CLINICAL PRACTICE

Emergency Treatment of Asthma

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 46-year-old woman who has had two admissions to the intensive care unit (ICU) for asthma during the past year presents with a 4-day history of upper respiratory illness and a 6-hour history of shortness of breath and wheezing. An inhaled corticosteroid has been prescribed, but she takes it only when she has symptoms, which is rarely. She generally uses albuterol twice per day but has increased its use to six to eight times per day for the past 3 days. How should this case be managed in the emergency department?

THE CLINICAL PROBLEM

Asthma is one of the most common diseases in developed countries and has a worldwide prevalence of 7 to 10%.[1] It is also a common reason for urgent care and emergency department visits. From 2001 through 2003 in the United States, asthma accounted for an average 4210 deaths annually and an average annual total of approximately 504,000 hospitalizations and 1.8 million emergency department visits.[2] The average annual rate of emergency department visits for asthma was 8.8 per 100 persons with current asthma. Rates were higher among children than among adults (11.2 vs. 7.8 visits per 100 persons), among blacks than among whites (21 vs. 7 visits per 100 persons), and among Hispanics than among non-Hispanics (12.4 vs. 8.4 visits per 100 persons). Women made twice the number of emergency department visits as men.[2] Approximately 10% of visits result in hospitalization.[1]

Asthma is a heterogeneous disease, with varied triggers, manifestations, and responsiveness to treatment. Some patients with acute severe asthma presenting to the emergency department have asthma that responds rapidly to aggressive therapy, and they can be discharged quickly; others require admission to the hospital for more prolonged treatment. The reasons for this difference in responsiveness to treatment include the degree of airway inflammation, presence or absence of mucus plugging, and individual responsiveness to β_2-adrenergic and corticosteroid medications. The major challenge in the emergency department is determining which patients can be discharged quickly and which need to be hospitalized.

STRATEGIES AND EVIDENCE

INITIAL ASSESSMENT IN THE EMERGENCY DEPARTMENT

Patients presenting to the emergency department with asthma should be evaluated and triaged quickly to assess the severity of the exacerbation and the need for urgent intervention (Fig. 1). A brief history should be obtained, and a limited physical examination performed. This assessment should not delay treatment; it can be performed while patients receive initial treatment. Clinicians should search for signs

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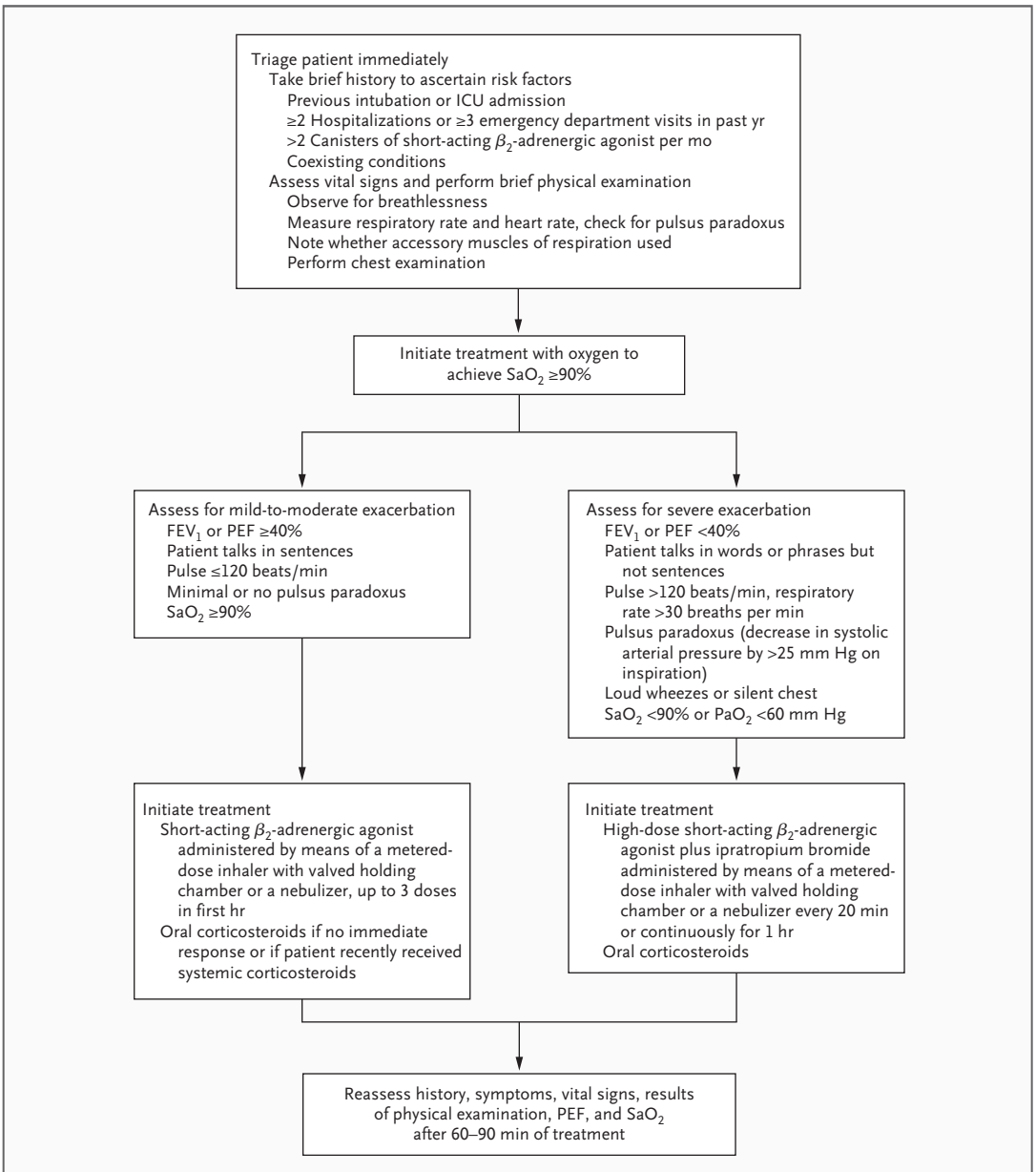

Figure 1. Initial Assessment of a Patient Presenting to the Emergency Department with Asthma.

Adapted from the National Asthma Education and Prevention Program Expert Panel Report 3.[3] FEV_1 denotes forced expiratory volume in 1 second, ICU intensive care unit, $PaCO_2$ partial pressure of arterial carbon dioxide, PaO_2 partial pressure of arterial oxygen, PEF peak expiratory flow, and SaO_2 arterial oxygen saturation.

of life-threatening asthma (e.g., altered mental status, paradoxical chest or abdominal movement, or absence of wheezing), which necessitate admission. Attention should be paid to factors that are associated with an increased risk of death from asthma, such as previous intubation or admission to an ICU, two or more hospitalizations for asthma during the past year, low socioeconomic status, and various coexisting illnesses.[3] The measurement of lung function (e.g., forced expiratory volume in 1 second [FEV_1] or peak expiratory flow [PEF]) can be helpful for assessing

the severity of an exacerbation and the response to treatment but should not delay the initiation of treatment. Laboratory and imaging studies should be performed selectively, to assess patients for impending respiratory failure (e.g., by measuring the partial pressure of arterial carbon dioxide [$PaCO_2$]), suspected pneumonia (e.g., by obtaining a complete blood count or a chest radiograph), or certain coexisting conditions such as heart disease (e.g., by obtaining an electrocardiogram).

TREATMENT IN THE EMERGENCY DEPARTMENT

All patients should be treated initially with supplementary oxygen to achieve an arterial oxygen saturation of 90% or greater, inhaled short-acting β_2-adrenergic agonists, and systemic corticosteroids (Fig. 1). The dose and timing of these agents and the use of additional pharmacologic therapy depend on the severity of the exacerbation.

β_2-Adrenergic Agonists

Inhaled short-acting β_2-adrenergic agonists should be administered immediately on presentation, and administration can be repeated up to three times within the first hour after presentation. The use of a metered-dose inhaler with a valved holding chamber is as effective as the use of a pressurized nebulizer in randomized trials,[4,5] but proper technique is often difficult to ensure in ill patients. Most guidelines recommend the use of nebulizers for patients with severe exacerbations; metered-dose inhalers with holding chambers can be used for patients with mild-to-moderate exacerbations, ideally with supervision from trained respiratory therapists or nursing personnel (see the Supplementary Appendix and a Video, both available at NEJM.org, for descriptions of how to use inhalers with and inhalers without a holding chamber, respectively). The dose administered by means of metered-dose inhalers for exacerbations is substantially greater than that used for routine relief: four to eight puffs of albuterol can be administered every 20 minutes for up to 4 hours and then every 1 to 4 hours as needed (Table 1). Albuterol can be delivered by means of a nebulizer either intermittently or continuously. A meta-analysis of results from six randomized trials indicated that intermittent administration and continuous administration have similar effects on both lung function and the overall rate of hospitalization,[6] whereas a Cochrane review of findings from eight trials suggested that continuous administration resulted in greater improvement in PEF and FEV_1 and a greater reduction in hospital admissions, particularly among patients with severe asthma.[7]

Albuterol is the inhaled β_2-adrenergic agonist most widely used for emergency management. Levalbuterol, the R-enantiomer of albuterol, has been shown to be effective at half the dose of albuterol, but randomized trials conducted in the emergency department have not consistently shown a clinical advantage of levalbuterol over racemic albuterol.[8,9] Pirbuterol and bitolterol are effective for mild or moderate exacerbations, but a higher dose is required than with albuterol or levalbuterol, and their use for severe exacerbations has not been studied.

Oral or parenteral administration of β_2-adrenergic agonists is not recommended, since neither has been shown to be more effective than inhaled β_2-adrenergic agonists, and both are associated with an increased frequency of side effects. The long-acting inhaled β_2-adrenergic salmeterol has not been studied for the treatment of exacerbations, though trials with formoterol (ClinicalTrials.gov numbers, NCT00819637 and NCT00900874) are under way.

Anticholinergic Agents

Because of its relatively slow onset of action, inhaled ipratropium is not recommended as monotherapy in the emergency department but can be added to a short-acting β_2-adrenergic agonist for a greater and longer-lasting bronchodilator effect.[10,11] In patients with severe airflow obstruction, the use of ipratropium together with a β_2-adrenergic agonist in the emergency department, as compared with a β_2-adrenergic agonist alone, has been shown to reduce rates of hospitalization by approximately 25%,[12,13] although there is no apparent benefit of continuing ipratropium after hospitalization.

Systemic Corticosteroids

In most patients with exacerbations that necessitate treatment in the emergency department, systemic corticosteroids are warranted. The exception is the patient who has a rapid response to initial therapy with an inhaled β_2-adrenergic agonist. Although most randomized, controlled

Table 1. Medications for Treatment of Asthma Exacerbation in the Emergency Department.*

Drug and Available Formulation	Dose	Comments
Short-acting β_2-adrenergic agonists		Adverse effects include tachycardia, palpitations, tremor, and hypokalemia.
Albuterol		
Metered-dose inhaler (90 μg/puff)	4–8 puffs every 20 min up to 4 hr, then every 1–4 hr as needed	
Nebulizer solution (0.63 mg/3 ml, 1.25 mg/3 ml, 2.5 mg/3 ml, or 5.0 mg/ml)	2.5–5 mg every 20 min over the first hr, then 2.5–10 mg every 1–4 hr as needed or 10–15 mg/hr continuously	For optimal delivery, dilute solution to a minimum of 3 ml at a gas flow of 6–8 liters/min. Use large-volume nebulizers for continuous administration.
Levalbuterol†		
Metered-dose inhaler (45 μg/puff)	Same as for albuterol, metered-dose inhaler; levalbuterol administered in half the milligram dose of albuterol has similar efficacy and safety	
Nebulizer solution (0.63 mg/3 ml, 1.25 mg/0.5 ml, or 1.25 mg/3 ml)	1.25–2.5 mg every 20 min over the first hr, then 1.25–5 mg every 1–4 hr as needed; levalbuterol administered at half the milligram dose of albuterol has similar efficacy and safety; continuous nebulization has not been evaluated	
Bitolterol		Has not been studied in patients with severe asthma exacerbations. Not available in the United States.
Metered-dose inhaler (370 μg/puff)	Same as for albuterol, metered-dose inhaler; bitolterol thought to be half as potent as albuterol on a milligram basis	
Nebulizer solution (2 mg/ml)	Same as for albuterol, nebulizer solution; bitolterol thought to be half as potent as albuterol on a milligram basis	
Pirbuterol, metered-dose inhaler (200 μg/puff)	Same as for albuterol, metered-dose inhaler; pirbuterol thought to be half as potent as albuterol on a milligram basis	Has not been studied in patients with severe asthma exacerbations.
Anticholinergic agents		Adverse effects include dry mouth, cough, and blurred vision.
Ipratropium bromide		Should not be used as first-line therapy; should be added to short-acting β_2-adrenergic agonist therapy for severe exacerbations. The addition of ipratropium to a short-acting β_2-adrenergic agonist has not been shown to provide further benefit once the patient is hospitalized.
Metered-dose inhaler (18 μg/puff)	8 puffs every 20 min as needed, for up to 3 hr	
Nebulizer solution (0.25 mg/ml)	0.5 mg every 20 min for 1 hr (three doses), then as needed; can be used with albuterol in one nebulizer	

Ipratropium bromide and albuterol		May be used for up to 3 hr during initial management of severe exacerbations. The addition of ipratropium to albuterol has not been shown to provide further benefit once the patient is hospitalized.
Metered-dose inhaler (each puff containing 18 μg of ipratropium and 90 μg of albuterol)	8 puffs every 20 min as needed, up to 3 hr	
Nebulizer solution (each 3-ml vial contains 0.5 mg of ipratropium bromide and 2.5 mg of albuterol)	3 ml every 20 min for 3 doses, then as needed	
Systemic corticosteroids: prednisone, prednisolone, and methylprednisolone	40–80 mg/day in one dose or two divided doses, given until peak expiratory flow reaches 70% of predicted value or a personal best value	There is no known advantage of higher doses of corticosteroids to treat severe asthma exacerbations or of intravenous administration over oral therapy, provided that gastrointestinal absorption is not impaired. The total course of systemic corticosteroids for an asthma exacerbation necessitating an emergency department visit or hospitalization may be 3 to 10 days. For corticosteroid courses of <1 wk, there is no need to taper the dose; for courses of 7–10 days, there probably is no need to taper, especially if patients are concurrently receiving inhaled corticosteroids. Adverse effects include adrenal suppression, growth suppression, osteoporosis, muscle weakness, hypertension, weight gain, diabetes, cataracts, Cushing's syndrome, and dermal thinning.

* Adapted from the National Asthma Education and Prevention Program Expert Panel Report 3.[3]
† Levalbuterol is the R-enantiomer of albuterol.

trials of corticosteroids in patients seen in the emergency department and those admitted to the hospital have been small, these studies individually[14,15] and collectively[16-18] show that the use, as compared with nonuse, of systemic corticosteroids is associated with a more rapid improvement in lung function, fewer hospitalizations, and a lower rate of relapse after discharge from the emergency department. Because comparisons of oral prednisone and intravenous corticosteroids have not shown differences in the rate of improvement of lung function or in the length of the hospital stay,[19-21] the oral route is preferred for patients with normal mental status and without conditions expected to interfere with gastrointestinal absorption. Although the optimal dose of corticosteroid is not known, pooled data from controlled trials involving patients seen in the emergency department or admitted to the hospital have shown no significant advantage of doses greater than 100 mg per day of prednisone equivalent.[19,20,22-25] The most recent guidelines from the National Asthma Education and Prevention Program (NAEPP) (Expert Panel Report 3) recommend the use of 40 to 80 mg per day in one dose or two divided doses.[3]

Inhaled Corticosteroids

Although high-dose inhaled corticosteroids are often used to treat worsening of asthma control and to try to prevent exacerbations, the evidence does not support the use of inhaled corticosteroids as a substitute for systemic corticosteroids in the emergency department.[26] Inhaled corticosteroids are, however, preferred for long-term asthma control. At the time of discharge from the emergency department, these agents should be continued in patients who have been taking them for long-term control and should be prescribed for patients who have not previously taken them. In a randomized, controlled trial of 1006 consecutively enrolled patients with acute asthma treated in a Canadian emergency department, the addition at discharge of inhaled budesonide (for 21 days) to treatment with oral corticosteroids (for 5 to 10 days) was associated with a 48% reduction in the rate of relapse at 21 days and with improvement in the quality of life with respect to asthma (as measured by the Asthma Quality of Life Questionnaire) and symptoms, as compared with treatment with oral corticosteroids alone.[27]

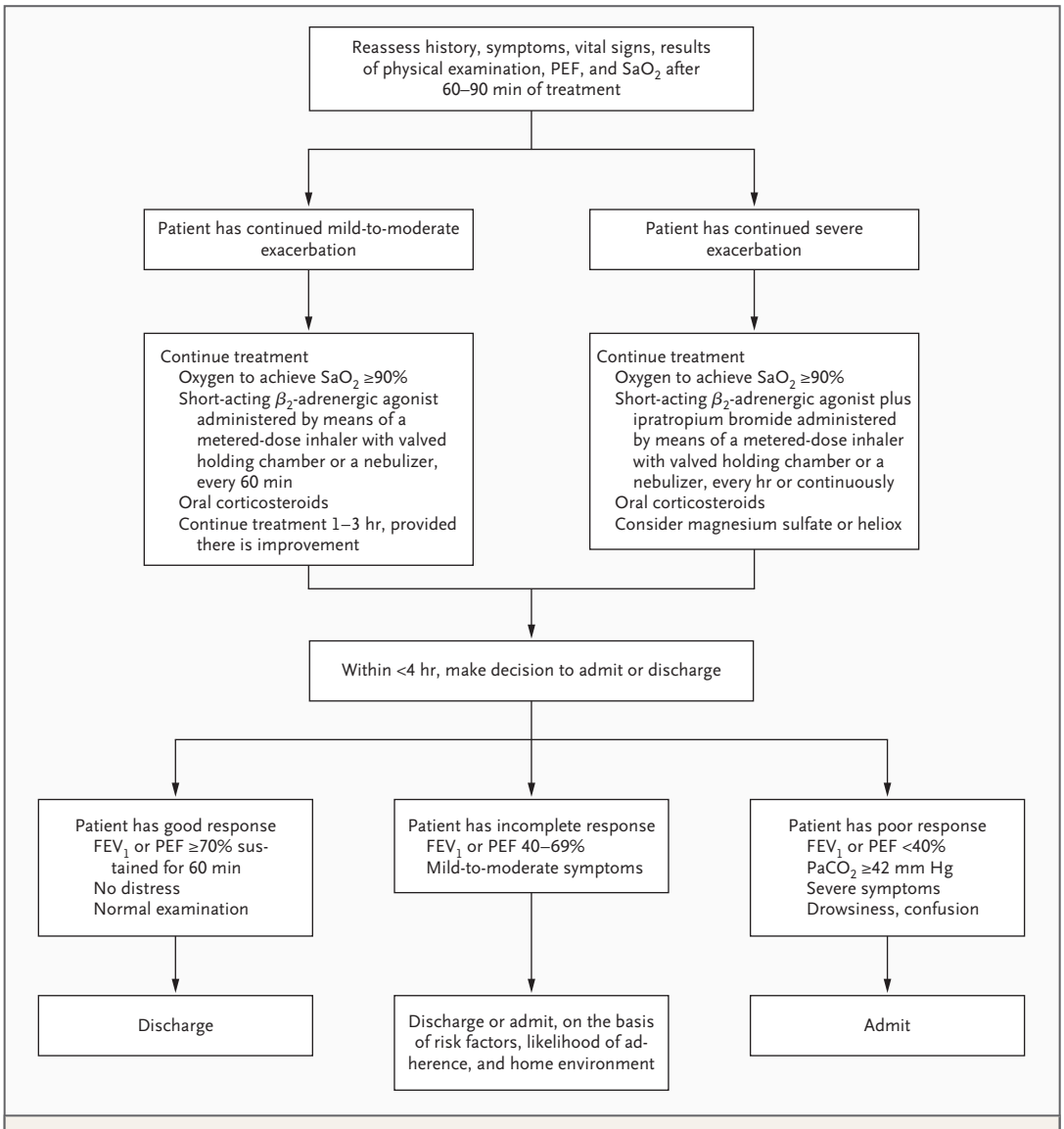

Figure 2. Continued Management of Asthma in the Emergency Department.

Adapted from the National Asthma Education and Prevention Program Expert Panel Report 3.[3] Heliox is a mixture of helium and oxygen, usually 79% and 21%, respectively, whose density is about one third that of air. FEV_1 denotes forced expiratory volume in 1 second, $PaCO_2$ partial pressure of arterial carbon dioxide, PEF peak expiratory flow, and SaO_2 arterial oxygen saturation.

Treatments That Are Not Recommended

Although methylxanthines were once a standard treatment for asthma in the emergency department, it is now clear that their use increases the risk of adverse events without improving outcomes.[28] Antibiotics should not be used routinely but rather should be reserved for patients in whom bacterial infection (e.g., pneumonia or sinusitis) seems likely. Similarly, neither aggressive hydration nor administration of mucolytic agents is recommended for acute exacerbations.[3]

ASSESSMENT OF RESPONSE TO TREATMENT

Patients should be reassessed after the first treatment with an inhaled bronchodilator and again at 60 to 90 minutes (i.e., after three treatments).[3] This assessment should include a survey of symptoms, a physical examination, and measurement of FEV_1 or PEF (Fig. 2). For the most severe exacerbations, this repeat assessment should probably include the measurement of arterial blood gases. Most patients will have clinically significant improvement after one dose of an inhaled

bronchodilator, and 60 to 70% will meet the criteria for discharge from the emergency department (see below) after three doses.[29-31] The degree of subjective and objective improvement that occurs in response to treatment predicts the need for hospitalization.[32-38] In a study of 720 patients treated in 36 Australian emergency departments, the need for hospital admission among patients assessed as having moderate asthma, as well as the need for ICU care of patients assessed as having severe asthma, was better predicted by the assessment of asthma severity after 1 hour of treatment than by the initial assessment in the emergency department.[38]

INDICATIONS FOR ADMISSION

After treatment in the emergency department for 1 to 3 hours, patients who have an incomplete or poor response, defined as an FEV_1 or PEF of less than 70% of the personal best or predicted value, should be evaluated for admission to the hospital. Patients who have an FEV_1 of less than 40%, persistent moderate-to-severe symptoms, drowsiness, confusion, or a $PaCO_2$ of 42 mm Hg or greater should be admitted. Patients who have an FEV_1 of 40 to 69% and mild symptoms should be assessed individually for risk factors for death, ability to adhere to a prescribed regimen, and the presence of asthma triggers in the home. The NAEPP Expert Panel Report 3 suggests that the decision to admit or discharge a patient should be made within 4 hours after presentation to the emergency department.[3]

MANAGEMENT OF RESPIRATORY INSUFFICIENCY

Patients with altered mental status, exhaustion, or hypercapnia should be considered for immediate intubation and ventilatory support. Because of high positive intrathoracic pressures, intubation and ventilation may lead to hypotension and barotrauma. Care should be taken to ensure adequate intravascular volume, and to avoid high airway pressures. A strategy of "permissive hypercapnia," achieved by adjusting the ventilator to correct hypoxemia while avoiding high airway pressures, was associated in an observational study with decreased mortality among patients with status asthmaticus,[39] and this approach has become standard.

Guidelines suggest that once a decision has been made in the emergency department to intubate a patient, the procedure should be semielective and performed under controlled conditions (vs. performed as an emergency procedure by the first available staff). Randomized trials have shown a benefit from noninvasive positive-pressure ventilation for acute exacerbations of chronic obstructive pulmonary disease, but most information used to guide the ventilation strategy for treating acute asthma comes from case reports or noncontrolled studies. A randomized crossover study that compared the use of bilevel positive airway pressure for 2 hours with standard care in children with acute asthma showed a significantly lower respiratory rate and improved scores on a questionnaire regarding asthma symptoms with bilevel positive airway pressure but no significant difference in arterial oxygen saturation, transcutaneous carbon dioxide levels, or other outcomes.[40] In a randomized, sham-controlled trial of the use of bilevel positive airway pressure in 30 adults with acute asthma, bilevel positive airway pressure was associated with a higher FEV_1 value at 4 hours and a lower rate of hospitalization (17.6%, vs. 62.5% with sham treatment).[41] These data suggest that noninvasive positive-pressure ventilation could be considered for patients who decline intubation and for selected patients who are likely to cooperate with mask therapy, but more data are needed to recommend this approach.

DISCHARGE FROM THE EMERGENCY DEPARTMENT

Patients may be discharged if the FEV_1 or PEF after treatment is 70% or more of the personal best or predicted value and if the improvements in lung function and symptoms are sustained for at least 60 minutes.[3] After discharge, patients should continue to use inhaled short-acting β_2-adrenergic agonists as needed and should be given oral corticosteroids for 3 to 10 days[3] (Table 2). Inhaled corticosteroids can be started at any time during treatment of the exacerbation, but initiation at the time of discharge, if not before, is prudent to reduce the risk of relapse.[27,42,43]

EDUCATION OF PATIENTS

The need for treatment in the emergency department often reflects inadequate maintenance therapy and insufficient knowledge of how to deal with a worsening of asthma control. Presentation to the emergency department provides a unique opportunity to educate patients about medications, inhaler technique, and steps that can reduce exposure to household triggers of allergic reaction and to ensure that discharged

Table 2. Recommendations for Discharge from the Emergency Department.*

Medications
Continue inhaled short-acting β_2-adrenergic agonists every 1–2 hr, as needed
Continue oral corticosteroids at a dose of 40–80 mg/day for 3–10 days
If course is <1 wk, no need to taper the dose
If course is 7–10 days, probably no need to taper, especially if patients are concurrently receiving inhaled corticosteroids
Continue or start an inhaled corticosteroid at a "medium dose" (e.g., beclomethasone [HFA], 240–480 μg/day; budesonide [DPI], 600–1200 μg/day; or fluticasone [DPI], 300–500 μg/day)
Education
Review purposes and doses of asthma medications with patient
Review inhaler technique with patient
Teach patient to monitor for signs and symptoms of poor asthma control
Provide patient with an asthma action plan
Follow-up
Advise patient to call primary care provider within 3–5 days after discharge
Schedule a follow-up appointment with provider to occur within 1–4 wk

* DPI denotes dry-powder inhaler, and HFA hydrofluoroalkane formulation.

patients have an asthma action plan and instructions for monitoring their symptoms and implementing their plan. A follow-up appointment should be scheduled with the patient's primary care provider or with an asthma specialist to occur 1 to 4 weeks after discharge. Guidelines also recommend that patients be encouraged to contact their asthma care provider within 3 to 5 days after discharge, when the risk of relapse is greatest,[3] although data are lacking to show that this action improves outcomes.

AREAS OF UNCERTAINTY

In patients with severe asthma that is refractory to standard treatment, intravenous magnesium sulfate is widely used,[44] but there is controversy regarding its efficacy. A meta-analysis of 1669 patients in 24 studies who received either intravenous magnesium sulfate (used in 15 studies) or nebulized magnesium sulfate (used in 9 studies) showed that intravenous treatment was weakly associated with improved lung function in adults but had no significant effect on hospital admissions; in children, the use of intravenous magnesium sulfate significantly improved lung function and reduced rates of hospital admission. The effect of nebulized magnesium sulfate is less substantiated.[45] Expert opinion[46] and guidelines[3] suggest that clinicians consider the use of intravenous magnesium sulfate in patients who have severe exacerbations and whose FEV_1 or PEF remains less than 40% of the personal best or predicted value after initial treatments. The results of a large multicenter trial in the United Kingdom[47] (Current Controlled Trials number, ISRCTN04417063) comparing treatment with intravenous or nebulized magnesium sulfate and standard treatment in patients with severe asthma are expected in 2011.

Heliox is a mixture of helium and oxygen, usually 79% and 21%, respectively, with a density about one third that of air, that reduces airflow resistance within regions of the bronchial tree where turbulent flow predominates. It is thought to reduce the work of breathing and to improve delivery of aerosolized medications. However, its role in the management of acute severe asthma is unclear. A Cochrane analysis of 544 patients in 10 trials led to the conclusion that heliox might be beneficial in patients with severe airflow obstruction who have not had a response to initial treatment,[48] and current guidelines reflect this conclusion.[3]

Since the administration of oral leukotriene inhibitors results in increases in the FEV_1 within 1 to 2 hours,[49,50] there has been interest in using these agents in the emergency department, but their usefulness in that setting is unclear. In a randomized, placebo-controlled trial of intravenous montelukast in 583 adults whose FEV_1 remained at 50% or less of the predicted value after 60 minutes of standard care, the use of montelukast significantly improved the FEV_1 at 60 minutes but did not reduce the rate of hospitalization.[51]

GUIDELINES

The NAEPP and the Global Initiative for Asthma have developed and updated evidence-based guidelines for the diagnosis and management of asthma.[3,52] The recommendations in this article are consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has chronic uncontrolled asthma necessitating daily rescue use of albuterol, but she has not been receiving

daily controller therapy. Her history of ICU admissions and excessive albuterol use indicate that she is at increased risk for death related to asthma.

Treatment with oxygen, aerosolized albuterol and ipratropium, and systemic corticosteroids should be initiated. The patient should be monitored closely and her signs and symptoms reassessed frequently, and a decision to admit or discharge her should be made within 4 hours after presentation. If she is discharged from the emergency department, she should be educated about medications, inhaler technique, and steps for monitoring symptoms and for managing exacerbations. Emergency department staff should provide her with a discharge plan, schedule a follow-up appointment, and ensure that she has adequate medications or prescriptions to last until that appointment. Because of her previous admissions to the ICU and her history of consistently poor asthma control, referral to an asthma specialist would be prudent.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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