Status Asthmaticus in Adult Patients

Desmond J. Young, MD
Gary A. Salzman, MD, FCCP

Asthma is a chronic inflammatory disorder of the airways associated with hyperresponsiveness, reversible airflow limitation, and respiratory symptoms.[1,2] It is one of the most common chronic diseases in the United States, with approximately 22 million adults affected at some point during their lives and 14 million adults currently affected.[3] Over half of those currently affected reported at least 1 attack during the previous year. In addition, there were over 4000 asthma-related deaths in 2002, with non-Hispanic blacks and women having a higher death rate than non-Hispanic whites and men.[3]

Asthma is also associated with a high economic toll. In 1998, the combined direct and indirect costs associated with asthma were an estimated US $11.3 billion.[4] Hospitalization accounted for the largest proportion of the direct cost, estimated at US $7.5 billion.[4]

Efforts to improve asthma-related outcomes have focused on eliminating symptoms with medication, normalizing pulmonary function, and educating asthma patients to avoid triggers and to recognize any objective or subjective sign of acute exacerbation. However, there often is a disconnect between patients' reported symptoms and the severity of their asthma. Patients' failure to recognize an asthma exacerbation can lead to a delay in seeking appropriate medical treatment and a more advanced exacerbation on presentation. When patients with acute asthma attacks do present, physicians must be able to recognize the exacerbation and initiate appropriate therapy. In many cases, exacerbations are refractory to initial therapy and require escalation of treatment, including hospital admission. Such severe asthma episodes are known as status asthmaticus. In status asthmaticus, early intervention with bronchodilators and corticosteroids is crucial to treat the bronchoconstriction and underlying inflammation and possibly prevent complications such as respiratory failure.

This article discusses the presentation of acute asthma attacks and reviews the diagnosis and management of status asthmaticus. For general management of asthma, physicians should refer to guidelines by the National Asthma Education and Prevention Program Expert Panel (www.nhlbi.nih.gov/guidelines/index.htm).

TAKE HOME POINTS

- Early recognition and treatment with bronchodilators and corticosteroids are crucial in an asthma exacerbation.
- There is often no correlation between patients' symptoms and the severity of an attack.
- A normal P_{CO_2} on arterial blood gas analysis, lactic acidosis, or change in level of consciousness during an asthma attack should alert the clinician to impending respiratory failure.
- If hypoxemia is out of proportion to the clinical findings of asthma, further investigation should be undertaken for a different diagnosis.
- The use of noninvasive positive pressure ventilation (NIPPV) in the treatment of status asthmaticus should be considered only by experienced physicians, and NIPPV should never be used outside an intensively monitored setting.

DEFINITION

Many terms have been used to describe severe acute asthma exacerbations, such as rapid-onset asthma attack, near-fatal asthma, acute asphyxic asthma, acute severe asthma, hyperacute asthma, and, at our institution, explosive asthma. Our best description of status asthmaticus is an asthma exacerbation that is refractory to or does not significantly improve with initial treatment and requires escalation of treatment, usually leading to hospital admission. For example, symptoms of respiratory compromise and the need for mechanical ventilation due to an asthma exacerbation imply the presence of status asthmaticus. In this review, status

Dr. Young is a pulmonary/critical care physician at the Georgetown Memorial Hospital system and is in private practice at Inlet Cardio Pulmonary and Associates, Pawleys Island, SC. At the time of submission, he was a pulmonary/critical care fellow at the Pulmonary/Critical Care Division, University of Missouri–Kansas City School of Medicine/Truman Medical Centers, Kansas City, MO. Dr. Salzman is a professor of medicine and chair, University of Missouri–Kansas City School of Medicine.

Table 1. Main Characteristics of Asthma Attacks with Sudden Versus Slow Evolution

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asthmaticus is defined as a severe asthma exacerbation requiring hospitalization for continued treatment of the signs and symptoms of an attack.

PRESENTATION OF AN ACUTE ASTHMA ATTACK

Acute asthma attacks may be related to bronchoconstriction, inspissation of secretions from hyperplastic mucous glands in an inflamed airway, or a combination of both.[5] In patients with asthma, various triggers (which can be unique to the individual) induce bronchospasm and airway inflammation. Inflammation, airway edema, mucous secretions, and bronchial smooth muscle contraction cause narrowing of airway passages, which limits air movement and can lead to status asthmaticus. In status asthmaticus, the process of exacerbation can take hours to weeks before symptoms develop.

The literature describes 2 types of acute asthma presentations to the emergency department (ED) whose clinical course and response to therapy appear to reflect the pathologic mechanisms underlying the exacerbation (**Table 1**).[6] With the first type, the exacerbation progresses quickly to airflow obstruction, usually within 3 to 6 hours of the initiation of the attack, but usually responds to bronchodilator therapy within 1 hour with a marked improvement in lung function.[7] In these sudden-onset asthma attacks, smooth muscle constriction is the predominant mechanism. With the second type, the exacerbation has a slower onset and responds poorly to bronchodilators because there is a greater degree of underlying airway inflammation and more mucous secretions and inflammatory cells in the airway. Most commonly, the inciting event or trigger is an upper respiratory infection, although there may be an allergic inflammatory component as well. These patients require anti-inflammatory treatment such as corticosteroids, and the response to anti-inflammatory treatment can take days. The slow-progression exacerbation represents the typical patient with status asthmaticus. It is important to note that some patients have features of both types of presentations.

Two studies that examined patients who died due to severe acute asthma exacerbations demonstrated that there are differences in the airways at a cellular level in patients with slow-onset versus sudden-onset exacerbation.[8,9] In sudden-onset deaths, the airway submucosa was predominantly composed of neutrophils, whereas in slow-onset fatal asthma, there were more eosinophils than neutrophils in the airway submucosa.

EVALUATION

History and Physical Examination

The symptoms of asthma vary but commonly include wheezing, dyspnea, chest tightness, and cough (**Table 2**). It can be challenging to differentiate asthma from other common causes of these symptoms, which include ischemic heart disease, congestive heart failure, vocal cord dysfunction (VCD), pneumothorax, pulmonary embolism, upper airway obstruction, epiglottitis, and chronic obstructive pulmonary disease (COPD). Determining that a patient has a history of asthma is very helpful in making the diagnosis, but caution should be taken as asthma can coexist with other diagnoses (eg, VCD).

In cases where the diagnosis of asthma is established, patients should be asked about when they were last asymptomatic in order to identify triggers. Common triggers include smoking, illicit drug use, occupational exposure, dust mites, cockroaches, animal dander, plant pollen, upper/lower airway infection, postnasal drip, nasal polyps, gastroesophageal reflux, premenstrual syndrome, stress, and medications. Many patients will be able to identify the inciting event. Recent ingestion or a history of allergy to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) may provide a clue to the diagnosis. Samter's triad has been

described as an association among aspirin/NSAID sensitivity, nasal polyps, and asthma. Aspirin-induced asthma is underrecognized and may be found in up to 20% of asthma patients.[10]

In patients with severe exacerbations, airway narrowing causes airflow trapping, dynamic hyperinflation, and an increase in both residual volume and functional residual capacity. The edematous airways trap air distally and do not allow complete exhalation, thus creating intrinsic or auto–positive end-expiratory pressure (auto-PEEP), which is the pressure of trapped air at the end of expiration as compared with atmospheric pressure.[11] Auto-PEEP accompanied by an increase in inspiratory and expiratory muscle contractions that occurs during acute respiratory failure can lead to large pressure changes that are transmitted to the mediastinal structures, affecting cardiac stroke volume. The result is an increasing difference between the maximal and minimal systemic systolic blood pressure, called pulsus paradoxus. Pulsus paradoxus is a decrease in systolic blood pressure of more than 10 mm Hg on inspiration; however, this finding is not specific for asthma.

On examination, patients may have accessory respiratory muscle use, upright posture, diaphoresis, or altered level of consciousness. Usually, patients are tachypneic and tachycardic. Chest hyperinflation may be observed. Auscultation of the chest can reveal polyphonic, diffuse wheezing, although this finding is not universal. Many other diseases can cause wheezing, and the intensity and tone of wheezing does not necessarily correspond to the degree of airflow obstruction in an asthma attack. No wheezing could represent extreme airflow obstruction with diminished respiratory excursion and poor air movement.

Peak Flow Measurements

Measuring peak expiratory flow rate (PEFR) or forced expiratory volume in 1 second (FEV_1) are the quickest ways to assess the severity of airway limitation, with the former being more practical in the acute setting. If data are available, the results of these tests should be compared with baseline PEFR. The patient should know his or her baseline PEFR if asthma education has been successfully implemented. Patients usually become symptomatic near a PEFR of 40% to 50% or less of the predicted value.[12] It should be noted that the correlation between the patient's subjective experience of symptoms does not always correspond to objective measurements of airflow obstruction. Some patients with life-threatening airway obstruction report few symptoms, while others report more symptoms at lesser degrees of obstruction.

Table 2. Common Signs and Symptoms of Acute Asthma Exacerbation

Subjective	Objective
Dyspnea	Tachypnea (severe, > 30 breaths/min)
Cough	Tachycardia (severe, > 120 bpm)
Wheezing	Upright positioning
Chest tightness	Pulsus paradoxus (severe, > 12 mm Hg)
Diaphoresis	Telegraphic speech
Sputum production	Sternocleidomastoid retraction
Exhaustion	Change in level of consciousness

Ancillary Studies

Cardiac assessment. Electrocardiography monitoring and evaluation of serial serum cardiac markers such as troponin can aid in differentiating asthma from an ischemic heart condition. The serum B-type natriuretic peptide level can be assessed quickly and can aid in differentiating dyspnea due to heart failure from other causes. Electrocardiography findings in patients with asthma can include sinus tachycardia, rightward axis deviation, and right ventricular strain, which can be a result of stress and airflow obstruction. In addition, supraventricular arrhythmias can occur, especially in the presence of aggressive β-agonist therapy. Hypokalemia and prolongation of the QTc interval are adverse side effects associated with the use of high-dose β-agonists.[13] Continuous electrocardiography monitoring is recommended in all patients who may have an arrhythmia and in older patients with underlying coronary artery disease.

Arterial blood gas (ABG) assessment. Most patients presenting with a severe acute asthma exacerbation should require only pulse oximetry monitoring because adequate oxygen saturation usually can be obtained with minimal amounts of supplemental oxygen. ABG is usually obtained in patients with severe respiratory distress, low oxygen saturations, depressed consciousness, and PEFR below 50% of baseline. The most common finding obtained from assessing ABG levels is respiratory alkalosis due to hyperventilatory hypocapnia and mild-to-moderate hypoxemia.[14,15] An ominous finding during an asthma attack is a normal P_{CO_2} on ABG analysis, which should alert the clinician to impending respiratory failure. The rising P_{CO_2} from expected hyperventilatory hypocapnia may represent respiratory muscle fatigue. Once overuse and fatigue of respiratory muscles commence, lactic acidosis may develop, which also heralds respiratory failure. If hypoxemia is out of proportion to the clinical findings of asthma, further investigation should be undertaken for a different diagnosis, such as

Table 3. Recommendations for Initial Treatment of Acute Asthma Exacerbation for the First Hour in the Emergency Department

Adapted with permission from Rodrigo GJ, Rodrigo C, Hall JB. Acute asthma in adults: a review. Chest 2004;125:1091.

FEV_1 = forced expiratory volume in 1 second; IV = intravenous; MDI = metered dose inhaler; PEFR = peak expiratory flow rate.

pneumonia or pulmonary embolism.[7] Any change in mental status should be evaluated for airway protection via intubation and possibly imaging of the head, depending on the findings of a detailed neurologic examination. If an intracranial process is suspected, appropriate studies should be undertaken.

Chest radiography is not mandatory. In presentations of possible or apparent pneumonia or pneumothorax, chest radiography would be appropriate. A pneumothorax or pneumomediastinum may be solely responsible for symptoms or may be a complication of asthma. Chest radiography can reveal lung volume expansion by showing flattened diaphragms and narrowing of mediastinal shadows. Evaluation of the cardiac silhouette and pulmonary vasculature can suggest pulmonary edema due to decompensated heart failure.

TREATMENT

Treatment of status asthmaticus usually begins prior to arrival at the ED and continues through outpatient management after hospitalization. The cornerstone of therapy in status asthmaticus is to identify and treat precipitating causes, consider alternative or concurrent diagnoses, and treat aggressively with anti-inflammatory therapy. Corticosteroids should be considered the primary treatment for status asthmaticus. Treatment, however, does not end with discharge from the hospital. One of the most important steps in managing asthmatic patients is the outpatient regimen of bronchodilator therapy and anti-inflammatory medications along with patient education to prevent future asthma exacerbations. The initial treatment of an acute asthma exacerbation is summarized in **Table 3**.[7]

Proven Therapy

Airway management and oxygen supplementation. A secured airway is of paramount importance in patients with cardiopulmonary failure. Oxygen can usually be administered via nasal cannula at low levels (< 5 L/min) and should be titrated for oxygen saturations above 92%; ABG sampling can possibly be avoided in this circumstance.[16] Increasing oxygen supplementation (100% oxygen) to obtain higher oxygen saturations or supernormal partial pressures of arterial oxygen may lead to the development of hypercarbia in patients with moderate to severe airway obstruction.[17] If supplemental oxygen is required, humidification is appropriate to prevent any bronchoconstriction triggered by dry-air tachypnea.[18]

β_2-Agonists. All patients with acute asthma exacerbations should receive inhaled β_2-agonists as first-line therapy. Intravenous (IV) β_2-agonists are associated with side effects such as cardiac arrhythmias and myocardial infarction. The safety and effectiveness of inhaled β_2-agonists have virtually eliminated the need for IV and subcutaneous administration. Shorter-acting agents, albuterol or salbutamol, should be used with a metered dose inhaler (MDI) with spacer, with the goal of achieving maximal bronchodilation while limiting side effects. Inhaled β_2-agonists are generally safe and well tolerated. Long-acting β_2-agonists are currently not recommended in the acute setting.

Albuterol is a racemic mixture containing equal quantities of (R)- and (S)-isomers, but only (R)-albuterol is a bronchodilator.[19] The pure (R)-enantiomer, levalbuterol, has similar bronchodilator properties and may have less systemic side effects, but the cost-effectiveness of levalbuterol needs further study.[20] Levalbuterol can be used in patients with known adverse side effects to albuterol. If the patient can cooperate with instructions, albuterol via MDI with spacer 4 puffs at 10-minute intervals could be the initial choice of therapy; nebulized delivery is also efficacious. There is evidence that 2.5 mg of albuterol administered via nebulizer every 20 minutes is equivalent to a single dose of 7.5 mg albuterol via nebulizer in the treatment

of acute bronchospasm in asthma patients with moderate to severe airway obstruction.[21]

Approximately two thirds of patients with an acute asthma attack will respond to the initial regimen.[22] In patients who do not respond (improvement in PEFR to > 40% of predicted) and have severe airway obstruction, further doses will not affect the immediate outcome and hospitaliztion will likely be required. The frequency of additional β_2-agonist treatments should be adjusted based on symptoms and objective data with careful observation for side effects, such as tremor, hypokalemia, or tachyarrhythmia.

Anticholinergics. Anticholinergic medications used alone are not as effective as β_2-agonists. However, the addition of ipratropium bromide to initial therapy with albuterol can have additive bronchodilator effects and is recommended for first-line therapy.[23] Inhaled ipratropium bromide is extremely well tolerated with minimal side effects. Options for delivery include MDI with spacer (4 puffs [~80 µg] every 10 minutes) or nebulized solution (500 µg per dose every 20 minutes). The long-acting anticholinergic tiotropium lacks data to support its use in asthma.

Corticosteroids. Inflammation is a key component of asthma and may be the major problem during an exacerbation in addition to bronchoconstriction. Therefore, corticosteroids are recommended for treatment of acute asthma episodes and should be given to all patients with status asthmaticus to hasten the resolution of the attack. Oral or IV routes of administration appear to be equally effective. The National Institutes of Health (NIH) guidelines recommend 120 to 180 mg/day of prednisone, prednisolone, or methylprednisolone in 3 or 4 divided doses for 48 hours and then 60 to 80 mg/day until PEFR reaches 70% of predicted.[2] The anti-inflammatory effect of corticosteroids as measured by improvement in pulmonary function is not immediate and can take up to 24 hours to occur.

Inhaled corticosteroids have been shown to improve lung function when given as first-line therapy. There are limited data comparing systemic and inhaled corticosteroids. In a recent small study, inhaled steroids were associated with earlier and greater improvement in lung function when compared with IV hydrocortisone.[24] There eventually may be a recommendation for using inhaled corticosteroids in first-line therapy.

Unproven Therapy

This section reviews treatments that have not been proven beneficial in blinded, randomized clinical trials for the treatment of status asthmaticus and, therefore, are not recommended at this time. These treatments include anesthetics, sedatives, antibiotics, magnesium sulfate, heliox, leukotrienes, and noninvasive positive pressure ventilation (NIPPV). Furthermore, aggressive hydration, chest physical therapy, and mucolytics have not been shown to improve exacerbations and are also not recommended.

Anesthetics/sedatives. General anesthetics,[25] lidocaine,[26] and inhaled furosemide[27] should not be involved in the treatment regimen as their use has no proven benefit. The use of sedatives in a patient with agitation or mental status changes has no role in the treatment of status asthmaticus unless the patient is mechanically ventilated.

Antibiotics. Antibiotics should not be used routinely in acute exacerbations of asthma. It is the responsibility of the medical community to slow the promotion of resistant bacteria by using antibiotics appropriately. Most asthma exacerbations that are caused by infection can be linked to a viral source.[28] Chlamydial pneumonia has been associated with some asthma exacerbations,[29] and certain macrolides may have a role as adjunctive therapy in the treatment of asthma pending further study.[30] For now, antibiotic use should be directed towards patients with evidence of pneumonia, sinusitis, or bronchitis who present with typical features of a bacterial infection, such as fever, purulent sputum with polymorphic leukocytes, or identification of an organism.[2]

Magnesium sulfate. Administered either as an inhalant or intravenously, magnesium sulfate may have a limited therapeutic role. In 1 study, magnesium sulfate (2 g IV) administered 30 minutes after initial treatment with a β_2-agonist and IV methylprednisolone was associated with a small improvement in pulmonary function in patients with FEV_1 levels below 20% of predicted.[31] However, a decrease in hospitalization rates was not found, and the current standard use of ipratropium bromide was not included in the study.

Leukotriene antagonists. Although leukotriene antagonists are useful in the management of chronic asthma in an outpatient setting, during acute exacerbations these agents have shown only a small improvement in pulmonary function.[32] Further studies are warranted before they can be recommended for routine use in status asthmaticus.

Heliox. Heliox mixtures, generally with 70% of helium and 30% oxygen, can improve delivery and retention of nebulized medications, reduce work of breathing (as measured by peak flow and pulsus paradoxus), and improve expiratory flow rates.[33–35] Notwithstanding, we were unable to find studies that showed improved outcomes in adult patients participating in randomized, blinded clinical trials in which the use of

heliox was compared with the standard treatment in acute asthma exacerbations or mechanically ventilated asthma patients. Heliox may have a role in the treatment of VCD,[36] but large trials are lacking.

NIPPV is an attractive therapy as it has been shown to be beneficial in other forms of acute respiratory failure.[37] However, unlike respiratory distress due to cardiogenic pulmonary edema and COPD, no randomized trials have shown that NIPPV provides a survival benefit in acute asthma exacerbations. NIPPV may have a role in correcting gas exchange abnormalities by using low inspiratory pressure with NIPPV via face mask.[38] The use of nasal bilevel pressure ventilation in selected patients has been shown to improve lung function, alleviate the attack faster, and significantly reduce the need for hospitalization.[39] NIPPV must be used with extreme caution in status asthmaticus, especially for the inexperienced user and until further studies are performed to define which patients will benefit. A delay in implementing invasive ventilation may be detrimental. The use of NIPPV in treatment for status asthmaticus should only be considered by experienced physicians, and NIPPV should never be used outside an intensively monitored setting (ED or the intensive care unit).

Theophylline. Theophylline therapy is not recommended for routine use in asthma exacerbation or acute asthma attack due to its side effects and a narrow therapeutic window.[5,6] Some experts, however, recommend a careful reserved use of theophylline in patient's refractory to standard therapy.[40] For now, theophylline should not be used until clinical trials show improved outcomes as compared with standard therapy.

RESPONSE TO THERAPY AND PATIENT DISPOSITION

Response to initial therapy is critical in determining whether patients with an asthma exacerbation should be admitted to the hospital. Several predictors have been found to be associated with better outcomes and can aid in avoiding unnecessary hospitalization. These predictors include a PEFR that exceeds 60% of the baseline value and an increase in PEFR of 50 L/min, both measured within 3 hours after treatment has begun.[40,41] The NIH guidelines recommend a PEFR value that is 70% of baseline for discharge and below 50% of baseline for admission, with PEFR values between 50% and 70% of baseline being indeterminate.[2] The combination of good clinical judgment and the aforementioned objective and subjective findings should ultimately influence the disposition of the patient.

A patient with an improved PEFR between 50% and 70% of predicted should have continued monitored therapy and a repeat spirometry with symptom evaluation. The disposition is such cases should be individualized. Patients should be monitored for side effects at least 60 minutes after the last treatment with β_2-agonists and for clinical stability prior to discharge from the ED.

If a patient is able to be discharged, adequate follow-up and compliance should be ensured. The patient should be supplied with a short course of corticosteroids, a long-acting β_2-agonist, and an as-needed short-acting β_2-agonist with specific instructions on proper use. The NIH guidelines recommend a steroid "burst" of prednisone or prednisolone 40 to 60 mg/day for 3 to 10 days or longer until a PEFR of 80% of personal best PEFR is achieved.[2] Corticosteroids can then be stopped as there is no evidence that tapering the dose of steroids prevents relapse.[42] Increased β_2-agonist inhaler use or worsening of symptoms warrants immediate return to a health care provider. Once diagnosed with asthma or discharged from the hospital, patients should receive a written asthma action plan that is either symptom-based, peak-flow–based, or both with appropriate education tailored to their asthma severity.

SUMMARY

Status asthmaticus is a common presentation to the ED. Early intervention with bronchodilators and corticosteroids is crucial to combat the bronchoconstriction and inflammation as well as possibly prevent complications such as respiratory failure. A careful history and physical examination can guide ancillary testing and treatment. Special attention and documentation of spirometric values should be an integral part of the evaluation of patients with asthma and influence patient disposition. The signs and symptoms of relapse should be explained to the patient and arrangement for follow-up with a medical care provider should be made before hospital discharge. Prevention of future asthma exacerbations by education and a written, understandable action plan can help patients identify worsening airflow obstruction, which can lead to initiating therapy at home and seeking medical attention quickly when necessary. For exacerbations that are difficult to manage, referral to or consultation with an asthma specialist is an option. **HP**

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