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# The Patient with Asthma in the Emergency Department

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**Abstract** Asthma is a highly prevalent disease that presents commonly to the emergency department (ED) in acute exacerbation. Recent asthma treatment guidelines have added content dedicated to the management of acute exacerbations. Effective management of an exacerbation requires rapid assessment of severity through physical examination, measurement of peak expiratory flow rate, and response to initial treatment. Most therapies are directed at alleviating bronchospasm and decreasing airway inflammation. While inhaled short-acting beta-agonists, systemic corticosteroids, and supplemental oxygen are the initial and often only therapies required for patients with mild moderate exacerbations, high-dose beta agonists and inhaled anti-cholinergics should also be given to patients with severe exacerbations. Adjunctive therapy with intravenous magnesium and Heliox-driven nebulization of bronchodilators should be considered for patients presenting with severe and very severe exacerbations. Early recognition and appropriate management of respiratory failure are required to mitigate the risk of complications including death. Disposition should be determined based on serial assessments of the response to therapy over the first 4 h in the ED. Patients stable for home discharge should receive medications, asthma education including a written asthma action plan, and should have follow-up scheduled for them by ED staff. Rapid implementation of evidence-based, multi-disciplinary care is required to ensure the best possible outcomes for this potentially treatable disease.

**Keywords** Emergency department · Asthma · Respiratory distress

## Key Points

- Peak expiratory flow meters aid in assessing severity and following the progress of patients with acute asthma exacerbations in conjunction with history, examination, and pulse oximetry. Predicted levels must factor in height in pediatric patients.
- Mild to moderate exacerbations should be treated with albuterol, by nebulizer or metered-dose inhaler (MDI) with holding chamber, and most patients should receive systemic corticosteroids (CS).
- Severe exacerbations should be treated with high-dose nebulized albuterol, ipratropium bromide, and CS, either by oral or intravenous route
- Adjunctive therapies such as intravenous magnesium should be considered for patients with ongoing severe airflow obstruction after the first 60 min of standard treatment. Such patients should also receive continuous high-dose albuterol and additional ipratropium bromide and CS as needed. Heliox should also be considered if available.
- Best available evidence suggests no benefit to doses greater than 100 mg of prednisone equivalent per day.
- Other options for very severe exacerbations not responding to standard therapy include ketamine and noninvasive positive pressure ventilation.

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- Determination of disposition should start after the first 60–90 min of treatment rather than at the time of initial presentation.
- Discharge from the emergency department should involve appropriate discharge medications, education, a written asthma action plan, and follow-up arrangements.

## Introduction

Patients of all ages present to the emergency department (ED) with respiratory distress and wheezing. Initial evaluation entails assessing the severity of the respiratory distress and determining if an acute exacerbation of asthma is the cause.

Asthma is a common condition that accounts for approximately 2 million ED visits, 500,000 hospitalizations, and over 4,000 deaths each year in the United States [1]. Because it involves both paroxysmal spasmodic narrowing of the bronchial airways and inflammation of the bronchi it is not surprising that patients experience sudden symptoms requiring prompt medical attention. Although improved medication regimens and step-up treatment plans have been successful in decreasing ED visits, in certain centers, acute asthma may still comprise 10% of all ED visits.

Asthma may be diagnosed for the first time in a patient presenting to the ED, but in the majority of cases, the patient will be aware of the underlying diagnosis of asthma and will communicate it in the field or at triage. This history is often helpful in the initial categorization of the problem and treatment approach, allowing the emergency practitioner to focus on initiating therapy, assessing severity, and identifying a triggering cause and co-morbid conditions. Previous work has reported that as many as 30% of patients carrying a diagnosis of asthma may not actually have asthma and requires the ED clinician to remain open to the possibility that the symptoms may be due to another disease entity mimicking an asthma exacerbation [2].

## Assessing the Severity of Respiratory Distress

Rapid initial assessment is required for the expert provision of emergency services and initial treatment should be started coincident with this assessment when suspicion for asthma is high. The universal concept of ABC—airway, breathing, and circulation—must be applied to the patient with severely symptomatic asthma. In respiratory failure, ventilatory support needs to precede detailed history and physical examination.

The presenting appearance of the patient provides key information (see Table 1). Vital signs showing high blood pressure, pulse rate, or respiratory rate are usually indications for aggressive emergency treatment. Limited ability to speak, assuming the tripod position, and using accessory muscles are worrisome for severe exacerbation. Signs of impending respiratory failure include drowsiness or confusion, diaphoresis, paradoxical thoracoabdominal movement, and a silent chest and should prompt preparations for intubation and mechanical ventilation. Vital signs showing low blood pressure and bradycardia signify reduced cardiac output, are indications for immediate resuscitative intervention, and should prompt a search for complications such as pneumothorax and pneumomediastinum.

**Table 1** Primary assessment

| |
|---|
| Signs of a severe asthma attack in an adult |
| Severe agitation |
| Hunched sitting position with arms supporting torso (tripod) |
| Limited ability to speak |
| Use of accessory muscles |
| Respiratory rate more than 30/min |
| Signs of a severe asthma attack in an infant |
| Use of accessory muscles |
| Supraclavicular and intercostal retractions |
| Nasal flaring |
| Paradoxical breathing |
| Cyanosis |
| Respiratory rate more than 60/min |
| Signs of impending respiratory arrest |
| Lethargy or confusion |
| Silent chest |
| Paradoxical thoracoabdominal movement |
| Bradycardia |

Pulse oximetry provides a guide regarding severity of exacerbation. Values below 90% on room air are concerning for severe exacerbation. Typically, however, the patient with a more serious condition is administered supplemental oxygen as an urgent treatment, and it is the pulse oximetry on oxygen that is assessed and followed in the ED.

An arterial blood gas (ABG) is a consideration for patients in whom there is incongruity between clinical impression and other clinical information, and may also be used to follow patients who are close to needing ventilatory support. In mild and moderate exacerbations, the ABG usually shows a respiratory alkalosis and does not typically add additional information relevant to clinical care in such cases. Normal or increased $CO_2$ implies severe disease and impending respiratory failure, although the converse is not necessarily true. Metabolic acidosis should be recognized as a marker of very severe disease.

Severity of airways obstruction is further evaluated by auscultating the chest, listening both for the quality and amount of wheezing and airflow. For example, the presence of inspiratory stridor or monophonic wheezing best heard over the neck or central airways may signify upper airway or large airway obstruction. Prolongation of the expiratory phase generally reflects the severity of acute asthma. In mild bronchospasm, the inspiration to expiration ratio may be 1:1; in severe bronchospasm, the ratio may be 1:3; a silent chest is a marker of very severe obstruction and impending respiratory failure.

However, studies have indicated that the practitioner cannot always accurately assess the degree of airway obstruction through clinical examination alone. As such, use of indices derived from a forced exhalation by the patient into a measurement apparatus has become a standard technique in EDs. Most commonly, a peak expiratory flow meter is used and yields the index of peak expiratory flow rate (PEFR); less commonly, a spirometer is employed and yields the index of forced expiratory volume in 1 s (FEV1). The advantages of this approach include objectivity and a numerical result to follow over the course of treatment, ideally with a comparison to the patient's historical baseline or predicted reference value (see Table 2).

In 2007, the National Asthma Education and Prevention Program (NAEPP) Expert Panel 3 (EPR3) published revised asthma management guidelines that included the addition of a chapter dedicated to the management of acute exacerbations [3]. These guidelines defined new PEFR cut points for defining the severity of acute exacerbations and stressed the use of serial measurements to gauge response to treatment. An initial PEFR of less than 40% of either the patient's baseline or predicted indicates a severe exacerbation. PEFR of 40–69% indicates a moderate exacerbation, while a PEFR of greater than or equal to 70% is typical of a mild exacerbation. A PEFR of less than 25% identifies a subset of patients at risk for respiratory arrest.

Unfortunately, a PEFR is not obtainable in all patients because of ability or effort. Children younger than 4–5 years of age cannot always be expected to perform this type of maneuver. Testing often cannot be performed by patients with particularly severe symptoms, however, clinical assessment is usually sufficient for accurate classification of severity in this subset of patients.

Most patients have worsening of asthma symptoms for a 2- to 7-day period prior to presenting to the ED. A subset of approximately 10% have onset of the attack in less than 6 h but tend to respond rapidly to treatment. Death from acute asthma episodes is reported in less than 0.1% of patients with asthma. Approximately half will suffer an out of the hospital death and half will succumb in the hospital setting. Near fatality has been defined as the occurrence of respiratory arrest and/or coma necessitating emergency tracheal intubation and mechanical ventilation, and the condition is distinguished from those patients who are electively intubated because of fatigue.

Despite research efforts, solid predictors of patients who are at risk for fatal or near-fatal episodes of asthma have not been identified because the associations are neither sensitive nor specific. Many risk factors occur too frequently in the general asthma population and too infrequently in subpopulations who are at risk for a fatal or near-fatal episode to allow precise application. For example, retrospective surveys indicate that 15–30% of asthma deaths occur in patients whose disease is categorized as only mild asthma.

Nonetheless, certain historical information is helpful in gauging the seriousness of the attack and has implications for prognosis, response to initial therapy, and disposition. History taking should be focused on identifying risk factors for fatal or near fatal exacerbations. Relevant history includes the severity of previous exacerbations, the types

**Table 2** Predicted peak expiratory flow rate for adults and children

| Predicted peak expiratory flow for age and height: adults (l/min) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Age (years) | Women's height (in.) | | | | | Men's height (in.) | | | | |
| | 55 | 60 | 65 | 70 | 75 | 60 | 65 | 70 | 75 | 80 |
| 20 | 390 | 423 | 460 | 496 | 529 | 554 | 602 | 649 | 693 | 740 |
| 30 | 380 | 413 | 448 | 483 | 516 | 532 | 577 | 622 | 664 | 710 |
| 40 | 370 | 402 | 436 | 470 | 502 | 509 | 552 | 596 | 636 | 680 |
| 50 | 360 | 391 | 424 | 457 | 488 | 486 | 527 | 569 | 607 | 649 |
| 60 | 350 | 380 | 412 | 445 | 474 | 463 | 502 | 542 | 578 | 618 |
| 70 | 340 | 369 | 400 | 432 | 461 | 440 | 477 | 515 | 550 | 587 |
| Predicted peak expiratory flow for height: children | | | | | | | | | | |
| Height (in.) | 39 | 43 | 47 | 51 | 55 | 59 | 63 | 67 | 71 | 75 |
| l/min | 110 | 160 | 210 | 260 | 320 | 370 | 420 | 475 | 530 | 570 |

Adapted from Refs. [46, 47]

and doses of medications the patient has been using, symptoms of comorbid acute illness such as pneumonia or myocardial ischemia, and chronic conditions such as cardiovascular disease, other chronic lung disease, poly-substance abuse, and psychiatric disease (see Table 3). For example, if a patient has previously been intubated for an asthma exacerbation, there is an almost 20-fold increase in likelihood this will be required again [4]. Although older case-control studies using retrospectively collected data suggest that excess use of short-acting beta-agonists (SABA) was a risk factor, more recent information suggests that patterns of use may be a marker for more severe asthma rather than causal of severe attacks [5]. More recently, the chronic use of long-acting beta-agonists (LABA) in patients with asthma has been associated with a small increased risk of asthma-related death and adverse events in a meta-analysis of over 60,000 patients from randomized, controlled trials [6]. While an increased risk of death was not observed in the trials that mandated the use of a LABA with an inhaled corticosteroid (ICS), LABA use either alone or with an ICS may identify patients at increased risk of severe exacerbations.

In summary, numerous pieces of information can be gathered and assimilated quickly in the ED to categorize the severity of an acute asthma exacerbation. Attention should focus on identifying patients at risk for fatal or near-fatal exacerbations. Mild, moderate, and severe categories can be assigned based on a combination of signs and symptoms of distress and objective measurement of impairment in PEFR (see Table 4). Although this information correlates only loosely with ultimate outcome and disposition for the acute episode, it provides the basis for decision making for the initial level of monitoring and treatment intensity.

**Table 3** Risk factors for fatal asthma exacerbation

| |
|---|
| Historical factors |
| History of intubation for asthma |
| History of ICU admission for asthma |
| Multiple hospital admissions for asthma in the past year |
| Multiple ED visits for asthma in the past year |
| Use of more than two albuterol MDI per month |
| Use of LABA without concurrent use of ICS |
| Limited awareness of symptom severity |
| Social factors |
| Low socioeconomic status |
| Poor access to healthcare |
| Substance abuse |
| Comorbid factors |
| Psychiatric Illness |
| Concurrent nonasthmatic lung disease |
| Cardiovascular disease |

Adapted from Ref. [3]

## Diagnosis

In the ED, typically the clinician uses a prior diagnosis of asthma or makes the presumptive diagnosis. The ED physician should be able to rely on the prior diagnosis in the following circumstances: patient has a history of bronchospasm from childhood that has been responsive to asthma medications; patient has a positive prior methacholine challenge test. In most other circumstances, the diagnosis would be presumptive, based on evidence for asthma and lack of evidence for other disease processes. In patients with a significant smoking history, distinguishing asthma from other forms of chronic obstructive pulmonary disease (COPD) can be challenging in the acute setting and the two diagnoses may coexist in the same patient.

## Triggering and/or Complicating Factors

Many patients with asthma are able to recognize their own triggers (see Table 5). These may have been identified through experience or specific testing. Triggers may include exposure to allergens, such as from grasses, trees, weeds, dust, dust mites, cockroach, fungi, and animals. They may also include exposure to irritants, such as smoke, chemical products, or occupational hazards. Asthma exacerbation may be induced by exercise or exposure to cold. It may be induced by use of aspirin or beta-blocking drugs.

Patients with underlying asthma may have an exacerbation when there is a complicating problem, such as infection, pneumothorax, or arrhythmia. In many settings, the most common precipitant of an asthma exacerbation is infection with a respiratory virus. Bacterial pathogens such as *Mycoplasma pneumoniae* or *Chlamydophila pneumoniae* are less common but may precipitate acute exacerbations and may cause concurrent pneumonia. Bronchospasm frequently increases with active sinusitis.

The clinician must also consider that the basis for the acute exacerbation may be medication noncompliance, medication change, or steroid dose reduction.

## Differential Diagnosis

Other medical conditions can be confused with asthma. Misdiagnoses may be present in up to 30% of outpatients [2], in 1% of general asthma admissions, and 10% of intensive care unit admissions.

**Table 4** Categorization of severity of asthma exacerbation: common clinical features and assessment of lung function

| Severity | Mild | Moderate | Severe |
|---|---|---|---|
| PEFR (% predicted or personal best) | ≥70% | 40–69% | <40% |
| Speech | Sentences | Phrases | Words |
| Mental status | Anxious | Agitated | Distressed |
| Accessory muscle use | No | Sometimes | Commonly |
| Oxygen saturation (%) | ≥95% | 90–95% | <90% |

Upper airway obstruction may masquerade as lower airway obstruction. In pediatric patients in particular, common conditions to be considered include rhinitis and sinusitis and less common conditions to be considered include epiglottitis and retropharyngeal abscess. Foreign body may be present in the upper airway or one of the larger lower airways. A child presenting for the first time with new onset wheezing should have a chest X-ray to evaluate for evidence of foreign body, congenital malformations, or childhood tumors. Angioedema may occur and cause upper airway obstruction.

In the pediatric population, croup and certain congenital and acquired anatomical problems may contribute to medium and large airway obstruction including chronic underlying diseases such as cystic fibrosis, bronchopulmonary dysplasia, and alpha-1 antitrypsin deficiency. The differential diagnosis of wheezing in pediatric patients should also include aspiration, as a result of gastroesophageal reflux or swallowing disorders, and primary cardiac conditions resulting in congestive heart failure (CHF) from congenital heart disease.

In the adult population, the differential diagnosis includes COPD, bronchiectasis, nonasthmatic bronchiolitis, endobronchial lesions, aspiration, pneumonia, pulmonary emboli, and cardiogenic pulmonary edema. Examples of other conditions associated with wheezing include upper airway obstruction, anaphylaxis and carcinoid syndrome.

Glottic dysfunction, otherwise known as vocal cord dysfunction (VCD), may be a form of a conversion reaction and is characterized by the paradoxical adduction of the vocal cords. Like in asthma, clinical features may include wheezing and even hypoxemia, however, the blood gas pattern is that of central alveolar hypoventilation, the wheezing is typically monophonic, and there may be stridulous or halting breathing over the neck. Although direct vocal cord visualization for dysfunctional movement and/or ventilation scanning to confirm a normal distribution can be done in the ED, frequently the patient is treated presumptively for asthma and laryngeal assessment is deferred.

**Table 5** Potential events antecedent to asthma attack

| Asthma triggers and exacerbating factors |
|---|
| Infection |
| Exposures |
| Allergens |
| Cigarette smoke |
| Chemical irritants |
| Aspirin |
| Cold temperature |
| Exercise |
| Alteration in medication |
| Out of medications |
| Change in medications |
| Steroid dose reduction |
| Other pulmonary or cardiac conditions |

## Testing in the ED

Patients with mild to moderate acute asthma exacerbation need little in the way of specialized testing. Vital signs and pulse oximetry are routinely monitored. All patients over the age of 5 should have PEFR measured at presentation to aid in assessing the severity of the acute exacerbation. PEFR should be checked sequentially over time starting 30–60 min after initiating treatment to gauge the response to initial therapy, guide the use of adjunctive therapies, and to aid decision making regarding the need for hospitalization. An alternative would be the performance of pulmonary function tests (PFTs) or spirometry, but this equipment is generally not available in EDs and the extra information gathered is typically not germane for emergency care.

When complicating conditions are being considered, additional diagnostic testing is warranted. A complete blood count and differential may be helpful to look for eosinophilia and infection. While mild elevation of the white blood cell count may simply be a nonspecific marker of stress or may reflect catecholamine or steroid treatment, marked elevations with or without bandemia may suggest infection. Measurement of electrolytes, blood urea nitrogen, and creatinine may be helpful to assess for hydration status and may be important preparatory information for certain treatment interven-

tions such as neuromuscular blockers (NMB) or diuretics, or for certain types of diagnostic testing, for example those using radiocontrast media. If applicable, a theophylline level should be checked.

A chest radiograph (CXR) is an option for the first presentation of bronchospasm but would not be expected to show more than hyperinflation. A CXR is indicated when other conditions are suspected, such as pneumothorax/pneumomediastinum, CHF, pneumonia, bullous disease, and fibrotic or interstitial lung disease. A CXR is usually done if the patient is being admitted to the hospital.

Obtaining an electrocardiogram (EKG) is important when there is a question of dysrhythmia or cardiac ischemia. In older patients with suspected or known cardiovascular disease, an EKG should be a routine test when there is a presentation of shortness of breath, with or without chest pain. Similarly, cardiac enzyme testing should be done in patients at risk for cardiac ischemia presenting with shortness of breath. B-type natriuretic peptide testing may help exclude concurrent acute decompensated CHF when a patient with a history of both CHF and asthma presents with shortness of breath and wheezing. Evaluation for pulmonary embolus (PE) may involve D-dimer testing or chest computed tomography (CT) scanning. In a patient otherwise felt to be low risk for PE, a negative high-sensitivity D-dimer test excludes PE in most patients. CT angiography of the pulmonary arteries in patients with a positive D-dimer or those felt to be at intermediate-high risk of PE can effectively exclude PE and may also identify other thoracic pathology [7]. Sinusitis is frequently a clinical diagnosis in the ED, but with the availability of CT scanning, the sinuses can be more accurately assessed if needed.

The question of the need for microbiology cultures in patients with wheezing is often raised in the ED. Sputum cultures are generally not needed for bronchitis. The high rate of viral infections, the variable quality of the submitted specimens, and the obligatory slow turnaround time do not make them cost-effective for decision making in the ED. When antibiotic therapy is indicated for bronchitis, the choice of drug is typically empiric. Sputum cultures generally also are not needed for community-acquired pneumonia that will be treated on an outpatient basis. For patients with concurrent pneumonia who will be treated in the hospital, however, it is reasonable to obtain sputum and blood cultures both of which should be obtained prior to the administration of antibiotics.

Clinical suspicion for influenza complicating asthma exacerbation should prompt rapid point of care testing for influenza in the ED as the effectiveness of antiviral therapy is thought to depend on early initiation. Confirmatory testing for seasonal as well as pandemic strains should be sent for all patients admitted to the hospital with a positive rapid assay and for those with a negative point of care test and strong clinical suspicion. This may also be helpful in triage when deciding on the most appropriate bed type and location to limit in-hospital spread of infection if there is a suspected outbreak of influenza.

In the pediatric population, viral testing is a consideration. Bronchiolitis, a viral infection of the bronchioles, is usually seen in children younger than 2 years old. Respiratory syncytial virus (RSV) is the most common etiology, occurring November to March, although other etiologies include parainfluenza and *Mycoplasma*. Antigen tests of nasal washings may detect RSV and be helpful in the management of high-risk patients.

## Treatment of Mild and Moderate Asthma Exacerbations

Most patients with mild exacerbations of asthma are managed at home or in the outpatient clinic. If a patient presents to the ED with the features of a mild exacerbation, the first-line medication is albuterol (also known as salbutamol) typically administered by MDI with a holding chamber (spacer) (ProAir®, Proventil®, Ventolin®). Nebulized albuterol is an alternative for patients who have difficulty using an MDI. A mild attack is confirmed when the patient experiences a prompt and complete response to initial treatment with SABA with resolution of wheezing, cough, and/or shortness of breath. These patients can often be discharged after education and scheduled follow-up but with no additional medical therapy. Patients and family members should be given specific instruction in the proper use of inhalers and spacer.

Patients with mild exacerbations who do not have a complete and immediate response to initial therapy with albuterol, and those presenting with features of a moderate exacerbation, should be treated similarly according to the 2007 NAEPP EPR3 guidelines. All patients should have initial and serial measurement of PEFR and all should immediately receive oxygen, a short-acting beta agonist, and systemic CS usually by the oral route.

Supplemental oxygen delivered by nasal cannula or mask should be provided as needed to ensure a peripheral oxygen saturation of at least 90% in most patients. Oxygen saturation should be maintained above 95% in pregnant patients or those with active cardiovascular disease.

Delivery of albuterol may be by MDI with a holding chamber or by nebulizer. Studies of adults and older children with acute asthma have shown that both modalities are effective in providing particles of the optimal 1–5 μm size to the lower airways. This results in no significant

differences in the rate of hospital admission, length of time spent in the ED, or PEFR [8]. As such, the choice of modality is often determined by the degree of respiratory distress including the patient's ability to time respiratory efforts with the use of an MDI, with more pronounced respiratory distress favoring use of a nebulizer.

The standard albuterol MDI delivers 90 μg of albuterol per puff. The recommended dose of albuterol for mild to moderate exacerbations, when administered by MDI with use of a spacer, is four to eight puffs given every 20 min as needed for up to three doses in the first hour in children, and every 20 min for up to 4 h in adults [3]. Levalbuterol has been added to the EPR3 guidelines as an alternative to albuterol. Whereas albuterol is a racemic mixture of (*R*)- and (*S*)-isomers, levalbuterol (Xopenex®) contains only the (*R*)-enantiomer. The (*R*)-albuterol has the bronchodilating properties, whereas the (*S*)-form has preferential pulmonary retention, a longer half-life, and possible proinflammatory effects [9]. Levalbuterol is delivered by MDI at 45 μg/puff but the number of puffs and timing of administration are otherwise the same as for albuterol. While there are in vitro and preclinical data that might suggest superiority of levalbuterol over racemic albuterol, clinical studies have supported the equivalency rather than superiority of levalbuterol in terms of the degree or bronchodilation, side effects, and rates of hospital admission [10]. It may, however, be reasonable to switch to levalbuterol in patients with dose-limiting adrenergic side effects after the first few doses of racemic albuterol.

The nebulizer dosage for children is 0.15 mg/kg (minimum dose 2.5 mg) every 20 min up to three doses and then 0.15–0.3 mg/kg up to 10 mg every 1–4 h as needed. For adults, the dose is 2.5–5 mg every 20 min as needed for three doses and then 2.5–10 mg every 1–4 h as needed thereafter. For levalbuterol, the pediatric dosing is 0.075 mg/kg (minimum dose 1.25 mg) for the first three doses and then 0.075–0.15 mg/kg up to 5 mg every 1–4 h as needed. For adults, the dosing is 1.25–2.5 mg every 20 min as needed for three doses and then 1.25–5 mg every 1–4 h as needed [3]. The mode of delivery is typically via a medication reservoir attached to a pipelike mouthpiece, but for infants and young children, a facemask device can be employed. Oxygen or compressed air at 6–8 l/min from a wall outlet or tank is connected by tubing to drive the nebulization.

Systemic corticosteroids (CS) are used to counter airway inflammation and hasten resolution of the asthma exacerbation. Because they act through ligand-dependent activation of nuclear receptors, gene regulation, and new protein synthesis, clinical benefits are thought to accrue gradually over 6–12 h.

Systemic CS should therefore be given promptly to all patients with a moderate exacerbation, to those presenting with mild symptoms that do not immediately resolve after initial therapy with albuterol, and to all patients with even mild symptoms who have recently taken systemic CS. CS have been shown to speed the resolution of airflow obstruction, to decrease the rate of hospital admission, and to decrease the rate of relapse and beta-agonist use after discharge [11–13]. Emergency physicians must remember to obtain a history of medications taken at home prior to presentation to the ED (e.g., prednisone) and those administered by pre-hospital providers as these medications may reduce the initial impression of severity.

Oral administration of CS is preferred over the intravenous (IV) route as both routes have been shown in studies to have equal efficacy [3] and oral administration can be accomplished without need for IV access. IV administration should be reserved for patients in whom oral absorption may be unreliable, for those unable to swallow, or in case of nausea and vomiting. Current guidelines also reflect evidence suggesting that moderate doses of CS are just as effective as higher doses. For example, a 2001 meta-analysis suggested that low (≤80 mg), medium (>80 mg and ≤360 mg), or high (>360 mg) dosing of methylprednisolone in the first 24 h resulted in similar therapeutic efficacy and changes in lung function. Although reference manuals often recommend repeat dosing every 6 h, high and frequent doses do not confer a therapeutic advantage [3, 14, 15].

Current guidelines recommend 40–80 mg of prednisone equivalents in one or two divided doses. For patients discharged from the ED, recommendations are for 40–60 mg of prednisone daily, or divided twice daily, for 5–10 days [3]. For patients at high risk of nonadherence or for those unable to pay for an outpatient prescription, a 2004 study found no difference in the rate of relapse following discharge from the ED with use of 160 mg depot methylprednisolone compared to an 8-day tapering of a total dose of 160 mg oral methylprednisolone [16]. For children, current recommendations are for 1–2 mg/kg in two divided doses in the first 24 h (max 60 mg/day), followed by an outpatient burst of 1–2 mg $kg^{-1}$ $day^{-1}$ (max 60 mg/day) for 3–10 days [3].

Current evidence does not support the use of increased doses of inhaled CS as a substitute for systemic CS to treat acute exacerbations. However, patients taking ICS as outpatients can continue their ICS even while on systemic CS. Furthermore, prescribing an ICS at the time of discharge for patients not previously on ICS may reduce the risk of relapse [17].

Finally, serial measurement of PEFR and reassessment of symptoms are key to determining the response to treatment. Typically, repeat measurement of PEFR is performed after 30–90 min of therapy and then every hour thereafter as indicated. Objective evidence of improvement

in PEFR provides reassurance that current management is effective and supports gradually tapering the frequency of SABA treatments. Once the patient's PEFR is ≥70% of either baseline or predicted, and the patient is no longer in distress, the PEFR is repeated 60 min later with no intervening therapy to ensure a sustained response in anticipation of discharge. Alternatively, if PEFR and symptoms are worsening, the clinician should promptly increase the intensity of current therapy, consider use of adjunctive treatments, and carefully assess the patient for signs of impending respiratory failure.

## Treatment of Severe Asthma Exacerbations

Patients with severe exacerbations have a PEFR <40% of baseline or predicted. Because not all patients with severe exacerbation will be able to reliably perform PEFR maneuvers, vital signs and physical exam are important indicators of severity. These patients often have more pronounced respiratory distress including a respiratory rate >30 and use of accessory muscles. Tachycardia is often pronounced with a heart rate >120 and a pulsus paradoxus (the drop in systolic blood pressure during inspiration) >25 mm Hg can be seen. Hypoxemia with an arterial oxygen saturation <90% on room air is common.

As such, these patients should be moved to an area of the ED equipped to manage respiratory failure and hemodynamic instability. They should be placed on monitors for continuous recording of the rhythm strip and pulse oximetry, and for frequent recording of the blood pressure. If end-tidal air stream $CO_2$ monitoring is available, it could be used in this situation to monitor for impending respiratory failure. Supplemental oxygen should be provided to ensure adequate tissue oxygen delivery, waiving concern regarding $CO_2$ narcosis if there is significant hypoxemia. Intravenous access should be established, preferably at two sites. Intravenous fluids will be needed in most pediatric patients and should be considered for adult patients.

### High-Dose Inhaled Bronchodilators

Therapy with high-dose bronchodilators and systemic CS should be started immediately. As with mild-moderate exacerbations, albuterol can be delivered either by MDI with a spacer or by nebulizer with equivalent outcomes so long as the degree of respiratory distress does not compromise the patient's ability to effectively coordinate use of a MDI. A typical dose of albuterol by MDI/spacer would be 8–12 puffs every 20 min up to 4 h and then every 1–4 h as needed thereafter assuming clinical improvement. It is common, however, to deliver albuterol via a nebulizer in patients with significant agitation, respiratory distress, and in the young and old. Initial nebulizer dosing for severe exacerbations can be given with the same frequency as for mild–moderate exacerbations but higher doses per treatment should be considered.

For severe exacerbations with significant respiratory distress, albuterol should be delivered by continuous nebulization. A 2003 meta-analysis of eight trials with over 450 patients concluded that, as compared with intermittent nebulizer treatments, albuterol by continuous nebulizer resulted is greater improvements in lung function, fewer hospitalizations, and no difference in side effects [18]. A typical dose by continuous nebulizer would be 15–20 mg delivered by high-volume nebulizer over 1 h. High-dose levalbuterol can be substituted for albuterol either by MDI/spacer or nebulizer and scheduled the same as in mild–moderate exacerbations. Note that levalbuterol has not been studied by continuous nebulizer, however, and should not be used via this mode of delivery.

Ipratropium bromide (Atrovent®) should also given with the first and subsequent treatments as a large body of evidence has demonstrated improved outcomes in patients with severe exacerbations. A 2005 meta-analysis of data from 32 randomized, controlled trials and over 3,600 patients concluded that the addition of inhaled ipratropium bromide to SABA resulted in greater improvements in lung function and decreased rates of hospital admission [19]. This is reflected in the 2007 NAEPP EPR3 guidelines that recommend the use of ipratropium in all patients with severe exacerbation. Ipratropium can be given via MDI with a spacer or by nebulizer. If the MDI with spacer approach is being used, eight puffs of ipratropium should be intermixed with albuterol treatments either as two separate MDI treatments or as eight puffs of the fixed combination product Combivent®. MDI treatments should be given every 20 min for three doses and then every 20 min as needed thereafter for up to 3 h. In children the dose is four to eight puffs every 20 min as needed up to 3 h [3]. Commonly, ipratropium is mixed with albuterol for nebulization with 0.5 mg of ipratropium (0.25–0.5 mg for children) mixed in the same nebulizer with albuterol and administered every 20 min. Ipratropium can also be mixed with albuterol for continuous nebulization. Of note, studies support the use of ipratropium for management of asthma exacerbations in the ED but have not shown benefit when added to SABA for hospitalized patients.

### Systemic Corticosteroids

Prompt initiation of systemic CS is critical to effective management of severe exacerbations. As mentioned above, when CS are given orally or IV, no difference in lung function or clinical outcomes has been observed even in

severe exacerbations, and no additional benefit is derived from doses exceeding 100 mg of prednisone equivalents per day. Patients with severe exacerbations, however, may have difficulty swallowing due to respiratory distress and may have nausea, vomiting, or comorbid conditions that make oral absorption unreliable. Under these circumstances, CS should be given IV. A typical dose would be 60–125 mg of IV methylprednisolone.

### Magnesium Sulfate

For patients with severe exacerbations and either suboptimal improvement or clinical deterioration after 30–60 min of therapy with oxygen, inhaled bronchodilators, and systemic CS, adjunctive therapy with intravenous magnesium sulfate should be strongly considered [3]. Magnesium sulfate is thought to cause relaxation of bronchial smooth muscle by inhibiting calcium influx into smooth muscle cells and may also have anti-inflammatory effects. Two recent systematic reviews found that IV magnesium sulfate had favorable effects on lung function and reduced hospitalizations both in adults and in children with the greatest benefits realized in those with more severe exacerbations [20, 21]. The recommended adult dose is 2 mg given intravenously over 20 min. The recommended pediatric dose is 25–75 mg/kg up to a maximum of 2 mg. No significant adverse events have been associated with IV magnesium in these doses and significantly higher doses have been used in other clinical settings with a very favorable safety profile. The low cost, ease of administration, and familiarity of use by most physicians make IV magnesium sulfate a useful adjunct for severe exacerbations.

Magnesium can also be delivered by nebulizer, however, studies are less clear as to benefit with conflicting evidence existing as to both short-term effects on lung function and clinical outcomes. A large, multicenter trial comparing intravenous to nebulized magnesium sulfate in the treatment of patients with severe exacerbations is ongoing and should shed additional light on the use of this therapy [22].

### Heliox

The recent NAEPP EPR3 guidelines now suggest consideration of Heliox-driven nebulization for patients with persistent severe symptoms despite standard and other adjunctive therapies [3]. Heliox is a mixture of helium and oxygen, typically at a ratio of 80:20 or 70:30 of helium to oxygen. Heliox's lower density compared to air/oxygen mixtures causes less turbulent gas flow most notably in the larger airways, results in improved dyspnea scores, and is thought to reduce the work of breathing by decreasing airway resistance. In some studies, Heliox has been reported to potentiate the bronchodilatory effects of beta-agonists when Heliox is used to power the nebulizer. These data, however, come from mostly small studies of varying methodologic quality. A 2006 meta-analysis of ten randomized, controlled trials involving almost 550 patients concluded that Heliox should not be used in all patients with acute asthma exacerbations but that it may be effective in improving lung function and possibly decreasing rates of admission in the most severely affected patients. There were insufficient data to evaluate the effects of Heliox on rates of intubation [23]. Helium is insoluble in human tissues and, as such, Heliox has no significant safety issues by itself.

If the clinician decides to use heliox, the practical setup is as follows. A commercial mixture of helium and oxygen is used, available in a portable cylinder, often as 80% helium and 20% oxygen or 70% helium and 30% oxygen. Administration is best via a nonrebreathing face mask to minimize mixing of heliox with room air. During administration of inhaled bronchodilators, heliox should be used to power a standard nebulizer. For patients with significant hypoxemia, supplemental oxygen can be provided via nasal cannula, although this increases the density of the gas mixture and may negate any clinical benefit. It should be noted that peak flow readings vary depending on the viscosity of the gas being delivered, and the relatively lower density of heliox would be expected to result in a higher peak flow compared to air unless standardization is done.

## Additional Treatments for Severe Asthma Exacerbations

The aforementioned therapies are consistent with the recommendations of the 2007 NAEPP EPR3 guidelines and reflect the best available data to guide management of asthma exacerbations. Patients with severe exacerbations who do not respond readily to the therapies detailed above present a significant management challenge. The goal of therapy for these patients is focused on averting respiratory failure and, if necessary, managing the complications of intubation and mechanical ventilation as this patient population has a reported mortality as high as 20% [24]. Despite an absence of high-quality data, smaller randomized studies, case series, and isolated case reports provide a rationale for considering additional therapeutic options.

### Parenteral Beta-Agonists

Subcutaneous terbutaline and epinephrine, when not contraindicated, have historically been used as alternatives if the

inhaled route were unavailable or failing. Data on the efficacy of subcutaneous beta agonists are extremely limited and this approach has not been clearly shown to change the course of patients who are not responding to inhaled high-dose albuterol. While epinephrine is generally well tolerated in this setting, deaths have been reported with the use of epinephrine to manage asthma patients with cardiac disease. In pregnant asthma patients, epinephrine may contribute to uterine vessel spasm making terbutaline the preferred agent in this patient population. A typical adult dose of subcutaneous epinephrine for treatment of severe asthma is 0.3 mg every 20 min up to three doses. Subcutaneous terbutaline can be given in adults at 0.25 mg every 20 min for three doses. Intravenous beta-agonists have been tried as well. Randomized controlled trials of intravenous terbutaline have produced conflicting evidence regarding whether the intravenous route or the inhaled route is more efficacious; there is agreement that the intravenous route is associated with more adverse effects such as tachycardia and hypokalemia [25, 26]. The conclusion of a meta-analysis of 15 randomized, controlled trials was that evidence is lacking to support the use of intravenous beta2-agonsits in ED patients with severe acute asthma, except possibly for those patients for whom inhaled therapy is not feasible [27]. Data on intravenous epinephrine are too limited to draw conclusions.

### Methylxanthines

For patients who do not respond to or are not able to take standard emergency treatment medications, intravenous aminophylline, at 5–6 mg/kg bolus and then 0.6–0.9 mg/kg/h has historically been used. A 2000 meta-analysis of 15 randomized, controlled trials comparing the addition of aminophylline to standard therapy with beta-agonists with or without CS, however, showed no difference in pulmonary function or hospital admission but did show a higher rate of arrhythmia and vomiting [28]. As such, current guidelines do not endorse the routine use of aminophylline in acute exacerbations [3].

### Leukotriene Receptor Antagonists

For patients who are responding suboptimally to standard emergency treatment medications, the addition of a leukotriene receptor antagonist, such as montelukast (Singulair®) or zafirlukast (Accolate®), could be considered. In oral form, these agents have an established role in the chronic management of asthma but their role in the treatment of acute exacerbations is less clear. Randomized, controlled trials of both oral and IV formulations of montelukast added to standard therapies have shown improvements in lung function but did not show a difference in clinical outcomes such as admission rate or hospital length of stay [29, 30]. There were no significant adverse events noted in any of these trials, however, making the addition of oral montelukast a reasonable adjunct in severely affected individuals.

### Ketamine

Ketamine (Ketalar®) is a rapid-acting dissociative anesthetic derived from phencyclidine that has potent analgesic, sedative, and amnestic properties while preserving respiratory drive and airway protective reflexes. Ketamine is commonly used for conscious sedation during painful procedures and is also used as an induction agent for endotracheal intubation. Research suggests that ketamine acts to relax bronchial smooth muscle by stimulating the release of catecholamines that act on beta2-adrenergic receptors, by inhibiting vagal tone, and possibly by a direct effect on smooth muscle cells [31]. Side effects include tachycardia, hypertension, hypersalivation, nausea and vomiting, increased intracranial pressure, and emergence reactions such as disorientation and hallucinations. The use of ketamine is relatively contraindicated in patients with active cardiovascular disease, increased intracranial pressure, alcohol intoxication, and altered mental status of unknown etiology.

A beneficial effect of ketamine in severe asthma remains to be definitively proven. Two small randomized, placebo-controlled trials of low-dose ketamine infusion have been reported, one in adults and one in children with severe asthma exacerbations. In these trials, no benefit was seen with regard to either lung function or hospital admission [32, 33]. Nonetheless, multiple case reports and small case series continue to report anecdotal benefit from ketamine, commonly at higher doses than those used in the controlled trials, with benefits seen in terms of alleviation of bronchospasm, improved oxygenation, and avoidance of intubation and mechanical ventilation. No clear dosing recommendation has emerged from these reports but boluses as high as 2 mg/kg and drip rates as high as 3 mg $kg^{-1}$ $h^{-1}$ have been reported in children [34].

### Noninvasive Positive Pressure Ventilation

Noninvasive positive pressure ventilation (NPPV), also known as noninvasive pressure support ventilation (NIPSV), represents the delivery of mechanically assisted breaths via a patient interface that is external to the body, such as a tightly fitting nasal or facial mask, rather than an internal artificial airway. It is also referred to as bilevel positive airway pressure ventilation (BiPAP®), based on the name of the noninvasive ventilator commonly used,

produced by Philips-Respironics. Studies have shown that NPPV is efficacious in acute respiratory failure related to exacerbations of COPD, acute cardiogenic pulmonary edema, and hypoxemic respiratory failure in immunocompromised hosts [35]. NPPV is contraindicated when respiratory failure is imminent, in patients with vomiting, and in patients with a depressed level of consciousness.

Improvements in pH and $pCO_2$ within 1.5–2 h are predictive of the eventual success of NPPV and if they do not occur, invasive mechanical ventilation should be considered. In general, however, a trial of NPPV is a reasonable option for ventilatory support in patients in whom there is a rapidly reversible cause of respiratory failure identified or in patients who are particularly high risk for complications of intubation and mechanical ventilation. Furthermore, barotrauma is uncommon, and adverse hemodynamic effects are unusual. Nosocomial pneumonia and sinusitis are also less common compared with patients who are intubated. For these reasons, NPPV is an attractive therapy for management of severe, difficult to treat asthma exacerbations.

The utility of NPPV in asthma, however, is not well defined and the number of studies addressing its use in patients with asthma with severe respiratory distress is limited. One case series reported an encouraging experience when NPPV was used in 17 patients with asthma complicated by acute hypercapnic respiratory failure; all survived, and 15 did not require intubation with coincident improvements in pH, $paCO_2$, oxygenation, and respiratory rate beginning within 2 h of initiation [36]. Another retrospective series of 22 patients with severe exacerbation treated with NPPV in the ICU revealed a subsequent rate of invasive mechanical ventilation of only 14% [37]. Two recent small randomized, controlled trials of NPPV in patients with severe exacerbations at risk for respiratory failure have shown improvements in both lung function and rates of admission [38] and in decreasing bronchodilator requirements as well as ICU and hospital length of stay [39]. Despite these encouraging preliminary results, the use of NPPV in patients with severe asthma is currently not recommended for routine management of severe exacerbations and should only be used selectively on a case-by-case basis by clinicians familiar with its risks.

## Management of Respiratory Failure in Severe Asthma

Intubation and mechanical ventilation can be life-saving for patients with severe asthma exacerbations complicated by respiratory failure. The severe airways obstruction and associated dynamic hyperinflation seen in such patients makes these procedures fraught with risks including hypotension, aspiration, barotrauma, hospital-acquired infection, and myopathy.

Patients presenting with respiratory arrest or severe hypopnea should be intubated immediately. Similarly, those in whom the level of consciousness is inadequate to enable inhaled therapies or to ensure airway protection should be intubated. Other indications for immediate intubation include a $paO_2$ of <60 mm Hg despite high-flow oxygen delivered by a non-rebreathing face mask and signs of exhaustion such as paradoxical thoraco-abdominal motion and a silent chest. If the patient's status is borderline, however, it may be reasonable to begin a trial of aggressive interventions while at the same time preparing for the possibility of intubation should the patient show signs of worsening respiratory acidosis or any of the above signs of respiratory failure.

Rapid-sequence intubation (RSI) is the standard approach for patients who are obtunded or who are in respiratory arrest. The largest diameter tube possible should be chosen to minimize resistance to airflow and to facilitate suctioning and bronchoscopy.

Commonly used induction agents for RSI include etomidate, propofol, and ketamine. Propofol and ketamine have theoretical advantages in that both are known bronchodilators. Propofol may be preferred for hypertensive patients for both its bronchodilating and vasodilating properties. A typical induction dose of propofol ranges from 1.5 to 3 mg/kg (IV). The use of propofol may cause unwanted hypotension in volume-depleted patients especially immediately after initiating positive pressure ventilation. As such, IV fluids should be given rapidly around the time of intubation to ensure adequate cardiac preload. Ketamine may be preferred in patients with hypotension for its bronchodilating properties and because it stimulates catecholamine release. A typical induction dose is 1–1.5 mg/kg (IV). Etomidate is the most hemodynamically neutral of the induction agents. The usual dose of etomidate is 0.3 mg/kg.

Paralysis during RSI can be achieved with either depolarizing or nondepolarizing NMB. Succinylcholine is commonly used because of its rapid onset and relatively short duration of action of 5–10 min. The usual dose is 1–1.5 mg/kg (IV). Note that succinylcholine is contraindicated in patients with a personal or family history of malignant hyperthermia and in those with hyperkalemia, neuromuscular disorders, increased intraocular pressure, and subacute burns. Alternatively, a nondepolarizing agent such as rocuronium or vecuronium can be used to avoid the risks associated with succinylcholine. These agents, however, last for 30–45 min and pose serious risks if the patient cannot be ventilated or intubated. Sugammadex, an investigational agent capable of rapidly and fully reversing the effects of rocuronium and

vecuronium, if approved for use, will greatly improve the safety profile of the nondepolarizing NMB.

Alternatives to RSI include awake nasotracheal intubation, awake orotracheal intubation over a fiberoptic bronchoscope, and orotracheal intubation with sedation but without paralysis. These methods all share in common the advantage of preserving the patient's respiratory effort thus ensuring some residual ventilation. Nasotracheal intubation may be less favorable in asthmatics because of the high frequency of nasal polyps in this population and the smaller size endotracheal tubes typically used. Orotracheal intubation using an induction agent without a NMB allows a standard direct laryngoscopy but avoids the dangers of complete paralysis in the events that the trachea cannot be successfully intubated.

Awake orotracheal intubation over a fiberoptic bronchoscope is another alternative to RSI for nonemergent intubation and is particularly useful for managing known or anticipated difficult airways. This method avoids the need for induction agents and NMB and allows the patient to remain sitting upright. Using topical oropharyngeal anesthesia with atomized lidocaine and light sedation, the endotracheal tube is loaded onto a fiberoptic bronchoscope and inserted through a bite block or hollow oral airway (e.g., Berman® intubating airway) into the oropharynx. The bronchoscope is passed through the cords into the trachea and used as a stilette to pass the endotracheal tube into place. The scope can be used to confirm proper tube placement and then is removed. In addition to avoiding deep sedation and paralysis, this method commonly avoids the increased dynamic hyperinflation and resultant hypotension that often accompanies bag-mask ventilation during a standard direct lanyngoscopic intubation. Awake fiberoptic intubation requires patient cooperation and may be limited by severe agitation or coughing; adequate topical anesthesia and low doses of sedatives and analgesics are usually but not always effective. Other complications include laryngospasm and aspiration although these are uncommon. This technique, however, requires a skilled operator familiar with use of a fiberoptic bronchoscope.

Independent of the intubation technique, it is necessary to provide additional sedative and analgesic medications such as propofol or versed, and fentanyl after intubation to ensure patient comfort and to prevent tachypnea, patient–ventilator dyssynchrony, and the resultant dynamic hyperinflation with its associated complications.

The goals of mechanical ventilation following intubation are to ensure adequate oxygenation and ventilation, and to prevent short term complications such as hypotension and barotrauma by improving dynamic hyperinflation. This is accomplished with a strategy known as permissive hypercapnia in which dangerous plateau pressures are avoided by limiting respiratory rate and tidal volumes, allowing full exhalation between breaths, and permitting some degree of respiratory acidosis. Hypercapnia itself is of little consequence in most patients and a blood pH down to 7.20 is generally safe and well tolerated. Initial ventilator setup should use either a volume-cycled or pressure-limited control mode, should target a minute ventilation of 8–10 l/min, and should limit plateau pressure to <35 cm $H_2O$. Tidal volumes should aim for 6–8 ml/kg of predicted body weight. The respiratory rate should be set initially to 10–12 breaths/min and the inspiratory flow rate or inspiratory times should be adjusted to provide an expiratory time long enough for full exhalation between breaths. Frequent measurement of ABGs should occur until stability is achieved. Continuous infusions of NMB may be necessary in patients resistant to high doses of sedatives and analgesics, although prolonged use of neuromuscular blocking agents and CS is associated with myopathy and should be used with caution [40]. Inhaled therapies such as continuous nebulizers and Heliox should be adapted to the ventilator circuit and oral therapies should generally be converted to the IV route.

Even with permissive hypercapnia, ED clinicians must be prepared to deal with potential complications of mechanical ventilation. Hypotension is common and if present, intravenous fluids should be administered and the patient should be evaluated for tension pneumothorax and pneumomediastinum. If pneumothorax is present, the chest must be vented with a needle or with placement of a chest tube. The possibility of autopositive end-expiratory pressure (auto-PEEP) from dynamic hyperinflation also needs to be considered; it may be empirically treated by removing the patient from the ventilator for a period followed by either additional sedation and analgesia and/or use of NMB to manage tachypnea and patient–ventilator dyssynchrony.

For the most severely affected and treatment-refractory patient, the emergency department clinician should be aware of salvage treatments such as the use of inhaled anesthetics and extracorporeal gas exchange as implementation of these modalities often requires consultation with multiple specialists and arranging transfer to other settings such as the operating room or specialized intensive care units. Note that alternative modes of mechanical ventilation that do not allow for a prolonged expiratory time such as high frequency oscillatory ventilation and airway pressure release ventilation are generally thought to be contraindicated in the setting of severe airflow obstruction due to the risk of worsening dynamic hyperinflation. As such, these modes have not been studied in asthma exacerbation and cannot be recommended as rescue strategies.

## Adverse Responses to Medications Used for Exacerbations

Albuterol is the mainstay of therapy for patients with acute asthma exacerbation. Commonly reported mild adverse effects associated with frequent dosing include tachycardia, tremor, and headache. If continuous high-dose albuterol is administered by nebulizer, tremor occurs in approximately 20% of patients [41] Albuterol is also known to cause hypokalemia by shifting potassium intracellularly. Preexisting hypokalemia should be corrected but aggressive replenishment of potassium during albuterol therapy is not recommended. Albuterol in high doses may cause arrhythmias but cause and effect are often difficult to sort out because patients may have concomitant hypoxia and acid–base abnormalities. There are rare reports of lactic acidosis with albuterol administration.

The most common adverse events associated with inhaled ipratropium included tremor, agitation, tachycardia, dry mouth, headache, nausea, vomiting, and dizziness. However, many of the reported side effects are minor and occur during administration of ipratropium for more than 12 weeks rather than in the setting of the acute treatment of exacerbations.

Systemic CS have a large number of known adverse effects but most are seen only with prolonged or repeated use. Short term use of systemic CS in the treatment of acute exacerbations is generally well tolerated. Common side effects include psychiatric disturbances such as insomnia, agitation, and even psychosis, worsening glycemic control in diabetics, and fluid retention in patients with underlying cardiovascular disease. Patients should be educated about these side effects and instructed to seek medical attention should they occur.

## Adverse Asthma Responses to Nonasthma Medications

The practitioner must be aware that certain medications are contraindicated or relatively contraindicated in patients with acute asthma exacerbations. Beta-blockers are in this category. Although cardioselective beta-blockers have been shown to be safe in short-term use in patients with mild–moderate reversible airways obstruction [42], their use is not well studied in acute exacerbation. As such, their use in patients with acute exacerbation should be avoided unless a strong indication exists and no alternative is available. Noncardioselective beta blockers such as propranolol, labetalol, and carvedilol should be avoided in acute asthma exacerbation.

Patients with aspirin allergy or with the syndrome of asthma, nasal polyposis, and aspirin sensitivity should not be given aspirin. There is an approximately 20% cross-reactivity with nonsteroidal anti-inflammatory drugs (NSAIDs). For such patients presenting with acute coronary syndrome or ischemic cerebrovascular accident, an ADP receptor antagonist such as clopidogrel (Plavix®) should be considered as an alternative.

## Treatments Not Recommended for Routine Use in Exacerbations

Antibiotics should not be given routinely to patients with asthma exacerbation unless there is a high clinical suspicion for concurrent acute bacterial infection such as pneumonia or sinusitis. Some studies suggest that chronic infection with *M. pneumoniae* or *C. pneumoniae* may play a role in acute exacerbations in some patients and research in nonasthmatic airways disease suggests a possible anti-inflammatory effect of macrolide antibiotics. Additional research is needed, however, to define the role of macrolides in asthma exacerbations before their routine use can be recommended.

Aggressive hydration should not be given as a matter of routine unless there is clinical history of poor oral intake, signs and symptoms of intravascular volume depletion, or hemodynamic instability. Careful clinical assessment of volume status should precede aggressive hydration.

Mucolytics should not be given as they have no demonstrable clinical efficacy in acute asthma and are known to induce bronchial irritation and bronchospasm. As mentioned above, methylxanthines are no longer recommended for routine use in acute asthma exacerbations but may be considered for use in severe, treatment refractory cases [3].

## Predicting Fatal or Near-Fatal Episodes

Near fatality has been viewed as the occurrence of respiratory arrest and/or coma necessitating emergency intubation and mechanical ventilation, and the condition is distinguished from those patients who are electively intubated because of fatigue. Despite research efforts, clinically reliable predictors of patients who are at risk for fatal or near-fatal episodes of asthma have not been conclusively identified. Patient characteristics associated with increased risk include lack of understanding or misinterpretation of the seriousness of symptoms, poor medical adherence, and coincident psychiatric illness and/or substance abuse. At risk patients are also likely to have had multiple ED visits, repeated hospitalizations, admission to the intensive care unit, and a history of respiratory failure. Histopathological findings suggest

that the type of acute asthma that leads to death may be a unique entity. Until studies are better able to explain why some patients with asthma die of a potentially reversible disease, ED management needs to focus on rapid evaluation and institution of therapies guided by the best available evidence.

## Predicting Response to Therapy

Early identification of patients with acute asthma who will require hospitalization or ICU admission would be helpful in the management of ED resources. It is not unusual for patients to be treated for several hours before a disposition decision is made. Additionally, because a substantial number of patients who are discharged from the ED suffer relapse and require a repeat visit within 2–14 days, it would also be helpful to prospectively identify this group.

Accurately predicting the clinical trajectories of individual patients, especially those with moderate or severe exacerbations, has proven difficult in practice. Many studies have attempted to identify factors predictive of response to therapy. There is general agreement that for the majority of patients presenting with acute asthma, there is no single universal parameter in the initial history, physical examination, or bedside testing that reliably predicts response. Similarly, multivariate formulas based on initial information have not been shown to improve predictive accuracy for all-comers.

Numerous studies have shown that repeat assessments, for example after the first hour of treatment, are better at predicting eventual response to therapy than assessments based on presentation. While multiple scoring systems have been published, no one system has proven broadly applicable. As such, repeat assessments focus on a combination of lung function and clinical data including the PEFR measured after initial treatment with inhaled bronchodilators and systemic CS. Although not universally predictive, a PEFR of less than 40% of predicted after initial therapies is associated with an increased need for hospitalization while a PEFR $\geq$70%, if sustained for 60 min after the last treatment, is typically an indication for discharge home. Other factors predictive of eventual need for hospitalization include ongoing use of accessory muscles and persistent hypoxemia after 1 h of therapy [43]. Patients with an incomplete response to initial interventions, such as those with persistent symptoms and PEFR 40–69% of predicted, will usually remain in the ED for ongoing treatment and reassessment. The NAEPP EPR3 guidelines suggest making a decision to admit or discharge these patients within 4 h of initial presentation [3].

## Disposition of the Patient with Asthma

The ultimate decision to admit or discharge the patient is based on a combination of factors including objective measures of lung function, symptoms and exam findings, and the patient's capacity to continue managing the exacerbation as an outpatient.

Decisions based on PEFR are complicated by several factors. Some patients with asthma have significant fixed airflow obstruction even during asymptomatic periods. The baseline personal best PEFR for these patients is likely more useful than the percent predicted but often this is not known by the patient or easily accessible in the medical record. In the very young and in a subset of adults not able to perform PEFR testing reliably, PEFR data may be unavailable altogether, necessitating greater reliance on clinical and social factors in decision making. Prior to making a decision about discharge, patients should be reassessed at least 60 min after the last bronchodilator treatment to ensure that gains in PEFR and clinical parameters are sustained.

Some features of the patient's case may prompt caution in decision making around disposition. Frequent ED visits, frequent hospitalizations, a history of intensive care unit admission, and prior intubation should weight the decision more toward admission. Furthermore, social and socioeconomic factors need to be considered such as the presence of poorly compensated psychiatric illness, substance abuse, limited understanding of asthma, limited access to healthcare, or an inability to pay for medications on discharge. The presence of one or multiple of these conditions may favor a brief admission to facilitate ongoing care.

With few exceptions, patients discharged after successful ED management of an exacerbation should be prescribed a burst of oral steroids. For patients in whom adherence or access may be limited, a depot formulation of intramuscular steroid may be provided. An ICS should be prescribed for all patients previously using an ICS and should be strongly considered in naïve patients to reduce the rate of relapse. ICS should be started on ED discharge and overlapped with systemic CS.

Discussion regarding avoidance of triggers should be undertaken, including counseling and medications for smoking cessation. Patients should be shown proper technique for use of inhalers including use of a holding chamber (spacer). The patient should be provided with a peak expiratory flow meter and instructed in its appropriate use. Outpatient follow-up with the patient's primary care provider or asthma specialist within 1 month should be arranged by ED staff and patients should be instructed to contact their provider within 3–5 days of discharge given the high rate of relapse in this period [3]. Patients presenting with a life-threatening exacerbation or

recurrent exacerbations should be referred to an asthma specialist.

All patients discharged from either the ED or the hospital should be provided with a written asthma action plan. A systematic review of 36 randomized trials of asthma self-education plans in adults showed significant reductions in hospitalizations, ED visits, and unscheduled visits to the doctor; best results were seen in patients who had written care plans [44]. A freely available asthma action plan can be obtained online from the National Institutes of Health [45].

## Conclusion

The full spectrum of acute exacerbations of asthma is addressed in the ED ranging from mild to life-threatening severity, straightforward to complicated presentations, and immediate to highly refractory responses to treatment. For all asthma cases, the goal is prevention of morbidity and mortality through rapid assessment and initiation of therapy, using the best available evidence to guide management. The provision of high quality care should be team based and focused on both medical interventions and patient education. Healthcare delivery should be coordinated between physicians, nurses, and respiratory therapists as well as social workers and case managers in the ED. Effective communication must also occur between ED clinicians and both inpatient and outpatient providers to ensure continuity of care and the best possible outcomes for patients with this potentially treatable disease.

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