Life-Threatening Asthma: Pathophysiology and Management

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Asthma prevalence and mortality have been increasing over the past 2 decades, despite advances in medical therapy. In 2003 the National Health Interview Survey reported over 4,000 asthma-related deaths. A small proportion of people with severe asthma use a large proportion of health-care resources and bear the burden of asthma-related morbidity and mortality. The management of acute asthma is complex and evolving. Understanding the phenotypes and pathophysiology of acute asthma will lead to increased recognition and characterization of populations at risk for fatal asthma. The early identification and appropriate management of acute asthma is critical in decreasing asthma morbidity and mortality. This paper reviews current pharmacologic and nonpharmacologic management of severe acute asthma. *Key words: asthma, exacerbation, fatal asthma, airway inflammation, mechanical ventilation, respiratory failure, corticosteroids, bronchodilators.* [Respir Care 2008;53(6):726–735. © 2008 Daedalus Enterprises]

Introduction

Asthma is a disease characterized by variable airway inflammation and airflow obstruction. Asthma management was revolutionized by the advent of inhaled corticosteroids, which greatly improved asthma control and decreased morbidity and mortality. Nevertheless, asthma-related mortality in the United States remains an important problem. There are approximately 4,000 asthma deaths per year (15 per million persons).[1] There are gender and racial disparities in asthma mortality. Women are more likely than men to die of asthma. Blacks have the highest risk of asthma-related hospitalization and death (3.7 per 100,000 persons, vs 1.2 per 100,000 persons in whites) (Fig. 1). The vast majority of the burden of asthma-related morbidity and mortality is carried by a small proportion of people with severe asthma.[2] In the United Kingdom there have been more asthma deaths in women and persons over 45 years old who have comorbid conditions, including respiratory infections, cardiac disease, and diabetes.[3] This underscores the fact that asthma-related morbidity and mortality is often multifactorial.
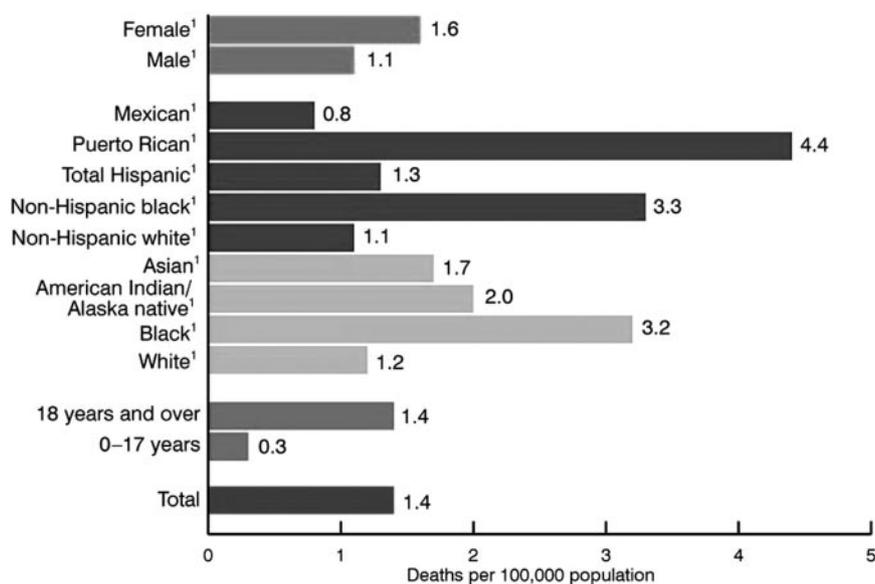
Fig. 1. Asthma deaths in 2003. 1. Age adjusted to 2000 United States standard population. (From Reference 1.)

Asthma exacerbation remains one of the most common reasons for presentation to the emergency department. Asthma-related emergency-department visits in the United States were 68 per 10,000 persons in 2002. However, blacks had a much higher rate of 210 per 10,000 persons. Griswold et al examined the characteristics of asthmatics that resulted in more emergency-department visits, and the number of emergency-department visits was associated with older age, non-white race, lower socioeconomic status, and more severe asthma (defined as a history of steroid use, prior hospitalization, and prior intubation for asthma).[4]

Acute Asthma Phenotypes and Pathophysiology

In 1922 Huber and Koessler documented that the pathology findings associated with fatal asthma included over-inflated lungs, mucus plugging of the large and small airways, Charcot Leyden crystals, epithelial damage, basement membrane thickening, and infiltration of the airway walls with eosinophils.[5] More recently, studies of the inflammation profiles of bronchoalveolar lavage fluid from patients with life-threatening asthma showed an increased influx of neutrophils,[6,7] eosinophils, mast cells,[6] and tumor necrosis factor alpha.[8] There is heterogeneity in the pathology findings from airway specimens from patients who died of asthma.[9] Inflammatory cells and pro-inflammatory mediators result in epithelial damage, extensive mucus plugging (Fig. 2), and increased endothelial permeability, with resultant airway edema.[10]

Asthma symptoms and the severity of airflow obstruction differ among subjects who present with life-threatening asthma. Picado[11] described 2 patterns of life-threatening asthma. The first life-threatening asthma phenotype presents with moderate-to-severe airflow obstruction that has an onset of days to weeks prior to presentation, is associated with airway-wall edema, mucus-gland hypertrophy, and inspissated secretions, and is slow to respond to treatment. The second life-threatening asthma phenotype is acute asphyxic (sudden-onset) asthma. This phenotype is less common, develops over minutes to hours, and is associated with acute bronchospasm and neutrophilic bronchitis.[11-13] Peak expiratory flow (PEF) values and the initial management of sudden-onset and slower-onset life-threatening asthma are similar; however, the sudden-onset subgroup has faster therapeutic response and shorter hospital stay.[14,15]

Risk factors for life-threatening asthma include the presence of more severe asthma signs and symptoms, prior intubation, steroid dependence, and nonadherence to inhaled corticosteroids.[16-18] Molfino and Slutsky found that important risk factors for life-threatening asthma are age, previous life-threatening asthma episodes, hospital admission within the past year, inadequate asthma management, psychological or psychosocial problems, and lack of access to medical care.[19,20] Other studies found increased risk of acute and life-threatening asthma associated with a lower forced expiratory volume in the first second (FEV_1) and current cigarette-smoke exposure.[21] Interestingly, the asthma mortality rate has not declined, despite our increased knowledge about the risk factors and the availability of better asthma controller medications.

Clinical Presentation and Assessment

The presentation of severe asthma is variable, which often leads to poor recognition of the severity of illness,
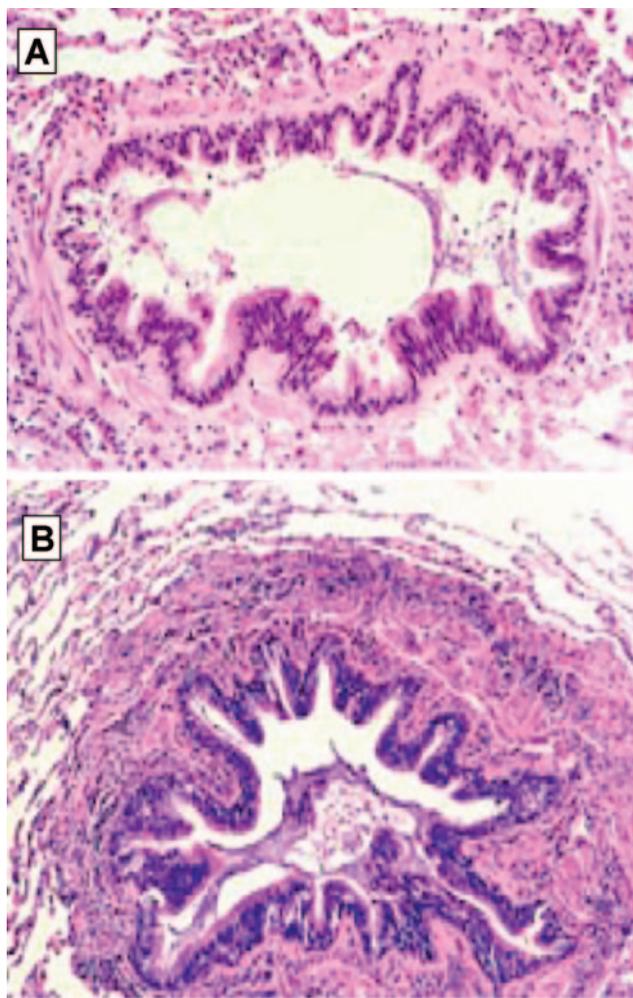
Fig. 2. Small airways in (A) a normal subject and (B) a subject who died of severe asthma: note the wall-thickening, more inflammatory cells, constriction of the airway, and mucus plugging. (From Reference 10, with permission.)

Table 1.   Markers of Severe Asthma Exacerbation

Difficulty talking in full sentences
Decreased FEV_1, or PEF < 40% of best or predicted (< 25% in life-threatening asthma)
Oxygen saturation < 90–92%
P_{aO_2} < 60 mm Hg
P_{aCO_2} > 42–45 mm Hg
Use of accessory muscles, tracheal tugging (increased work of breathing)
Pulsus paradoxus (> 15-mm Hg drop with inspiration); absence may indicate muscle fatigue
Quiet chest
Patient seated upright and unable to lie supine
Cyanosis and sweating
Confusion
Decreased level of consciousness
Hypotension or bradycardia

FEV_1 = forced expiratory volume in the first second
PEF = peak expiratory flow
(Adapted from References 24-27.)

which in turn results in greater morbidity.[22-24] The clinical examination can be misleading, and key clinical features must be taken into consideration when assessing a patient with acute asthma (Table 1). Occasionally, asthmatics with poor perception of the severity of their asthma[22] may appear deceptively well despite severe decrements in lung function, which can mislead the clinician.[23] Inadequate history and physical examination, lack of lung-function measurements, misuse or misinterpretation of arterial blood gas values and chest radiographs, insufficient use of systemic corticosteroids, and over-reliance on inhaled bronchodilators are among the problems that can occur during the initial hospital management of acute asthma.[20]

Estimates of the severity of airflow obstruction are generally inaccurate when clinicians rely solely on the history and physical examination.[24] Objective measurements of lung function would thus seem reasonable, but lung-function measurements are obtained from fewer than 30% of patients treated for acute asthma in the emergency department,[28] probably based on the assumption that patients with acute asthma are unable to perform these tests. However, Silverman et al demonstrated that patients with acute asthma are often able to perform spirometry appropriately,[29,30] and the results can be used for risk stratification and treatment.[31] A PEF < 40% of baseline and/or an FEV_1 < 40% of predicted (or < 1 L) are generally considered consistent with severe exacerbation, and those values below 25% are considered consistent with life-threatening asthma.[24] In general, spirometry is a more reliable index than PEF, because PEF measurements have significant variability, with poor short-term and long-term reproducibility,[32-35] and PEF may not accurately reflect airways resistance in acute asthma. PEF, however, is an acceptable measurement if the FEV_1 maneuver cannot be performed.

The debate is ongoing regarding whether lung-function tests are essential during the assessment of all patients with acute asthma.[36] Nevertheless, if done well, these tests would seem to add important information to the overall determination of the airway-obstruction severity. Moreover, serial measurements can be used to follow response to therapy and can predict the need for hospitalization. The National Asthma Education and Prevention Program's 2007 asthma guidelines recommend that if FEV_1 or PEF is < 25% of predicted and fails to improve by > 10% after initial treatment, hospitalization and close monitoring are indicated.[24]

Exhaled nitric oxide is a noninvasive measure of lung and airway inflammation, and elevated exhaled nitric oxide occurs in severe allergic asthma. Exhaled nitric oxide measurements may predict future asthma exacerbations[37] and response to therapy with corticosteroids.[38,39] How-

ever, routine use of this biomarker is still controversial. Serial exhaled nitric oxide measurements used to adjust asthma-maintenance therapy did not decrease exacerbations or steroid dose.[40] In contrast, exhaled nitric oxide during asthma exacerbation has not been extensively studied. Gill et al[41] compared exhaled nitric oxide measurements obtained in the emergency department to spirometry and clinical markers of asthma severity, and found no correlation. Moreover, exhaled nitric oxide was not a useful marker of asthma severity. The use of exhaled nitric oxide in the acute setting warrants further study but is not recommended for routine use at this time.

Alveolar ventilation decreases with worsening asthma exacerbation, increased respiratory muscle fatigue, and bronchospasm. Arterial blood gas values (eg, P_{aCO_2}) can also be used to assess the extent to which alveolar ventilation is compromised. Alternatively, capnography (measurement of mixed expired CO_2, CO_2 production, and end-tidal CO_2) can be used to calculate alveolar ventilation and dead-space ventilation.[42-45] Alternatively, Corbo et al found high concordance between arterial blood gas values and end-tidal carbon dioxide levels in patients with acute asthma.[44]

Arterial blood gas analysis can usually be reserved for patients whose room-air oxygen saturation is $< 90–92\%$ and/or who do not respond to initial treatment and have a persistent $FEV_1 < 30\%$ of predicted.[46] $P_{aCO_2} > 42–45$ mm Hg is worrisome for impending respiratory failure and is an indication for consideration of mechanical ventilation. Because hypocarbia is often present in acute asthma, as a response to dyspnea, even a normal P_{aCO_2} may indicate respiratory muscle fatigue, and such patients should be closely observed and admitted to a high-dependence unit or intensive care unit for monitoring. Arterial desaturation and hypercapnia usually occur concomitantly and are often used to describe life-threatening asthma. In contrast to arterial blood gas analysis, pulse oximetry is inexpensive and easy to obtain in all patients with life-threatening asthma.[24]

Management of Acute Asthma

Pharmacologic Management

The cornerstones of acute asthma therapy are bronchodilators, corticosteroids, and oxygen. Bronchodilators, including β agonists and anticholinergics, are the first-line of therapy for acute asthma (Table 2).[24] β agonists provide immediate symptom relief and decrease bronchoconstriction and airflow obstruction. The major adverse effects of β agonists are tachyarrhythmia and severe tremors. Inhalation of β agonist is preferable to intravenous administration because the inhalation route delivers the medication directly to the site of action, which minimizes systemic

Table 2. Drug Dosages for Severe Acute Asthma

Drug	Dosage
Albuterol via nebulizer	2.5–5.0 mg every 20 min for 3 doses, then 2.5–10 mg every 1–4 h as needed, or 10–15 mg/h continuously
Albuterol via MDI	4–8 puffs every 20 min, up to 4 h, then every 4 h as needed
Ipratropium via nebulizer	0.5 mg every 20 min for 3 doses, then as needed (may be mixed with albuterol)
Ipratropium via MDI	8 puffs every 20 min as needed up to 3 h
Prednisone/methylprednisolone	40–80 mg/d in 1–2 divided doses until peak expiratory flow reaches 70% of predicted

MDI = metered-dose inhaler
(Adapted from Reference 24.)

adverse effects.[24,47,48] Current recommendations suggest that metered-dose inhaler with holding chamber is as efficacious as nebulizer in acute asthma.[49,50] Remember, however, that with a metered-dose inhaler, effective aerosol delivery requires a specific patient maneuver that may be difficult for an acutely dyspneic patient.

Most asthmatics respond to initial therapy with improvement in airflow obstruction, but in the small proportion of patients who have persistent obstruction despite aggressive treatment, continuous inhaled β agonist (one nebulization every 15 min or > 4 per hour) may be indicated.[24] Camargo et al found that continuous administration of nebulized β agonist improved lung function, reduced the need for hospitalization, and was generally well tolerated.[51] When using such an aggressive dosing strategy, careful monitoring is required, and the delivered dose should be titrated to effect (and adverse effects).

Inhaled formoterol is a newer long-acting β agonist that has an onset of action comparable to that of albuterol. However, formoterol has not been extensively studied in the acute setting. A recent study found similar PEF increase with nebulized formoterol 24 μg versus albuterol 600 μg via metered-dose inhaler with spacer in 3 separate doses.[52] Adverse events were similar between the treatment groups. Prior studies with inhaled formoterol showed similar efficacy.[53,54] Further studies are needed to determine the role of formoterol in acute asthma.

The addition of anticholinergics should be considered in acute asthma; the potential benefits include improved lung function and reduced recovery time.[55-57]

Asthma exacerbations are associated with substantial airway inflammation, and corticosteroids are potent anti-inflammatory agents that are essential to the treatment of acute asthma and should be administered as soon as pos-

sible (see Table 2).[24] Oral and intravenous corticosteroids have similar efficacy in the treatment of acute asthma.[58,59] Inhaled corticosteroids may be as effective as systemic steroids if the inhalation route provides appropriate lung delivery, but replacing systemic corticosteroids with inhaled corticosteroids in severe acute asthma is usually not recommended.[24] A dose-response effect curve exists for corticosteroids in acute asthma, but there is little evidence that greater than 50 mg of prednisolone per day is needed. A post-exacerbation course of oral corticosteroids decreases relapse rate.[60]

Cysteinyl leukotrienes are potent inflammatory mediators responsible for eosinophil chemoattraction, airway inflammation, mucus production, and bronchoconstriction. Increased cysteinyl leukotriene is observed in the urine of some adults and children with acute asthma.[61] In children with mild-to-moderate asthma exacerbations, leukotriene antagonists were additive to the effects of β agonists.[62,63] Zafirlukast (20 mg twice daily) improved FEV_1 and dyspnea in the emergency department, resulted in sustained FEV_1 improvement, and decreased the risk of relapse.[64] Montelukast improves FEV_1 shortly after infusion, and this effect lasts for hours and occurs concomitantly with a decreased bronchodilator dose.[65,66] Leukotriene antagonists should be considered as adjunctive therapy in patients with severe airflow obstruction from asthma.

Use of methylxanthines (eg, aminophylline and theophylline) in acute asthma is controversial because of their narrow therapeutic index. Intravenous theophylline improves FEV_1, PEF, and asthma dyspnea-scale score in asthma exacerbation.[67,68] A recent Cochrane review found improved lung function with the addition of aminophylline to inhaled β agonists and corticosteroids in children over age 2 years with severe asthma. There were no differences in adverse effects, except for more nausea and vomiting. No differences, however, were found in overall mortality, intensive-care-unit admission, or hospital stay.[69] On the contrary, some studies have found greater toxicity without any benefits.[70] Thus, methylxanthines may have some benefit in the treatment of acute asthma, but they should not be used as first-line therapy. Rather, they should be considered only in subjects with severe exacerbation refractory to initial therapy.

Other therapies for refractory life-threatening asthma include inhaled racemic epinephrine, intravenous epinephrine, and magnesium sulfate.[24] Inhaled racemic epinephrine is highly efficacious in cases of upper-airway obstruction, for instance in children with croup. It may also benefit the treatment of acute asthma.[71,72] A meta-analysis of inhaled racemic epinephrine or the L isomer of epinephrine in refractory asthma found bronchodilation and PEF-improvement similar to albuterol (salbutamol).[72] Intravenous epinephrine is associated with a higher risk of adverse events, including cardiac events, acute myocardial infarc-

tion, and arrhythmia, so its use should be limited.[73-75] Magnesium has beneficial effects on smooth-muscle relaxation and inflammation.[76] A systematic review indicated that intravenous magnesium may provide benefits, especially in severe exacerbations.[2] A recent Cochrane review concluded that the addition of nebulized magnesium to β agonist improved lung function, and there was a trend toward lower hospital admission rate.[25,77]

Nonpharmacologic Management

Oxygen therapy should be administered to maintain an oxygen saturation of $> 90\%$.[24] High oxygen concentration should be avoided, because it may worsen carbon dioxide retention, delay recognition of worsening respiratory failure (due to lack of recognition of progressive desaturation), and reduce cardiac output.[78-80] Helium/oxygen mixture (heliox), which is typically 80% helium and 20% oxygen, has a lower density than air, which decreases the flow turbulence and flow resistance and thus improves delivery of both oxygen and aerosolized medication to the distal lung.[81] The lower gas density also facilitates exhalation, thereby reducing air trapping and intrinsic positive end-expiratory pressure (PEEP). In a meta-analysis by Colebourn et al, heliox increased PEF by an average of 29%, but the effects on recovery from acute asthma were not characterized.[82] A series of small randomized controlled trials were included in a recent Cochrane review of 544 nonintubated asthmatics. Heliox improved pulmonary function only in the subgroup of patients with the most severe airflow obstruction, and did not improve outcomes or decrease the risk of hospital admission.[83] On the contrary, other studies found improvements in asthma with heliox-propelled nebulized bronchodilators, especially when heliox is administered within the first hour of presentation of a severe exacerbation.[84-86] No complications or adverse events have been reported associated with heliox. However, because heliox is not currently supported by high-grade evidence, its routine use cannot be recommended.[87-89]

Noninvasive Mechanical Ventilation

A small proportion of asthmatics have progressive respiratory failure despite aggressive pharmacologic and nonpharmacologic therapies. The role of noninvasive ventilation (NIV) in these situations is uncertain. A Cochrane review of randomized controlled trials of NIV resulted in the inclusion of one trial of 30 patients that showed promise. In that study NIV was associated with better FEV_1, forced vital capacity, PEF, respiratory rate, and hospital admission rate.[90] Fernandez et al performed a retrospective review of patients with status asthmaticus treated over a 7-year period. Of 33 patients who required mechanical
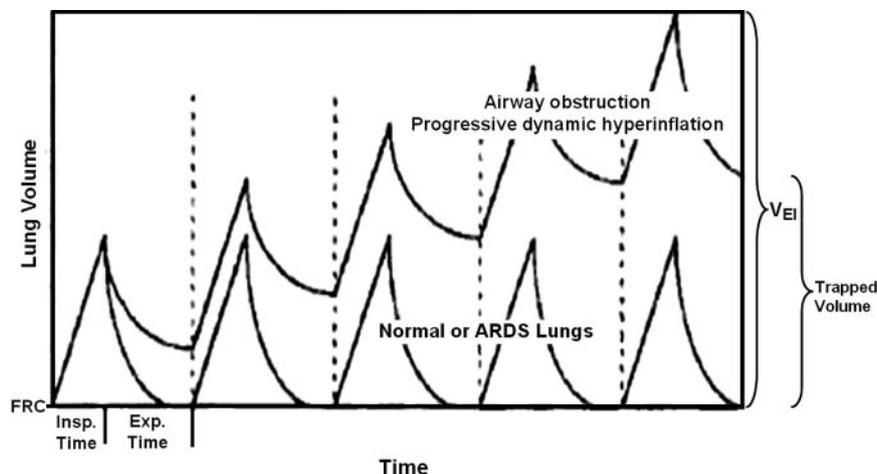
Fig. 3. Mechanical ventilation in lungs with and without airflow obstruction. The lower curve, which represents the unobstructed normal lung (or a stiff lung, in acute respiratory distress syndrome [ARDS]), shows a return of the lung volume to baseline functional residual capacity (FRC) at the end of each expiration. The upper curve, which represents a lung with airflow obstruction, shows slow expiratory flow and incomplete exhalation, resulting in progressive dynamic hyperinflation, until a lung volume is reached at which the increased lung elastance allows the entire V_T to be exhaled. Insp. time = inspiratory time. Exp. time = expiratory time. V_{EI} = end-inspiratory lung volume. (Adapted from Reference 97, with permission.)

ventilation, 11 required invasive ventilation because of higher CO_2 level, acidosis, or altered mental status. Of the remaining 22 patients who received NIV, 3 additional patients required intubation for progressive respiratory failure. There were no differences in intensive-care-unit stay, median hospital stay, or mortality between the treatment groups.[91] Additional studies have given inconsistent results. Thus, NIV is still controversial and warrants further study with randomized controlled trials.[92-95] Patients must be carefully selected. Those with a high risk of death, altered mental status, severe acidosis, or hemodynamic instability should be immediately intubated and not have a trial of NIV.

Invasive Mechanical Ventilation

The decision to intubate a patient in status asthmaticus is largely based on clinical judgment that respiratory failure is progressing despite maximal therapy. When it is apparent that intubation is warranted, there should be no delay of intubation, because the patient can deteriorate rapidly and succumb to respiratory failure and acidosis.

Current invasive ventilation strategies aim to improve gas exchange, increase alveolar ventilation, minimize air trapping (intrinsic PEEP), and avoid volutrauma/barotrauma (ventilator-induced lung injury). Airways resistance in life-threatening asthma is dramatically increased by bronchoconstriction and mucus plugging. Increased airways resistance is most prominent on exhalation, which produces dynamic hyperinflation (air trapping, intrinsic PEEP)[96,97] (Fig. 3), which is identifiable on the ventilator flow graphics, or by an performing end-expiratory-hold
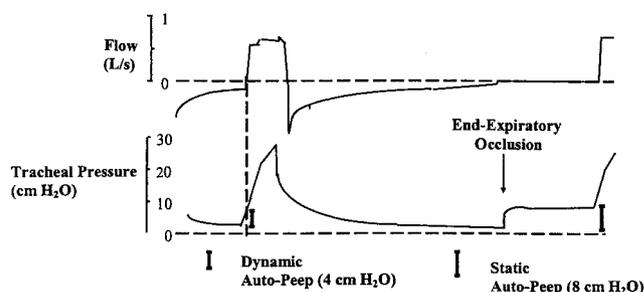

Fig. 4. Flow and tracheal-pressure waveforms, showing the determination of intrinsic positive end-expiratory pressure (auto-PEEP) in a passive ventilated patient. Note that the expiratory flow signal does not return to zero before the next breath is given; this is a sign of incomplete exhalation. Dynamic auto-PEEP is measured as the airway pressure at the instant that flow crosses zero. Static auto-PEEP is measured by occluding the airway opening at end-expiration until lung and airway pressures equilibrate. (From Reference 96.)

maneuver in a passive ventilated patient (Fig. 4).[96] As intrinsic PEEP increases, compliance decreases and gas exchange worsens. The breath-triggering work can also increase with intrinsic PEEP because it places a threshold load on the respiratory muscles. Applied PEEP under these circumstances can equilibrate circuit and intrinsic PEEP to reduce this load, decrease the work of breathing, and improve ventilator triggering (Fig. 5).[98]

There have been no randomized controlled trials to determine the best mechanical ventilation mode in life-threatening asthma. Indeed, the ventilation mode is probably less important than providing settings that minimize dynamic hyperinflation and intrinsic PEEP. The ventilation settings involve low tidal volume, avoiding high re-
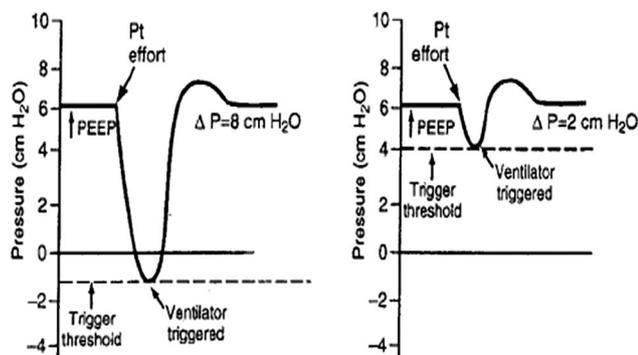
Fig. 5. Pleural-pressure tracings from a patient with 6 cm H_2O intrinsic positive end-expiratory pressure (intrinsic PEEP). In the left panel the applied circuit PEEP is set at 0 cm H_2O and the triggering threshold is 1 cm H_2O below that (dashed line). The ventilator is triggered when the patient's inspiratory effort reduces the pleural pressure to that threshold (nearly 8 cm H_2O). In contrast, the right panel shows the same patient with an applied circuit PEEP of 5 cm H_2O and a trigger threshold below that (dashed line). Under those circumstances the patient only has to generate 2 cm H_2O in the pleural space to initiate the breath. Pt = patient. ΔP = change in pressure. (From Reference 98, with permission.)

spiratory rate,[99] and maintaining a low inspiratory-to-expiratory ratio (eg, < 1:2 or 1:3). Using low tidal volume (and limiting end-inspiratory plateau pressure to < 30 cm H_2O) may also reduce regional lung over-stretch injury. Importantly, lower tidal volume and slower respiratory rate may substantially decrease alveolar ventilation and thus cause hypercapnia and respiratory acidosis. Tolerating acidosis (permissive hypercapnia) is important in this circumstance, and pH < 7.20 (or even 7.10) may be acceptable if it reduces the risk of lung over-stretch injury.[100]

Appropriate sedation may be very important to enhance patient-ventilator synchrony and comfort. Benzodiazepines are commonly used for sedation and to induce amnesia. Midazolam has a rapid onset of action and induces adequate sedation in most patients. Propofol is another effective sedative, and has additional bronchodilation effect. However, long-term use of propofol increases the risk of infection, pancreatitis, and hypertriglyceridemia. Opiates are not a substitute for sedatives, but may be important to control pain. They should be used carefully in life-threatening asthma, however, because of their potential to induce hypotension, histamine release, and vagally mediated bradycardia.[101]

The use of anesthetics in the management of status asthmaticus is controversial. Anesthetics such as halothane and ketamine administered in low doses have been used to induce potent bronchodilation and to avoid intubation in patients with severe asthma.[102,103] The use of halothane has been reported in case reports and case series, but a randomized trial has not been performed. Halothane decreases peak airway pressure and dead-space ventilation,

which improves gas exchange.[104] Halothane is associated with hypotension that generally responds to vasopressors. Ketamine is administered intravenously and has sedative, analgesic, and bronchodilation properties. Ketamine can be used for intubation and as an infusion for refractory asthma. Because of its sympathomimetic effects, its use should be avoided in hypertension, increased intracranial pressure, or pre-eclampsia.[105] No evidence-based recommendations exist regarding the use of halothane in status asthmaticus.

The use of neuromuscular blockade may be necessary in patients with severe respiratory failure and who are difficult to ventilate. Paralytics (eg, vecuronium, atracurium, cis-atracurium, pancuronium) decrease chest-wall stiffness, eliminate muscle loading from patient-ventilator dyssynchrony, lower the risk of barotrauma, and decrease oxygen consumption. These drugs can be used in intermittent boluses or continuous infusion. Continuous infusion should be accompanied by measurements of the degree of paralysis (eg, 2 stimulation responses out of 4 in train-of-4 testing). It is important to emphasize that paralytic use should be minimized because of the high risk of neuromuscular weakness and myopathy, particularly in patients concomitantly receiving corticosteroid therapy.[101] Additionally, paralytics cause excessive airway secretions, histamine release (vecuronium), and tachycardia and hypotension (pancuronium).[101]

Outcome and Prognosis

Afessa et al analyzed prospective data on prognostic factors, clinical course, and outcome of patients with status asthmaticus treated in an inner-city university medical center. There were 132 admissions of 89 patients: 79% were female, and 67% were African American. The mortality rate was 8.3%, and all the deaths occurred in females. Nonsurvivors had higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores, higher P_{aCO_2}, and lower arterial pH. Twenty-one percent of the patients who required mechanical ventilation died.[106]

Summary

The impact of adequate treatment of chronic asthma on the occurrence of asthma exacerbation and death cannot be underestimated. Undoubtedly, a small proportion of patients with severe asthma bear the burden of exacerbations, and some exacerbations are unavoidable. However, disparities in access to care and medications increase the risk of asthma morbidity and mortality. Future efforts to improve outcomes should focus on identifying populations at risk and addressing health-care-access disparities.

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Discussion

Sorkness: Neil, you showed a slide about high doses of albuterol, and part of the rationale was that additional receptors are available. What did you mean by that?

MacIntyre: I am not a pharmacologist, so maybe that's a poor choice of terms, but the point is, you may get more bronchodilation with a higher dose. The problem is that you run into adverse effects, and that's why we usually limit the dose to the FDA [Food and Drug Administration] approved dose. Bruce, are you going to help me here?

Rubin:[*] Actually, I'm going to hurt you! I'm not familiar—I mean, steroids will unmask receptors, but I don't think there are more receptors available as you give more β agonist. In fact, you may down-regulate them, causing tolerance.

One of the problems with the study that showed the dose response is that there is a time element involved as you give more doses.[1] The slide you showed used peak flow as an outcome. They used fairly low doses, 2.55 mg and 7.5 mg via jet nebulization, so it's hard to extrapolate. The other concern is that β agonists increase heart rate, they decrease potassium, they increase mucus secretion, and we know that the frequent use of β agonists may be

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associated with more severe asthma. So I wonder how hard we can "flog this horse" and whether we're actually helping the patient by pushing this that hard. We already know that with corticosteroids you don't have to go so high; you don't have to give mega-doses for the same effects. I don't think that similar studies have been done with β agonists.

1. Sheffer AL, editor. Fatal asthma. (Lung biology in health and disease, vol 115. Lenfant C, series editor). New York: Marcel Dekker; 1998.

MacIntyre: So increasing the dose is not the right thing to do?

Rubin: I would argue that we don't have data to show one way or another, and that we have to beaware that we may be doing harm.

Stoloff:[†] In writing the 2007 NAEPP [National Asthma Education and Prevention Program] guidelines[1] section on exacerbations, we had a much more robust data set to work from now, so we looked at that. Carlos Camargo ran that program, and it's exactly what Bruce is alluding to: we looked at what happened in the populations where they gave 5 mg albuterol to start, and then 5, 5, 5, versus some other ways, and it turned out that the adverse effects were greater than the benefit in the world literature. So we didn't identify the presence of other receptors. We found that the benefit was from starting earlier, with aggressive but appropriate dosing.

1. Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda, Maryland: National Institutes of Health, National Asthma Education and Prevention Program; 2007. NIH Publication No. 08-4051. http://www.nhlbi.nih.gov/guidelines/asthma/asthgldn.pdf. *Accessed April 1, 2008.*

MacIntyre: Let me address this from another perspective. Let's set the receptor argument aside for a moment. Patients in acute bronchospasm have much more difficulty getting aerosol into the lungs, because the airways are narrowed and plugged with mucus, so they can't do the breathing maneuver that gets aerosol to the small airways. So to get the same effect you would from 2.5 mg of nebulized albuterol in a stable asthmatic, you may need several times that dose to get a similar amount of drug to the small airways in somebody who is having difficulty breathing.

Rubin: The largest study of fatal asthma was the Prairie Provinces study.[1] What we determined[2] was that there is some bronchospasm, some edema, and inflammation, but these

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† Stuart W Stoloff MD, Department of Family and Community Medicine, University of Nevada, Reno, Nevada, representing Monaghan/Trudell Medical.

patients drown in their secretions. They're absolutely plugged with secretions, and β agonists aren't going to move those secretions out. Corticosteroids probably won't do it. Giving more of the β agonist may in fact induce secretions. So it's hard to know how much of this is helpful.

1. Hessel PA, Mitchell I, Tough S, Green FH, Cockcroft D, Kepron W, Butt JC. Risk factors for death from asthma. Prairie Provinces Asthma Study Group. Ann Allergy Asthma Immunol 1999;83(5):362-368.
2. Rubin BK, Tomkiewicz R, Fahy JV, Green FY. Histopathology of fatal asthma: drowning in mucus. Pediatr Pulmonol 2001;23(Suppl):88-89.

Colice: Neil, giving more β agonist will decrease the receptors acutely, and the bronchodilation effect plateaus, but the systemic adverse effects do not; the heart rate and hypokalemia effects continue to increase as you increase the dose. I would be worried about giving that large a dose of albuterol.

Diette: An observation we made in a paper on exacerbations—that I think isn't necessarily apparent epidemiologically—is that most asthma deaths are outside the hospital.[1] Here we're talking about in-hospital management, but in a study I participated in we used a publicly available nationwide federal data set that captures all the hospitalizations in the United States, and we could account for only about a third of the number the CDC [Centers for Disease Control and Prevention] reported as the annual asthma death rate. About two thirds aren't captured by hospitalizations.

There's also a race difference; blacks and whites die at about the same rate once they're in the hospital. In fact, there's actually a slight advantage for blacks once they're in the hospital, but they're much less likely to get to the hospital. Though there's a lot of action in the hospital, most of the mortality is outside of the hospital, and there's disparity in the out-of-hospital mortality. We didn't find an

explanation in that data set of whether that is related to medication use or lack of medication use. It's a system failure, because if people are dying in the pre-hospital arena, they're not getting the treatment they need.

1. Krishnan V, Diette GB, Rand CS, Bilderback AL, Merriman B, Hansel NN, Krishnan JA. Mortality in patients hospitalized for asthma exacerbations in the United States. Am J Respir Crit Care Med 2006;174(6):633-638.

Stoloff: Sarah Aldington and Richard Beasley studied the frequency and the number of puffs you need from a rescue inhaler to obtain the bronchodilation in different populations.[1] What was surprising was how little they needed. They looked at somewhere as a maximum— of consecutive puffs 30 seconds apart or so—4 to 6 puffs maximum: that was it. We thought the sicker the person is, the more puffs you keep pushing, but when they looked at all the data, it turned out to be much less. That was enlightening.

1. Aldington S, Beasley R. Asthma exacerbations: assessment and management of severe asthma in adults in hospital. Thorax 2007;62(5):447-458.

MacIntyre: Jesse Hall's review[1] argued for pushing the β agonist and using heart rate as a guide, the idea being that if you reach a toxicity level with the β agonist, you'll see a rise in heart rate. Many protocols are written to push the β agonist while watching for tachycardia, on the premise that it's difficult to get the drug into the lung and thus difficult to get the effects on the lung, and that heart rate is a marker of toxicity.

1. Rodrigo GJ, Rodrigo C, Hall JB. Acute asthma in adults: a review. Chest 2004;125(3):11081-1102.

Myers: You showed compelling data that there may be a slight advantage to continuous (versus intermittent) nebulization, and I think that's where clinical practice is drifting. About the con-

cept of dosing to effect, I think we're going to run into a problem there. We've got to get more protocolized or standardized, because the Joint Commission's big push now is medication safety and medication reconciliation. We're dumping undiluted albuterol into a large-volume nebulizer, and at some point a Joint Commission surveyor is going to ask, "How much albuterol did you give that patient?" We've got to be careful how we do that.

MacIntyre: Yes, but the protocol is not just, "Give as much albuterol as possible and damn the torpedoes." We're watching response. Is the patient better? Is there a high heart rate or tremor or any other adverse effect? If so, the albuterol is either stopped or adjusted.

McCormack: Is there any role for levalbuterol in the patient with life-threatening asthma?

MacIntyre: I know of no data that levalbuterol is superior to racemic albuterol.

Colice: It's hard to know in the acute setting when somebody's really sick, because you don't know how much of the drug is getting to the lungs. In a stable patient if you give 16 cumulative puffs of albuterol over 2 hours, you'll increase their heart rate about 10-15 beats/min, and that's assuming you're starting at 60-70 beats/min. In these ICU [intensive care unit] patients, their heart rate is 90-100 beats/min, and if you assume that that's all from the albuterol and that their normal heart rate is 70 beats/min, then they're already quite tachycardic. If you look at the potassium response after 8-16 puffs, you're talking about 0.5-1.5 mEq/L, so the potassium continues to go down, the heart rate continues to go up, and the bronchodilator effect plateaus. So I can understand the point about following tachycardia, but it's tough in the ICU, where some-

body's heart rate is 110 beats/min already.

MacIntyre: Mind you, this should never be done outside the ICU setting.

Stoloff: For the guidelines,[1] we looked at the data on ipratropium bromide and we found that its role is not in someone who ends up in the hospital. Its major benefit is in the sicker individual who has a lower FEV_1 or markedly diminished peak flow, around 30% of their predicted normal, who benefits from that medication compounded with the albuterol—*in the emergency department*. It may keep them from getting hospitalized, and that was the total advantage of the medication.

1. Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda, Maryland: National Institutes of Health, National Asthma Education and Prevention Program; 2007. NIH Publication No. 08-4051. http://www.nhlbi.nih.gov/guidelines/asthma/asthgldn.pdf. *Accessed April 1, 2008.*

MacIntyre: That's where it's been studied. I think it's reasonable to say that if you get somebody into your ICU who's not received ipratropium, ipratropium would be something to add.

Stoloff: Studies identified in the guidelines looked at adding ipratropium in the ICU and did not find benefit. The only benefit identified was in the emergency room or the office, in a very severe asthma exacerbation with FEV_1 or peak flow of less than 30% of the patient's normal. These are quite sick individuals, and they're the only ones who benefit from the addition of ipratropium to the inhaled short-acting bronchodilator.

MacIntyre: So, Stuart, let me get this straight. Somebody who had respiratory arrest in the emergency department is now in your ICU and

intubated, and has not received ipratropium: you would not consider it?

Stoloff: No, I would consider it. We were looking at population studies. One of the concerns was that people continued to use ipratropium. They'd already administered it in the emergency department, and now the patient's hospitalized and they want to continue doing it because they're giving them everything. There's no data to support that after you've tried it. We're more concerned about continuing its use than about initiating its use.

Pierson:[*] Aren't there data that show that a very large proportion of mechanically ventilated people in ICUs receive inhaled bronchodilators, predominantly in the absence of evidence for either need or response? It's widely prevalent in my experience, in the units I work in, that if you've got anything remotely wrong with your lungs, you're going to get ipratropium as well as albuterol on a pretty regular basis. I can't defend that, but I believe it's the prevailing practice.

MacIntyre: In the ARDS [acute respiratory distress syndrome] Network we're doing an albuterol trial, on the idea that albuterol will help reduce lung edema and improve outcomes in ARDS. It's interesting, because the permission slip states that not only might we add a treatment to the medications group, we might also remove medications from the control group.

Moores: With an intubated patient who's getting continuous nebulization in your protocol, how do you balance the aerosol delivery with your ventilation strategy? In that group is it difficult to do with continuous nebulization, given the ventilator settings you

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need to deliver the aerosol, with regard to how you maximize aerosol delivery through the endotracheal tube? In an intubated patient, if you give the nebulizer intermittently, you could change the settings and probably get away with it, but with continuous nebulization the ventilator settings with which you deliver the aerosol would seem to contradict your overall ventilation strategy.

MacIntyre: The way to get aerosol through the endotracheal tube is with a very slow flow and a very long inspiratory time, which is exactly the opposite of what you want to do with somebody with airways obstruction, because it will worsen air trapping. "Continuous" nebulization is a bit of a misnomer, because usually what you're doing is nebulizing upstream in the inspiratory limb, so that during expiration it's charging the circuit and the next breath drives it into the lungs. How to set the ventilator pattern to do that maximally is tricky, and it's a balancing act. I think reducing air trapping is more important than optimum aerosol delivery.

Moores: Would the group that is most prone to air trapping benefit from intermittent administration instead of continuous? That way you wouldn't have to have a long inspiratory time all the time, so you wouldn't necessarily have cumulative air trapping.

MacIntyre: I understand your point: give a little air trapping, take it away, give a little air trapping, take it away.

Sorkness: Are there any nuances to your summary that are not applicable to pediatric patients, or are these principles applicable to both adults and kids?

MacIntyre: Can I ask my friend Bruce, my favorite pediatrician? Are the principles involved with managing life-threatening asthma different in pediatric patients than in adults?

Rubin: I don't think that there are important differences. Comorbidities may be different, and those need to be accounted for. You get the same air trapping, and the response to therapy appears to be similar. I don't believe that there are very substantial differences.

Donohue: At the journal club at my institution, my fellows and I reviewed a paper that found that in COPD [chronic obstructive pulmonary disease] exacerbation a high dose of β agonist did not lower the oxygen tension. We used to talk about a very high dose of albuterol as preferential to a vasodilator. Is that still important?

1. Polverino E, Gómez FP, Manrique H, Soler N, Roca J, Barberà JA, Rodríguez-Roisin R. Gas exchange response to short-acting beta2-agonists in chronic obstructive pulmonary disease severe exacerbations. Am J Respir Crit Care Med 2007;176(4):350-355.

Rubin: That may be one difference in pediatrics. One of the first papers on that, by Asher Tal,[1] was published in *Chest*, and most of the studies that have been reported about that initial paradoxical improvement in profusion before ventilation have been in pediatrics. We tend to recognize it, give oxygen, and just carry on.

1. Tal A, Pasterkamp H, Leahy F. Arterial oxygen desaturation following salbutamol inhalation in acute asthma. Chest 1984; 86(6):868-869.

MacIntyre: That's an observation that's been around for a long time in adults—that as you bronchodilate, you may actually worsen the $\dot{V}/\dot{Q}$ [ventilation-perfusion] matching.

Donohue: Bruce, years ago we used to see an entity called systemic gas embolization syndrome in teenagers and others, where we used very high pressure to ventilate asthmatics. Does anybody still see that? These patients would get a reticular rash in the distribution of the internal mammary artery, because the air would be entering the systemic circulation in status asthmaticus, and it was a life-threatening event. I've seen about 3 cases, but I haven't seen it in about 20 years, since I stopped taking care of young people in the ICU.

Rubin: I've not seen that. Fortunately, we have very few kids who end up intubated and ventilated. As shown by Neil, fatal asthma is, fortunately, uncommon in kids, and many of them are out-patient deaths. Apparently it's difficult to predict. Colin Robertson and his colleagues in Australia suggested that about a third of the children who died had what would have been assessed as having mild asthma, a third appeared to have moderate asthma, and the final third had what would be considered severe asthma.[1] That's a little misleading, because a much, much greater number had mild asthma to begin with. But as far as the deaths go, they appeared to be evenly distributed in terms of severity classification before the incident.

1. Robertson CF, Rubinfeld AR, Bowes G. Pediatric asthma deaths in Victoria: the mild are at risk. Pediatr Pulmonol 1992;13(2): 95-100.

McCormack: Greg commented about the proportion of people who don't make it to the hospital. In thinking about people who die of asthma, access to health care is obviously an issue. I wonder what medications these individuals have used at home prior to presentation at the hospital. For example, do we know how many of those people have used nebulizers and steroids at home and have gone through the algorithm and just haven't made it, versus people who run out of their β agonist or haven't treated themselves at home? Is that information known about patients who die from asthma?

Donohue: I don't know that, but the question reminds me of something Meredith asked about levalbuterol, and

I completely agree with the comments here that the data don't substantiate it. We know from the levalbuterol data that in patients who use high doses of β agonist the blood S-albuterol levels are very high in some of the patients coming in. Their curves have shifted. That doesn't mean they're going to respond to levalbuterol or not, but they do have shifted curves, so we know that a lot of people are using very high doses, when we measure that when they enter the emergency department.

Kercsmar: You're right that you can use the S-albuterol level as a marker. Some people who come in and have the most obstruction have been using a lot of β agonist. But it should also be made clear that there is no evidence that the S-albuterol is a bronchoconstrictor.

Donohue: Or that it's pro-inflammatory.

Kercsmar: Correct.

MacIntyre: To get to your question, Meredith [McCormack], most of the deaths are recorded in the hospital, because even if they go into respiratory arrest at home, the emergency medical services people bring them into the emergency department before they're officially pronounced dead. Many of them are that way.

Donohue: A lot of the SMART [Salmeterol Multicenter Asthma Research Trial] deaths were outside the hospital.[1]

1. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The salmeterol multicenter asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006;129(1):15-26.

Colice: Neil, of the patients who die in the hospital, the deaths are almost always respiratory, is that correct?

MacIntyre: Yes.

Colice: So we don't see cardiac deaths?

MacIntyre: Every death, at the end of the day, is a cardiac arrest. They get refractory hypoxemia and acidosis that can't be managed, and they have a cardiac arrest.

Colice: So this whole argument about albuterol is probably irrelevant, because they don't die from albuterol deficit or albuterol excess.

MacIntyre: They don't die from unexplained cardiac arrhythmias; they die from arrhythmias that are clearly related to hypoxemia and acidosis.

Colice: I was struck that you talked about plateau pressure but not peak pressure.

MacIntyre: Peak pressure probably is important at the beginning of the breath; the more normal airways and alveoli are exposed to those, so, unlike in ARDS, where we're less concerned about peak pressure, we probably ought to be concerned about peak pressure in obstructive lung disease.

Rubin: Two comments to Jim. When we talk about fatal asthma, I've heard people call home death from asthma a steroid-deficiency disease. And although there may be a number of patients with poorly controlled asthma who aren't taking steroids, Monica Kraft and others[1] found that people who are dying of asthma often have a neutrophilic inflammation, and steroids probably aren't going to do a whole lot there, according to the current speculation. Perhaps we should be looking at different ways to clear the airways of secretions and reduce the neutrophilic inflammation in these patients who come in with very severe, life-threatening asthma. In the Prairie Provinces study,[2] there was histologic evidence from the pathology side that there was a lot of neutrophilic inflammation, but I was struck that a number of those who died at home had these massive mucus secretions that may have suddenly occluded an airway and produced an asphyxia death.

1. Sutherland ER, Martin RJ, Bowler RP, Zhang Y, Rex MD, Kraft M. Physiologic correlates of distal lung inflammation in asthma. J Allergy Clin Immunol 2004;113: 1046-50.
2. Hessel PA, Mitchell I, Tough S, Green FH, Cockcroft D, Kepron W, Butt JC. Risk factors for death from asthma. Prairie Provinces Asthma Study Group. Ann Allergy Asthtma Immunol 1999;83(5):362-368.

Diette: Jerry Krishnan studied patients' therapy adherence after hospitalization,[1] and within 2 weeks of discharge from hospitalization— including for nearly fatal asthma— patients' adherence to both oral and inhaled corticosteroids was abysmal. A handful of people took the prescribed asthma drugs as instructed, but most did not, and some hardly used them at all. I think part of this issue of who's at risk has to do with not taking full advantage of available therapies.

1. Krishnan JA, Riekert KA, McCoy JV, Stewart DY, Schmidt S, Chanmugam A, et al. Corticosteroid use after hospital discharge among high-risk adults with asthma. Am J Respir Crit Care Med 2004;170(12):1281-1285.