by reviewing current guideline recommendations, reviewing the scientific basis of the guidelines, and highlighting gaps in our knowledge in treatment of refractory acute or near-fatal asthma.

Keywords: asthma, fatal asthma, near-fatal asthma

Background

Life-threatening asthma captures the attention of both the medical community and the public, fueled by recent high profile asthma deaths in the media [New York Post, 2010; The Guardian, 2010; thebottlenosewordpress.com, 2010; Wall Street Journal, 2010]. Increased focus on the issue of near-fatal and fatal asthma began in the late 1980s and early 1990s at a time of rising asthma prevalence, morbidity, and mortality. Epidemiologic risk factors associated with fatal asthma include female gender, African-American race, socioeconomic status, substance abuse, frequent urgent care, prior near-fatal events, and excess short-acting beta agonist (SABA) use (Table 1) [Awadh *et al.* 1996; Suissa *et al.* 1994; Greenberger *et al.* 1993; Kallenbach *et al.* 1993; Rodrigo and Rodrigo, 1993]. Autopsy studies hint at two distinct

mechanisms of fatal asthma. Long-course fatal asthma is more common and accounts for 85% of cases of fatal asthma. Long-course fatal asthma has a protracted onset lasting days to weeks, and often occurs on a background of poorly controlled asthma and nonadherence to inhaled corticosteroids (ICS). Autopsies reveal airway mucus plugs mixed with inflammatory cells and denuded epithelium, mucosal edema, and submucosal eosinophilia [Hyzy *et al.* 2008]. Short-course fatal asthma, accounting for 15–20% of cases, includes episodes that escalate rapidly over several hours and culminate in death. The pathology of fatal short-course asthma is notable for an absence of mucus plugs ('empty airways') and a high ratio of neutrophils to eosinophils [James *et al.* 2005]. Data suggest that some cases of short-course fatal asthma may actually be unrecognized anaphylaxis to food allergens

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or aspirin, or due to other sudden massive irritant or allergen exposure [Plaza *et al.* 2002; Tough *et al.* 1996; O'Hollaren *et al.* 1991]. Overestimation of the frequency of short-course fatal asthma may occur when 'empty airways' are an artifact of tissue sectioning and processing techniques [Kuyper *et al.* 2003].

Fortunately, death from asthma in the developed world is relatively uncommon. In the United States, rates peaked at just under 6000 cases in 1995–1996 and have now decreased to approximately 3500 deaths in 2007 [National Center for Health Statistics, 2009]. Worldwide, there are approximately 250,000 deaths annually, although there is significant regional variability and precise estimates from the developing world are limited [Bousquet *et al.* 2007]. Most fatal events occur outside of the hospital but 'near-misses', or near-fatal events, are commonplace, with anywhere from 2–20% of patients with acute asthma admitted to intensive care, and 2–4% intubated for respiratory failure [Sears, 2008; Krishnan *et al.* 2006; Pendergraft *et al.* 2004; McFadden and Warren, 1997]. Fortunately, outcomes of acute severe asthma are improving, with fewer complications and fewer in-hospital deaths [Gupta *et al.* 2004]. Recently, the estimated risk of death for hospitalized patients with asthma in the US was 0.5% [Krishnan *et al.* 2006]. The reduced overall death rate from asthma is likely related to more widespread use of ICS, and lower

in-hospital deaths perhaps related to improved ventilator strategies reducing complications in those who make it to the hospital alive [Kao *et al.* 2008; Suissa *et al.* 2000; Darioli and Perret, 1984; Menitove and Goldring, 1983].

Every physician who has had the harrowing experience of caring for a patient with near-fatal or fatal asthma is well aware of gaps in our knowledge of the best pharmacologic approach to treatment. Current guidelines define a severe exacerbation as one in which an individual has a forced expiratory volume in 1 second (FEV₁) or peak expiratory flow (PEF) <40% predicted. Near-fatal asthma describes those with impending respiratory failure, or actual respiratory arrest. Established treatments for severe exacerbations include administration of oxygen, frequent or continuous inhaled beta agonists, and oral or intravenous corticosteroids (Table 2). Regardless, questions remain about identifying patients who will fail to respond to treatment and the best route and frequency for administration of pharmacologic interventions. In this review we focus on pharmacologic approaches to life-threatening asthma by reviewing current guideline recommendations, reviewing the scientific basis of the guidelines, and highlighting gaps in our knowledge in treatment of refractory acute or near-fatal asthma.

Table 1. Risk factors for death from asthma.

Asthma history
Previous severe exacerbation (intensive care or intubation)
Two or more hospitalizations in the past year
Three or more emergency department visits in the past year
Hospitalization or emergency department visit in the past month
Use of more than two canisters of short-acting beta agonist in the past month
Difficulty perceiving or articulating asthma symptoms
Social history
African-American race/ethnicity
Low socioeconomic status
Urban residence
History of substance abuse
Major psychosocial problems
Sources: Kallenbach <i>et al.</i> [1993], Rodrigo and Rodrigo [1993], Greenberger <i>et al.</i> [1993], Suissa <i>et al.</i> [1994], Awadh <i>et al.</i> [1996], Kikuchi <i>et al.</i> [1994], Magadle <i>et al.</i> [2002], Eckert <i>et al.</i> [2004] and Serrano <i>et al.</i> [2006].

Table 2. Treatments for acute severe or near-fatal asthma.

Established treatments
Inhaled beta agonists (intermittent or continuous)
Systemic corticosteroids (intravenous or oral)
Inhaled anticholinergics (current data supports ED use)
IV magnesium (current data supports ED use)
Alternative/controversial treatments for refractory cases
Systemic beta agonists (intravenous epinephrine or terbutaline)
Phosphodiesterase inhibitors (aminophylline, theophylline)
Heliox
Paralytics
Inhalational volatile anesthetics
Investigational treatments
Intravenous montelukast
Inhaled corticosteroids
Ineffective or harmful therapies
Antibiotics (in the absence of defined infection)
Aggressive hydration
Mucolytics (acetylcysteine)
Chest physiotherapy

Established treatments: beta agonists

Initial treatment of acute asthma universally involves administration of SABAs. Two thirds of patients presenting to the emergency department (ED) respond rapidly to bronchodilators and achieve a peak flow or FEV₁ of 70% predicted after receiving between 5 and 7.5 mg of albuterol. Unfortunately, one third of patients are nonresponders. Several mechanisms have been proposed for this failure and include extensive mucus plugging or airway edema as well as altered beta-receptor number and function [Rodrigo and Rodrigo, 1998; Strauss *et al.* 1997]. Understanding mechanisms underlying failure to respond to bronchodilators may eventually lead to approaches targeting the dosage and delivery of bronchodilators in select patients. For now, a sizable body of data suggests that under most circumstances, administration of inhaled beta agonists by metered dose inhaler (MDI) is as efficacious as administration via nebulizer [Dolovich *et al.* 2005; Cates, 2003]. However, patients in acute respiratory distress may be unable to use an MDI with adequate technique to ensure drug delivery. When administering SABAs via nebulizer, either repetitive or continuous administration is recommended. This recommendation is derived from a meta-analysis of 393 adults pooled from six studies, including studies of patients with severe exacerbations (FEV₁ <50%). No difference was found in the rate of improvement of pulmonary function or in the hospitalization rate with continuous *versus* intermittent therapy [Rodrigo and Rodrigo, 2002]. However, patients with life-threatening asthma were specifically excluded from these studies, and thus most guidelines do not make specific recommendations for either repetitive or continuous dosing in this group of patients. A small study of hospitalized children in impending respiratory failure suggested more rapid improvement with continuous nebulization [Papo *et al.* 1993]. Most of the remaining data supporting any advantage to continuous delivery comes from the ED setting, and it is unclear whether this can be generalized to the inpatient or ICU setting [Lin *et al.* 1993; Rudnitsky *et al.* 1993].

How effectively bronchodilators reach the lower airways in the setting of acute bronchospasm and extensive mucus plugging remains an unresolved question. Some practitioners have favored systemic beta agonist administration in acute severe asthma patients based on this concern. Although a number of systematic reviews suggest

at the very least equivalence, and perhaps superiority of inhaled compared with systemic beta agonists, the majority of studies were performed on more typical moderate to severe patients presenting to the ED who were not in acute respiratory failure [Travers *et al.* 2002; Ruddy *et al.* 1986]. Whether or not systemic delivery benefits intubated patients with refractory hypercapnea and high airway pressures remains unclear. One study of children in intensive care showed a trend towards improvement with intravenous terbutaline after failure to improve with inhaled SABA. However, this small trend toward improvement occurred at the cost of arrhythmias and elevated troponin levels even in this young age group [Bogie *et al.* 2007]. Others report that cardiovascular adverse effects of systemic beta agonists are rare, even in adults [Cydulka *et al.* 1988]. Some experts have suggested that systemic administration be considered for patients who fail to respond to inhaled medication. Results of a double blind crossover study in which additional improvement with subcutaneous epinephrine was observed in patients who failed to respond to inhaled SABAs supports this recommendation [Appel *et al.* 1989].

There are distinct issues regarding delivery of inhaled beta agonists in mechanically ventilated patients with acute severe asthma. Delivery rates of 0.9–97.5% for MDI and 0–42% for nebulizers have been reported [Dhand and Mercier, 2007]. In recent years, both bench models and imaging studies using radiolabeled aerosols have been used to help outline factors impacting delivery of inhaled medications in mechanically ventilated patients. Using these techniques, approximately 11% of delivered dose from an MDI reaches lower airways, similar to that achieved in ambulatory patients [Fink and Dhand, 2000; Ruffin *et al.* 1981]. Nebulizers are somewhat less efficient, with a significant portion of each dose deposited in the endotracheal tube and 6–10% arriving at the lower airways [Miller *et al.* 2003]. Thus, higher doses are needed if a nebulizer is used in order to adjust for lower efficiency of delivery. Numerous ventilator-, patient-, and device-related factors contribute to variable inhaled drug delivery in ventilated patients. Ventilator related factors include ventilator mode, tidal volume, respiratory rate, inspiratory waveform, breath triggering mechanism, and humidity. Patient related factors include severity of airway obstruction, degree of dynamic hyperinflation, and patient-ventilator synchrony

[Dhand, 2007; Fink *et al.* 1999]. Device-related factors include MDI or nebulized delivery, HFA or CFC propellants, and the position of the spacer or nebulizer in the circuit. Currently available data suggest that administration by MDI offers a number of advantages over administration by nebulizer. The rate of aerosol production is variable both across different lots of single nebulizer models and among different models [Hess *et al.* 1996; Loffert *et al.* 1994; Alvine *et al.* 1992]. There is also a greater influence of ventilator mode and lung mechanics on nebulized delivery [Hess *et al.* 2003]. Nebulizers unfortunately can occasionally be a source of aerosolized bacteria and nosocomial infection [Hamill *et al.* 1995; Craven *et al.* 1984]. MDIs can be administered quickly using less respiratory therapist time and are thus more cost effective [Bowton *et al.* 1992]. HFA-propelled MDIs deliver less drug in ventilated patients than CFC MDIs and thus dosing may need to be adjusted accordingly. Humidity in the ventilatory circuit reduces delivery by as much as 50% compared with dry circuits and so humidification of air during treatment is not recommended [Dhand, 2004]. Use of serial measurement of the peak-to-plateau pressure gradient in ventilated patients during a severe asthma exacerbation can be used to assess response to bronchodilator therapy, with a significant fall in gradient of about 15% or greater considered consistent with an adequate response. Lack of an appropriate response may prompt consideration of use of higher doses of inhaled therapy or perhaps systemic administration as long as there is no evidence of adverse effects.

Inhaled anticholinergics

Despite the existence of few appropriate studies, use of anticholinergics during inpatient care of acute severe asthma is commonplace. There is solid evidence for this practice in ED care, where anticholinergics combined with inhaled beta agonists improved PEF and FEV₁ more than inhaled beta agonists alone [Rodrigo and Rodrigo, 2000, 1999]. Systematic reviews of early ED administration of inhaled anticholinergics combined with beta agonists have found that treatment with inhaled anticholinergics reduced admission rates by 30–45% (number needed to treat 6–14 to prevent one admission) [Rodrigo and Castro-Rodriguez, 2005]. Particular benefit was noted for the subgroup of patients with moderate to severe obstruction. Although use of both drugs has been adopted in the inpatient setting, two studies in hospitalized children comparing

inpatient use of inhaled anticholinergics with beta agonists compared with beta agonists alone suggested no added benefit to the use of inhaled anticholinergics [Craven *et al.* 2001; Goggin *et al.* 2001]. One double-blind, placebo-controlled trial of 106 adults extended treatment with inhaled anticholinergics and beta agonists compared with inhaled beta agonists alone from the ED until 36 hours into the hospital stay. No difference in PEF was observed at 60 hours, however patients who continued anticholinergics along with beta agonists during their hospital stay achieved better lung function earlier in their hospitalization and had shorter lengths of stay [Brophy *et al.* 1998]. Inhaled anticholinergics may be particularly useful when bronchospasm is induced by administration of beta-blockers. Moreover, targeting a different pathway of airway smooth muscle relaxation seems intuitively logical, especially given evidence of impaired response to beta agonists in this patient population.

Established treatments: corticosteroids

Although guidelines all recommend systemic corticosteroids for severe asthma exacerbations, the best route of delivery remains controversial. For the general management of moderate to severe acute asthma, guidelines recommend 1–2 mg/kg of prednisone or its equivalent once daily or in divided doses (maximum 60 mg/day) until PEF is 70% predicted or personal best, usually approximately 5–10 days for adults [US Department of Health and Human Services, 2007]. Both US and international guidelines suggest that for a general population of patients presenting for care with acute asthma, intravenous (IV) and oral steroids have similar effects. In the US guidelines, IV steroids are suggested as an option for hospitalized patients, and are recommended for patients admitted to intensive care. International guidelines favor oral medications even in the most severe patients, reserving IV corticosteroids for patients who are unable to take medications orally [British Thoracic Society, 2009]. However, most studies supporting the purported equivalence of oral and IV corticosteroids are small and often underpowered to detect differences between these two groups and included patients who had not previously received ICS [Engel *et al.* 1990; Jonsson *et al.* 1988; Ratto *et al.* 1988]. A systematic review by Manser and colleagues is widely quoted to support the contention that IV and oral medication are equivalent [Manser *et al.* 2000], but this review pooled

only two studies containing 88 patients; the larger of these two studies contained 70 patients and was an unblinded trial. The most adequately powered study comparing oral and IV steroids showed no difference in the primary outcome of PEF, however the two groups were not comparable since those that received IV steroids had lower initial lung function [Cunnington *et al.* 2005].

Some, but not all of the classic studies from the mid-1970s suggest that IV steroids act more rapidly than oral steroids. A single oral 40 mg dose of methylprednisolone significantly improved PEF in 2 h with peak effect at 9 h in subjects with chronic asthma whereas administration of 200 mg IV hydrocortisone improved peak flow in 1 h with a peak effect at 5 h [Ellul-Micallef *et al.* 1974]. A subsequent study showed that a single 40 mg IV dose of prednisolone phosphate improved FEV₁ to 115% of pretreatment value within 1 h, with a peak effect (150% of pretreatment value) at 5 h without confounding by concomitant treatment with other medications (bronchodilators) [Ellul-Micallef and Fenech, 1975]. In contrast, McFadden and colleagues found no difference in lung function between placebo and either 0.25, 0.5, or 1 g of intravenous hydrocortisone on serial measurements of lung function from 30 min to 6 h in patients with acute asthma concomitantly treated with bronchodilators [McFadden *et al.* 1976]. These conflicting results may be due to differences among the populations included in each of these studies (chronic asthma *versus* acute asthma), the different corticosteroid preparations used, or concomitant treatments. Within the limitations of the data, IV steroids may have a more rapid onset of action and peak effect than oral steroids in acute severe asthma, particularly in cases where patients have exacerbations despite treatment with inhaled and/or oral corticosteroids. The possible mechanisms by which corticosteroids may exert 'rapid effects' remain a puzzle. Most anti-inflammatory effects of corticosteroids occur slowly due to the effects of these agents on mRNA transcription and protein synthesis. However, nongenomic effects of corticosteroids (those that do not require alterations in mRNA transcription or protein synthesis) include rapid and direct effects on airway vasculature resulting in vasoconstriction and reduced airway edema. Other nongenomic effects of corticosteroids that could possibly affect airway function include effects on cell membrane fluidity, effects on non-glucocorticoid receptors, and alterations in

secondary messengers and ions [Haller *et al.* 2008; Tillmann *et al.* 2004; Wanner *et al.* 2004]. In light of the limitations of current data comparing oral and intravenous corticosteroids and questions about the timing of beneficial effects, the possibility of an earlier onset and peak effect of IV steroids may offer critical improvement early on in near-fatal asthma. Data overall is insufficient to recommend oral over IV steroids in hospitalized acute severe asthma patients.

Data guiding our practice regarding steroid dosing in a general population of patients with acute asthma is somewhat better than information guiding route of administration. No benefit is achieved when higher than standard doses of prednisone (50–100 mg) are given to hospitalized patients [Manser *et al.* 2000]. However, the body of data guiding dosing in critically ill patients is minimal. In the absence of good data in this area, experts recommend either initial high-dose steroids for the first 24 h (80–125 mg in divided doses) or oral prednisone 120–180 mg/day in three or four divided doses for 48 h. Higher-dose therapy in the specific setting of critical care is supported by at least one study where 25 patients with acute severe asthma were randomized to methylprednisolone in doses of 125, 40, or 15 mg while other concomitant treatments were held constant. The 125-mg group had a significant improvement in FEV₁ by the end of the first day of treatment, whereas the 40 mg group did not show an improvement in FEV₁ until the middle of the second day. The 15 mg group showed no improvement in FEV₁ after 3 days [Haskell *et al.* 1983].

Some patients respond poorly to corticosteroid treatment. Poor response to steroids in chronic asthma has been linked to alterations in function of histone deacetylase (HDAC), an enzyme critical to regulation of mRNA transcription. Following binding of glucocorticoid to their cytosolic receptor, the activated glucocorticoid/receptor complex binds to both cAMP response element binding protein (CREB)/histone acetyltransferase (HAT) and HDAC2. HAT activity is inhibited, whereas HDAC2 is activated, decreasing histone acetylation and reducing chromatin uncoiling. Decreased chromatin uncoiling reduces access of the glucocorticoid/receptor complex to glucocorticoid responsive elements in promoters involved in inactivation of inflammatory genes and activation of anti-inflammatory

pathways [Barnes, 2009]. It is unclear whether mechanisms involved in poor responses to steroids in certain patients with chronic asthma are similar to those involved in poor response to steroids in acute asthma. Interestingly, some studies of chronic severe asthma with persistent airway eosinophilia suggest that the steroid dose–response curve is shifted and patients with apparent steroid resistance may in fact respond to high dose systemic administration of corticosteroids [ten Brinke *et al.* 2004]. It remains to be seen whether a shift in the typical dose response curve to corticosteroids is also present in patients with acute asthma presenting after failure of both inhaled and perhaps outpatient oral steroids. Significant adverse effects including hyperglycemia, hypokalemia, neuropsychiatric effects, metabolic alkalosis, hypertension, and volume overload/edema can occur with continued use of high-dose steroids. Longer-term adverse effects of glucocorticoids including osteoporosis, cataracts, avascular necrosis, immunosuppression, and adrenal insufficiency are also significant concerns. Dosing should be reduced or discontinued as rapidly as possible.

Alternative therapies for refractory cases: aminophylline and magnesium

In both the initial ED treatment guidelines and inpatient recommendations for treatment of severe asthma, adjunct treatments are considered in order to decrease the likelihood of intubation. The most commonly used and most studied treatment in this regard is intravenous magnesium. Pharmacologic actions of magnesium include inhibition of calcium channel function in smooth muscle, and reduction in acetylcholine release, but precise mechanisms of action remain unclear. In systematic reviews, administration of IV magnesium reduced hospitalization in a subgroup of patients experiencing severe exacerbations unresponsive to initial treatment. This effect is limited to earlier in the course of treatment and when response to inhaled beta agonists is poor [Rowe *et al.* 2000]. There is no data to support benefit of magnesium in refractory inpatients or in the ICU, although little work has been done specifically in these areas.

Historically, IV aminophylline was administered in cases of acute severe asthma in addition to systemic beta agonists. There is currently little data to support this practice. In a systematic review of 15 studies, no significant benefit was identified although there was significant

heterogeneity and limitations in the quality of the data. There was no improvement in airflow and no reduction in admission rates, but there were higher rates of palpitations, arrhythmias, and vomiting in the aminophylline group [Parameswaran *et al.* 2000]. Again, most of these studies were in patients in the ED. One study in hospitalized children suggested improvement with IV aminophylline above that observed with systemic steroids, inhaled beta agonists, and inhaled anticholinergics. Although there was no difference in length of stay, a lower rate of intubation as well as some improved physiologic outcomes were observed albeit with increased side effects [Yung and South, 1998]. Although use of phosphodiesterase inhibitors such as theophylline and aminophylline in asthma overall has varied over time, recent interest in these drugs has been revived as possible treatment adjuncts in ‘steroid-resistant’ asthma [Barnes, 2009]. It would be interesting to investigate whether there is any benefit to adding theophylline or aminophylline in patients with long-course near-fatal asthma, especially those exacerbating through high-dose outpatient ICS and oral corticosteroids.

Heroic measures: sedation, paralysis, helium–oxygen mixtures (heliox), and inhaled anesthetics

Although not classically thought of as part of pharmacologic treatment of severe acute asthma, care in the selection of drugs used for intubation and sedation are important to management. The intubation and post-intubation period can be fraught with pitfalls. Post-intubation hypotension is common, and can result from a combination of hyperinflation, auto-PEEP, hypercapnea-related vasodilatation, and volume depletion. Hypotension can be compounded by drugs used for intubation and by initial mechanical ventilation. Although succinylcholine is often the drug of choice for rapid sequence intubation, it can trigger release of histamine, and some suggest it should be avoided. Alternatives for induction include the intravenous general anesthetic etomidate or the short-acting neuromuscular blocker rocuronium. Both have minimal hemodynamic effects and do not promote histamine release. In past years there was some enthusiasm for use of ketamine in acute severe asthma due to its bronchodilating properties. This enthusiasm waned due to adverse effects including dissociative states reported with its use. Moreover, ketamine does not block laryngeal reflexes and

therefore increased secretions and laryngospasm may occur with its clinical use, which is currently rare. Propofol has significant bronchodilating properties, but bolus injections are associated with hypotension in 20% of patients, so low dose infusion with a gradual titration is recommended if used. Use of inhalational anesthetics with bronchodilating effects including halothane and isoflurane has been reported, but the logistics of delivering anesthetic agents outside of the operating room are complicated and may not be feasible in many settings [Mutlu *et al.* 2002]. Paralytics may be considered in the setting of persistent patient–ventilator dyssynchrony and hyperventilation despite sedation, but their use has been linked to risk of myopathy, particularly when used together with high-dose corticosteroids [Behbehani *et al.* 1999; Leatherman *et al.* 1996]. For analgesia, synthetic opioids are preferred to morphine due to histamine release associated with morphine.

An early study examined administration of helium-oxygen mixtures (heliox) in seven intubated patients with refractory near-fatal asthma and found peak airway pressures decreased by 35% and mean P_{CO_2} was reduced by 33 mmHg [Kass and Terrigino, 1999; Gluck *et al.* 1990]. Helium is more viscous and less dense than air and reduces turbulent airflow, but effects are transient [Bag *et al.* 2002]. A recent study used an 80:20 mixture of heliox through a closed system to deliver albuterol to patients with severe acute asthma and found a significant improvement in FEV₁ lasting 3 h [Kress *et al.* 2002]. A systematic review on the use of heliox pooled 10 studies and found no difference in pulmonary function, no effect on hospital admission, but did suggest a greater improvement in pulmonary function in a subgroup with the lowest pulmonary function [Rodrigo *et al.* 2006].

Harmful therapies

A number of therapies that are not evidence based or that are potentially harmful are still used at times in certain practice settings. Antibiotics are vastly overused in the absence of evidence of specific infection such as pneumonia or bacterial sinusitis, and efforts should be made to restrict their use to situations where a clear infection is present [Graham *et al.* 2001]. Aggressive hydration has been advocated to facilitate secretion clearance, but there is no clear data illustrating benefit and potential for harm. Mucolytics such as acetylcysteine may worsen

airflow obstruction, and chest physical therapy has not been shown to be of any benefit [Sandilands and Bateman, 2009]. Sedation of an anxious patient in respiratory distress without a stable airway is potentially dangerous. The potential for long-acting beta agonists to contribute to acute severe asthma is currently a subject of intense controversy and discussion is beyond the scope of this review, but should be kept in mind as a possible contributing factor in select cases. There is no role for long-acting beta agonists in acute asthma care apart from continuation of outpatient therapy.

Investigational therapies: inhaled corticosteroids and intravenous leukotrienes

Generally, ICS are not considered an effective treatment for acute asthma. Doubling of the dose of ICS is not effective at averting mild exacerbations, and there is conflicting data about the effectiveness of quadrupling ICS [Quon *et al.* 2010]. More recently, there has been interest in the efficacy of the addition of inhaled to systemic corticosteroids in acute asthma based on the rapid onset of action of their non-genomic effects [Horvath and Wanner, 2006; Kumar *et al.* 2000]. Rodrigo pooled 17 studies including 460 adults and 663 children to assess the benefit of adding single or multiple doses of ICS in place of or in addition to systemic corticosteroids in acute asthma in the ED [Rodrigo, 2006]. One small study included in this systematic review suggested an increased likelihood of discharge, and another demonstrated greater improvement in PEF at 60 and 120 minutes when ICS were given in addition to systemic steroids. Effects were most notable when multiple doses were used [Nuhoglu *et al.* 2005; Sung *et al.* 1998; Guttman *et al.* 1997]. Although the majority of this work was performed in the ED with patients experiencing mild to moderate exacerbations, it suggests that further investigation of the effects of early ICS in acute asthma is warranted.

Several studies have evaluated IV leukotriene modifiers in acute severe asthma [Montuschi and Peters-Golden, 2010; Montuschi *et al.* 2007]. Camargo and colleagues found that addition of IV montelukast to standard therapy in acute asthma produced a rapid improvement of FEV₁, within 10 minutes [Camargo *et al.* 2003]. In a recent study, 583 adults with an FEV₁ <50% were randomized to either IV montelukast or placebo. Following study medication infusion, all participants received corticosteroids.

IV montelukast increased FEV₁ compared with placebo, with a significant improvement noted within 20 minutes, and with a difference of 100 ml persisting at 60 minutes (95% CI 0.04–0.16) [Camargo *et al.* 2010]. Patients with near fatal asthma were not included in this study, but a rapid, early improvement in lung function in the course of acute severe asthma could potentially be of value in severe exacerbations.

Preventing relapse

The strongest predictor of death from asthma is a prior episode of near-fatal asthma. Follow-up mortality rates after a near fatal asthma have been estimated to be as high as 15–22% [Rodriguez-Trigo *et al.* 2008; Marquette *et al.* 1992]. In a non-randomized observational study, patients with a history of near-fatal asthma enrolled in a program with close follow up and treatment according to GINA guidelines experienced no deaths, whereas a group of subjects who declined participation in this program had a subsequent mortality rate of 15% [Rodriguez-Trigo *et al.* 2008]. Patients with near-fatal asthma need to be monitored carefully for adherence to ICS, undergo frequent follow up, and receive intensive asthma education. Assuring access to controller medications at a reasonable cost is critical. Some patients experiencing near-fatal episodes appear to have impaired perception of hypoxia, hypercapnia, or airflow obstruction [Magadle *et al.* 2002; Kikuchi *et al.* 1994]. Others have alexithymia, a poor ability to identify and express body sensations, which may lead to delays in care [Serrano *et al.* 2006; Eckert *et al.* 2004]. Patients with poor perception of airflow obstruction or difficulties in articulating symptoms should perform regular peak flow monitoring and have close follow up. Attention to modifiable risk factors is critical. Apart from intensive asthma education, attention to modifiable risk factors such as active smoking or environmental tobacco exposure, substance abuse, aspirin sensitivity, and food allergies is important [Patrawalla *et al.* 2010; Pietinalho *et al.* 2009; Yoshimine *et al.* 2005; Levenson *et al.* 1996]. Since 85% of near-fatal asthma is slow onset, it should at the very least be potentially preventable.

Conclusion

Fatal asthma is tragic and although often unexpected, may be preventable in many cases. Identification and careful management of outpatients at risk for death from asthma can help

prevent such tragedies. Risk factors for fatal asthma should be identified at routine visits and such patients warrant close follow up. Standard therapies for acute severe asthma such as inhaled beta agonists and systemic steroids are often effective, but may be insufficient to avert a near-fatal or fatal attack. There is limited available evidence for treatment of near-fatal asthma, a fact reflected by the significant variability in asthma critical care practice [Babl *et al.* 2008]. Much of the data guiding treatment in this setting has been generalized from studies of acute asthma in the ED and from general populations of hospitalized patients with acute asthma. Further research to define optimal care of patients experiencing near fatal asthma is still needed.

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Conflict of interest statement

Dr Reibman and Dr Rogers have been clinical investigators for Novartis, Genentech, and Boehringer-Ingelheim Pharmaceuticals.

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