

Acute asthma, prognosis, and treatmentJennifer E. Fergeson, DO, Shiven S. Patel, MD, and Richard F. Lockey, MD *Tampa, Fla*

Asthma affects about 300 million people globally and accounts for 1 in every 250 deaths in the world. Approximately 12 million people in the United States each year experience an acute exacerbation of their asthma, a quarter of which require hospitalization. Acute asthma should be differentiated from poor asthma control. Patients with acute asthma will exhibit increasing shortness of breath, chest tightness, coughing, and/or wheezing. In contrast, poor asthma control typically presents with a diurnal variability in airflow and is a characteristic that is usually not seen during an acute exacerbation. The history should include a review of comorbidities, adherence to medications, previous episodes of near-fatal asthma, and whether the patient has experienced multiple emergency department visits or hospitalizations, particularly those requiring admission to an intensive care unit involving respiratory failure, intubation, and mechanical ventilation. Patient education is important to ensure that the patient understands that asthma is mostly a chronic disease and necessitates the avoidance of allergens, prevention of infections, adherence with routine vaccinations, management of comorbid conditions, and adherence to treatment regimens. This article is a structured review of the available literature regarding the diagnosis and management of acute asthma. (*J Allergy Clin Immunol* 2016;■■■:■■■-■■■.)

Key words: Asthma flare, acute asthma, asthma attack, wheezing, acute asthma diagnosis, acute asthma management

Asthma exacerbations are avoidable with appropriate regular therapy and patient education. Despite this, asthma affects about 300 million people globally and accounts for 1 in every 250 deaths.¹ In the United States alone, approximately 12 million people each year experience an acute exacerbation of their asthma, a quarter of which require hospitalization.² In Europe approximately 30 million people have asthma, and 15,000 people die yearly from this disease.³ This article is about acute asthma and its diagnosis, prognosis, and treatment.

From the Department of Internal Medicine, Division of Allergy and Immunology, University of South Florida.

Disclosure of potential conflict of interest: R. F. Lockey is a board member for the *Journal of Allergy and Clinical Immunology—In Practice and Allergy, Asthma & Immunology Research*, has consultant arrangements with Merck and AstraZeneca, is employed by the University of South Florida College of Medicine, has received payment for lectures from Merck and AstraZeneca, has received royalties from Informa Publishing, and has received travel support from national and international congresses for presentations. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication April 5, 2016; accepted for publication June 14, 2016.

Corresponding author: Jennifer E. Fergeson, DO, 13000 Bruce B. Downs Blvd (111D), Tampa, FL 33612. E-mail: jfergeso@health.usf.edu.

0091-6749/\$36.00

© 2016 Published by Elsevier Inc. on behalf of American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaci.2016.06.054>

Abbreviations used

COPD: Chronic obstructive pulmonary disease
 EPR-3: Expert Panel Report 3
 ICS: Inhaled corticosteroid
 MDI: Metered-dose inhaler
 NPPV: Noninvasive positive pressure ventilation
 OCS: Oral corticosteroid
 PaCO₂: Partial pressure of arterial carbon dioxide
 PEF: Peak expiratory flow
 PvCO₂: Venous partial pressure of carbon dioxide
 SABA: Short-acting β -agonist
 SCS: Systemic corticosteroid

Various clinical symptoms and signs can assist the clinician in determining the severity of acute asthma (*Fig 1*).^{2,4} To prevent severe asthma exacerbations, the goals for the physician managing subjects with asthma include (1) recognition of patients who are at a greater risk for near-fatal or fatal asthma; (2) education of the patient to recognize deterioration in their disease; (3) provision of an individual action plan for the patient to manage the exacerbation and to know when to seek professional help; and (4) management of comorbidities, such as rhinitis, sinusitis, obesity, gastroesophageal reflux disease, obstructive sleep apnea, chronic obstructive pulmonary disease (COPD), vocal cord dysfunction, and atopic dermatitis.⁵⁻⁹

PHYSICAL EXAMINATION

Clinical estimates of severity based on an interview and physical examination can result in an inaccurate estimation of disease severity; audible wheezing is usually a sign of moderate asthma, whereas no wheezing can be a sign of severe airflow obstruction. Symptoms of severe asthma include chest tightness, cough (with or without sputum), sensation of air hunger, inability to lie flat, insomnia, and severe fatigue. The signs of severe asthma include use of accessory muscles of respiration, hyperinflation of the chest, tachypnea, tachycardia, diaphoresis, obtundation, apprehensive appearance, wheezing, inability to complete sentences, and difficulty in lying down. Altered mental status, with or without cyanosis, is an ominous sign, and immediate emergency care and hospitalization are required. A detailed examination should include examining for signs and symptoms of pneumonia, pneumothorax, or a pneumomediastinum, the latter of which can be investigated by means of palpation for subcutaneous crepitations, particularly in the supraclavicular areas of the chest wall. Special attention should be paid to the patient's blood pressure, pulse, and respiratory rate. Tachycardia and tachypnea might be suggestive of a moderate-to-severe exacerbation, whereas bradycardia might indicate impending respiratory arrest. Pulsus paradoxus is often present and might correlate with the severity of exacerbation (*Fig 1*).^{2,3,5,10}

	Mild	Moderate	Severe	Subset: Respiratory Arrest Imminent
Symptoms				
Breathlessness	While walking	While at rest (infant—softer, shorter cry, difficulty feeding)	While at rest (infant—stops feeding)	
	Can lie down	Prefers sitting	Sits upright	
Talks in	Sentences	Phrases	Words	
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
Signs				
Respiratory rate	Increased	Increased	Often > 30/minute	
		Guide to rates of breathing in awake children:		
		Age	Normal rate	
		< 2 mo	< 60/min	
		2–12 mo	< 50/min	
		1–5 yr	< 40/min	
		6–8 yr	< 30/min	
Use of accessory muscles; suprasternal retractions	Usually not	Commonly	Usually	Paradoxical thoracoabdominal movement
Wheeze	Moderate, often only end expiratory	Loud; throughout exhalation	Usually loud; throughout inhalation and exhalation	Absence of wheeze
Pulse/minute	< 100	100–120	> 120	Bradycardia
		Guide to normal pulse rates in children:		
		Age	Normal rate	
		2–12 mo	< 160/min	
		1–2 yr	< 120/min	
		2–8 yr	< 110/min	
Pulsus paradoxus	Absent < 10 mm Hg	May be present 10–25 mm Hg	Often present > 25 mm Hg (adult), 20–40 mm Hg (child)	Absence suggests respiratory muscle fatigue
Functional assessment				
PEF percent predicted or percent personal best	≥ 70 percent	~ 40–69 percent or response lasts < 2 hours	< 40 percent	< 25 percent (Note: PEF testing may not be needed in very severe attacks)
PaO ₂ (on air)	Normal (test not usually necessary)	≥ 60 mm Hg (test not usually necessary)	< 60 mm Hg: possible cyanosis	
and/or				
Pco ₂	< 42 mm Hg (test not usually necessary)	< 42 mm Hg (test not usually necessary)	≥ 42 mm Hg: possible respiratory failure	
SaO ₂ percent (on air) at sea level	> 95 percent (test not usually necessary)	90–95 percent (test not usually necessary)	< 90 percent	
	Hypercapnia (hypoventilation) develops more readily in young children than in adults and adolescents.			

FIG 1. Acute asthma severity: clinical signs and symptoms. Originally published as Fig 5-3 in EPR-3. PaO₂, Arterial oxygen pressure; Pco₂, partial pressure of carbon dioxide.

DIFFERENTIAL DIAGNOSIS OF ACUTE ASTHMA

The differential diagnosis of acute asthma includes COPD, vocal cord dysfunction, bronchitis, bronchiectasis, epiglottitis, foreign body, extrathoracic or intrathoracic tracheal obstruction, cardiogenic pulmonary edema, noncardiogenic pulmonary edema, pneumonia, pulmonary embolus, chemical pneumonitis, and hyperventilation syndrome.^{3,5}

ACUTE ASTHMA TRIGGERS

Risk factors for asthma exacerbations can be identified from the clinical history. The patient interview should include questions about recent events, including (1) upper or lower respiratory tract infections; (2) cessation or reduction of medication; (3) use of concomitant medication, such as nonselective β -blockers; and (4) allergen or pollutant exposure.^{2,10}

PREDICTORS OF FATAL OR NEAR-FATAL ASTHMA

Major risk factors for near-fatal and fatal asthma are recognized, and their presence makes early recognition and treatment of an asthma exacerbation essential. The history should include a review of previous episodes of near-fatal asthma and whether the patient has experienced multiple emergency department visits or hospitalizations, particularly those requiring admission to an intensive care unit, involving respiratory failure, intubation, and mechanical ventilation. A history of allergic asthma and other known or suspected allergic symptoms should be obtained. For example, Nelson et al⁴ identified allergy to the mold *Alternaria* species and several dust mite species as a trigger for severe asthma.¹⁰

Adherence to medical treatment should be reviewed; poor adherence with prescribed therapies is a major risk factor. Inadequate therapy can include excessive use of β_2 -agonists, concomitant use of β -blockers, and failure to prescribe or use inhaled corticosteroids (ICSs) as a primary therapy. Recent withdrawal of oral corticosteroids (OCSs) suggests that the patient is at greater risk for a severe exacerbation. Lack of a written asthma action plan is another risk factor. Limited access of the patient to appropriate health care and lack of education about appropriate management strategies are additional risk factors. Socioeconomic factors associated with severe asthma exacerbations include the nonadherent adolescent or elderly asthmatic patients living in inner-city environments. Certain ethnic groups within a population might have a higher incidence of severe asthma, such as Americans of African or Spanish inheritance. Comorbidities, such as chronic lung, psychiatric, and cardiovascular diseases are other risk factors.^{10,11}

PHYSIOLOGIC AND LABORATORY PARAMETERS

Serial measurements of lung function facilitate quantification of the severity of airflow obstruction and response to therapy. Measurement of peak expiratory flow (PEF) rate provides a simple, quick, and cost-effective assessment of the severity of airflow obstruction. Patients can be supplied with an inexpensive PEF meter and taught to perform measurements at home to detect deterioration of their asthma. An individual management plan will be based on the personal best PEF value. Predetermined PEF values can be set, at which time the patient is alerted to the degree of severity of symptoms and can institute appropriate therapy, consult their physician, or both (Fig 2). In nonacute settings assessment of PEF and spirometry before and after administration of a bronchodilator can indicate the likely degree of improvement in lung function, which can be achieved by using adequate therapy. PEF values of 50% to 79% of predicted or personal best value signify the need for immediate treatment with an inhaled short-acting β -agonist (SABA). Values of less than 50% indicate the need for immediate medical care. Values of less than 35% indicate a possible severe life-threatening episode. This treatment should be administered with a SABA by using a nebulizer or metered-dose inhaler (MDI). SABA dose, response, and further management are depicted in Fig 2.^{2,11-14}

FEV₁ is measured by means of spirometry to assess the volume of air exhaled over 1 second and is the most sensitive test for airflow obstruction. FEV₁ is less variable than PEF and is independent of effort once a moderate effort has been made by the patient. Postbronchodilator reversibility should be assessed,

and an increase in FEV₁ of 12% or greater and 200 mL or greater is diagnostic of asthma.^{2,11}

Most patients do not require laboratory testing for the diagnosis of acute asthma. If laboratory studies are obtained, they must not delay asthma treatment. Laboratory studies might assist in detecting other comorbid conditions that complicate asthma treatment, such as infection, cardiovascular disease, or diabetes. Measurement of brain natriuretic peptide and a 2-dimensional transthoracic echocardiogram aid in the diagnosis of congestive heart failure. For patients taking diuretics who have comorbid cardiovascular disease, serum electrolytes might be useful because frequent SABA administration can cause transient decreases in serum potassium, magnesium, and phosphate levels. A baseline electrocardiogram and monitoring of cardiac rhythm are appropriate in patients older than 50 years and those with comorbid cardiovascular disease or COPD. A complete blood cell count might be useful in patients with fever or purulent sputum; however, modest leukocytosis is common in asthmatic patients, and patients with corticosteroids might have a corticosteroid-induced neutrophil leukocytosis. Serum theophylline levels are essential for patients taking theophylline because of its narrow therapeutic window.¹¹

Chest radiographs are not usually necessary for the diagnosis of acute asthma if examination of the chest reveals no abnormal findings other than the expected clinical signs and symptoms associated with an acute exacerbation. If a complication is suspected, such as pneumonia, pneumothorax, pneumomediastinum, congestive heart failure, or atelectasis secondary to mucous plugging, a chest radiograph should be obtained.¹¹

Arterial blood gas analysis should be considered in patients who are critically ill and have oxygen saturations of less than 92% or an FEV₁ of less than 30% who do not respond to intensive conventional treatment. Proper interpretation of the pH, arterial oxygen pressure, and partial pressure of arterial carbon dioxide (Paco₂) might help further assess the severity of an acute asthma exacerbation (Fig 1). For example, a breathless asthmatic patient presenting with a Paco₂ of 45 mm Hg or greater indicates a life-threatening attack and the need for transfer to a medical intensive care unit for further care. Less than 10% of asthmatic patients presenting to the emergency department have arterial oxygen values of less than 50 mm Hg and carbon dioxide levels of greater than 45 mm Hg.^{14,15} Lactic acidosis is common in patients with severe acute asthma. However, increased lactic acid levels are also associated with high doses of inhaled β_2 -agonist treatment.¹⁶

Venous blood gases have been evaluated as a substitute for arterial measurements because venous blood is easier to obtain. However, The Expert Panel Report 3 (EPR-3) does not recommend substituting venous partial pressure of carbon dioxide (Pvco₂) for arterial blood gas. Arteriovenous correlation for partial pressure of carbon dioxide is poor, and therefore Pvco₂ cannot be relied on as an absolute representation of Paco₂. However, a normal Pvco₂ has a good negative predictive value for a normal Paco₂. Therefore it might be used as a screening test to exclude hypercapnic respiratory distress.^{11,17}

TREATMENT

Treatment is based not only on assessment of lung function parameters but also on clinical findings and the efficacy of previous treatment. A seasonal exacerbation of asthma in a pollen-sensitive patient is more easily treatable than an

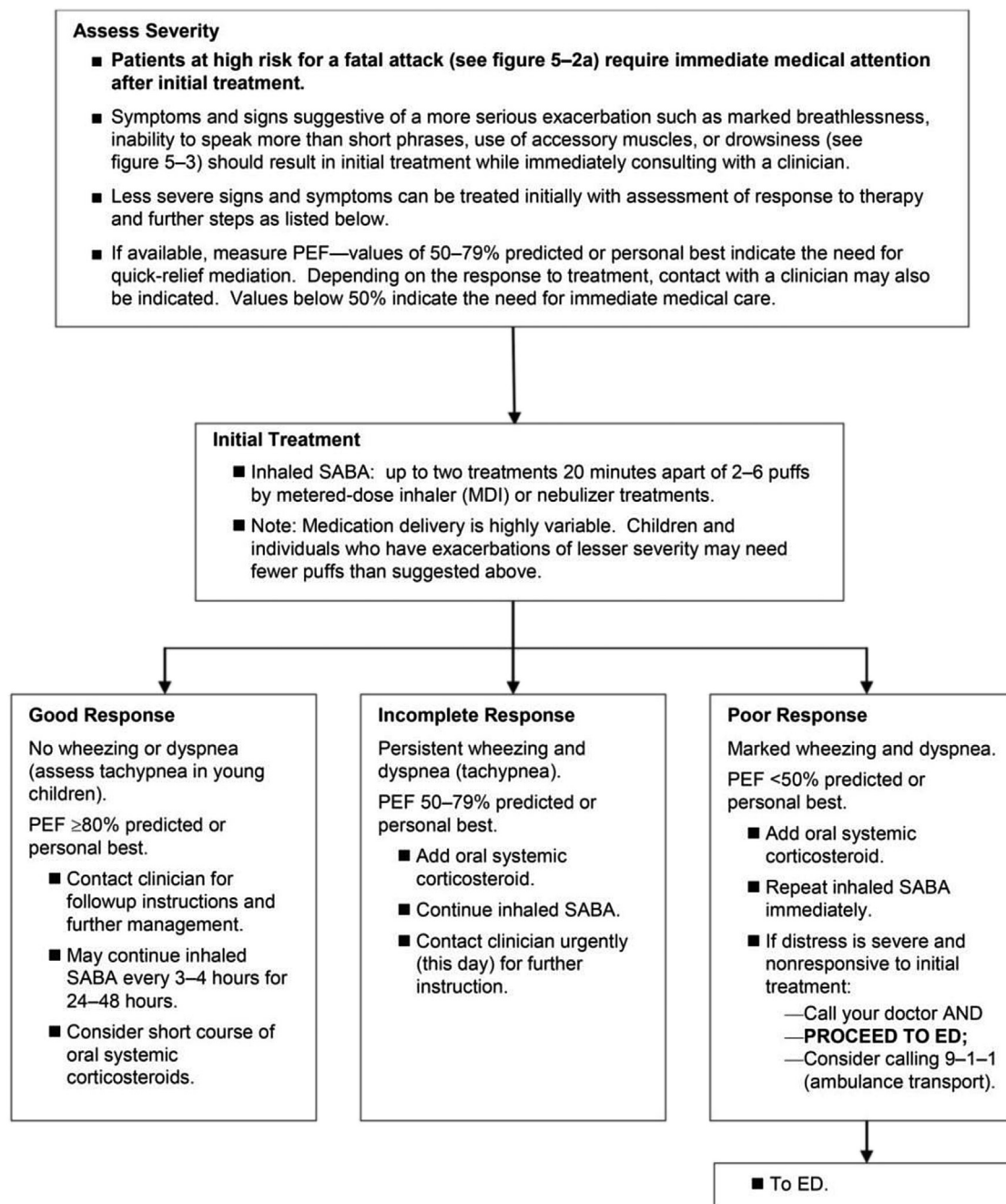


FIG 2. Management of asthma exacerbations: home treatment predicted. Originally published as Fig 5-4 in EPR-3. ED, Emergency department.

exacerbation triggered by a viral infection. Allergic asthma is more likely to respond immediately to an inhaled β_2 -agonist and an adjustment in ICSs, whereas the infected patient is more likely to require a systemic corticosteroid (SCS).³ A patient who is overusing short-acting β_2 -agonists might be refractory to nebulized β_2 -agonists and will usually require an SCS. Physician knowledge of an individual patient will suggest whether an SCS is required or whether an exacerbation can be managed on high doses of ICSs.^{3,11,18}

There are various national and international guidelines available for the diagnosis and management of acute asthma. In particular, the EPR-3 guidelines are referenced in this article because it is centered on a systematic review of the published scientific literature and provides the best evidence for clinical practice guidelines. EPR-3 recommended treatment choices in order of introduction in the acute setting are listed below and depicted in Fig 3. Treatment options and their recommended doses are listed in Fig 4.

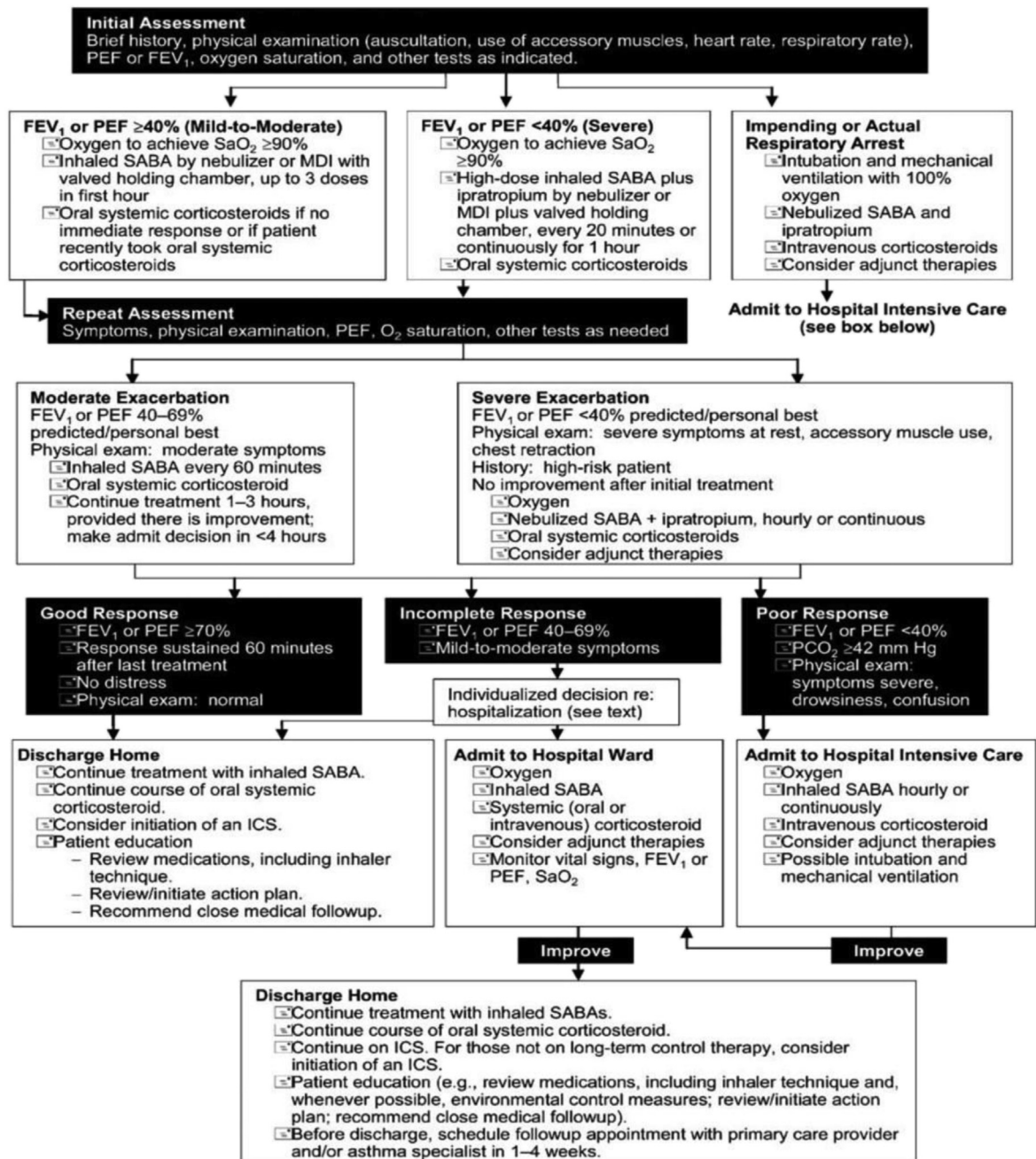


FIG 3. Acute asthma management: emergency department and hospital-based care. Originally published as Fig 5-6 in EPR-3. P_{CO_2} , Partial pressure of carbon dioxide; SaO_2 , arterial oxygen saturation.

Primary treatment choices include:

1. SABAs inhaled through an MDI or by means of nebulization;
2. anticholinergics inhaled through an MDI or by means of nebulization;
3. corticosteroids (parenteral, oral, or inhaled); and
4. oxygen.

Some patients might not respond to primary treatment and show signs of worsening asthma. Other treatments are sometimes used in these patients and might include:

1. epinephrine, either intramuscular or subcutaneous;
2. magnesium sulfate, parenteral;

3. heliox-driven albuterol nebulization;
4. intubation and mechanical ventilation; and
5. noninvasive positive pressure ventilation (NPPV).

SABAs

EPR-3 guidelines recommend the use of only selective SABAs in high doses (ie, albuterol and levalbuterol) because of the risk of cardiotoxicity, especially in elderly asthmatic patients. Initial treatment should begin with albuterol, either administered through an MDI with a spacer device or mask (children <4 years of age) or nebulizer.

Medication	Dosages		Comments
	Child Dose*	Adult Dose	
Inhaled Short-Acting Beta₂-Agonists (SABA)			
Albuterol			
Nebulizer solution (0.63 mg/3 mL, 1.25 mg/3 mL, 2.5 mg/3 mL, 5.0 mg/mL)	0.15 mg/kg (minimum dose 2.5 mg) every 20 minutes for 3 doses then 0.15–0.3 mg/kg up to 10 mg every 1–4 hours as needed, or 0.5 mg/kg/hour by continuous nebulization.	2.5–5 mg every 20 minutes for 3 doses, then 2.5–10 mg every 1–4 hours as needed, or 10–15 mg/hour continuously.	Only selective beta ₂ -agonists are recommended. For optimal delivery, dilute aerosols to minimum of 3 mL at gas flow of 6–8 L/min. Use large volume nebulizers for continuous administration. May mix with ipratropium nebulizer solution.
MDI (90 mcg/puff)	4–8 puffs every 20 minutes for 3 doses, then every 1–4 hours inhalation maneuver as needed. Use VHC; add mask in children <4 years.	4–8 puffs every 20 minutes up to 4 hours, then every 1–4 hours as needed.	
Bitolterol			
Nebulizer solution (2 mg/mL)	See albuterol dose; thought to be half as potent as albuterol on mg basis.	See albuterol dose.	Has not been studied in severe asthma exacerbations. Do not mix with other drugs. Has not been studied in severe asthma exacerbations.
MDI (370 mcg/puff)	See albuterol MDI dose.	See albuterol MDI dose.	
Levalbuterol (R-albuterol)			
Nebulizer solution (0.63 mg/3 mL, 1.25 mg/0.5 mL, 1.25 mg/3 mL)	0.075 mg/kg (minimum dose 1.25 mg) every 20 minutes for 3 doses, then 0.075–0.15 mg/kg up to 5 mg every 1–4 hours as needed.	1.25–2.5 mg every 20 minutes for 3 doses, then 1.25–5 mg every 1–4 hours as needed.	Levalbuterol administered in one-half the mg dose of albuterol provides comparable efficacy and safety. Has not been evaluated by continuous nebulization.
MDI (45 mcg/puff)	See albuterol MDI dose.	See albuterol MDI dose.	
Pirbuterol			
MDI (200 mcg/puff)	See albuterol MDI dose; thought to be half as potent as albuterol on a mg basis.	See albuterol MDI dose.	Has not been studied in severe asthma exacerbations.
Systemic (Injected) Beta₂-Agonists			
Epinephrine 1:1,000 (1 mg/mL)	0.01 mg/kg up to 0.3–0.5 mg every 20 minutes for 3 doses sq.	0.3–0.5 mg every 20 minutes for 3 doses sq.	No proven advantage of systemic therapy over aerosol.
Terbutaline (1 mg/mL)	0.01 mg/kg every 20 minutes for 3 doses then every 2–6 hours as needed sq.	0.25 mg every 20 minutes for 3 doses sq.	

FIG 4. Dosages of drugs for asthma exacerbations. Originally published as Fig 5-5 in EPR-3. *Children 12 years of age and younger. ED, Emergency department; VHC, valved holding chamber. Notes: There is no known advantage for higher doses of corticosteroids in patients with severe asthma exacerbations nor is there any advantage for intravenous administration over oral therapy provided gastrointestinal transit time or absorption is not impaired. The total course of SCSs for an asthma exacerbation requiring an ED visit or hospitalization can last from 3 to 10 days. For corticosteroid courses of less than 1 week, there is no need to taper the dose. For slightly longer courses (eg, up to 10 days), there is probably no need to taper, especially if patients are concurrently taking ICSs. ICSs can be started at any point in the treatment of an asthma exacerbation.

Medication	Dosages		Comments
	Child Dose*	Adult Dose	
Anticholinergics			
Ipratropium bromide			
Nebulizer solution (0.25 mg/mL)	0.25–0.5 mg every 20 minutes for 3 doses, then as needed	0.5 mg every 20 minutes for 3 doses then as needed	May mix in same nebulizer with albuterol. Should not be used as first-line therapy; should be added to SABA therapy for severe exacerbations. The addition of ipratropium has not been shown to provide further benefit once the patient is hospitalized. Should use with VHC and face mask for children <4 years. Studies have examined ipratropium bromide MDI for up to 3 hours.
MDI (18 mcg/puff)	4–8 puffs every 20 minutes as needed up to 3 hours	8 puffs every 20 minutes as needed up to 3 hours	
Ipratropium with albuterol			
Nebulizer solution (Each 3 mL vial contains 0.5 mg ipratropium bromide and 2.5 mg albuterol.)	1.5-3 mL every 20 minutes for 3 doses, then as needed	3 mL every 20 minutes for 3 doses, then as needed	May be used for up to 3 hours in the initial management of severe exacerbations. The addition of ipratropium to albuterol has not been shown to provide further benefit once the patient is hospitalized. Should use with VHC and face mask for children <4 years.
MDI (Each puff contains 18 mcg ipratropium bromide and 90 mcg of albuterol.)	4–8 puffs every 20 minutes as needed up to 3 hours	8 puffs every 20 minutes as needed up to 3 hours	
Systemic Corticosteroids			
<i>(Applies to all three corticosteroids)</i>			
Prednisone	1-2 mg/kg in 2 divided doses (maximum = 60 mg/day) until PEF is 70% of predicted or personal best	40–80 mg/day in 1 or 2 divided doses until PEF reaches 70% of predicted or personal best	For outpatient "burst," use 40–60 mg in single or 2 divided doses for total of 5–10 days in adults (children: 1–2 mg/kg/day maximum 60 mg/day for 3–10 days).
Methylprednisolone			
Prednisolone			

FIG 4. (Continued).

Treatment should be continued until the patient has stabilized or a decision to hospitalize is made. Studies show that either an MDI or nebulizer for delivery of inhaled SABAs produces similar outcomes. Nebulizer treatment might be preferred in patients who are unable to cooperate with an MDI because of the severity of acute asthma, age, or agitation. Additionally, continuous nebulization should be considered in patients with very severe asthma based on evidence of reduced admissions and improved pulmonary function.^{11,19–21}

Levalbuterol (R-albuterol) nebulizer solution can be administered in a similar fashion. Notably, levalbuterol administered at one-half the milligram dose of albuterol is found to provide comparable efficacy and safety. However, the efficacy of continuous nebulization has not been evaluated. Continuous administration of albuterol through large-volume nebulizers might be more efficacious when compared with intermittent administration in patients with severe asthma.¹¹

For patients unable or unwilling to use an MDI/spacer or nebulizer, epinephrine can be used, either injected subcutaneously or intramuscularly, as long as the patient is carefully monitored for

signs of adrenergic toxicity. At this time, there is no proved advantage of use of epinephrine over SABAs. If there is no immediate response to epinephrine, treatment should be discontinued, and the patient should be hospitalized.¹¹

IPRATROPIUM BROMIDE

Ipratropium bromide is a quaternary derivative of atropine sulfate available as a nebulizer solution. It provides competitive inhibition of acetylcholine at the muscarinic cholinergic receptor, thus relaxing smooth muscle in the large central airways. It is not a first-line therapy but can be added in patients with severe asthma, particularly when albuterol is not optimally beneficial. It can be administered with albuterol or levalbuterol and can be used for up to 3 hours in the initial management of acute asthma. There is increasing support for adding ipratropium bromide to β_2 -agonist therapy in children with more severe asthma exacerbations. Studies indicate that combined therapy reduces the risk of hospital admission by 25%.^{11,21,22}

CORTICOSTEROIDS: TREATMENT IN THE AMBULATORY SETTING

High-dose ICSs can be initiated in selected patients. Evidence suggests equivalence in treatment of mild asthma exacerbations with OCSs. However, because of limited data, high-dose ICSs should be reserved for patients with mild asthma and those who refuse or cannot tolerate OCSs (eg, have brittle diabetes or experience major side effects from SCSs). Guidelines recommend at least quadrupling the recommended dose of ICS. For example, a top recommended maintenance dose of fluticasone can be increased from 220 μ g administered as 2 puffs 2 times/d to 220 μ g administered as 4 puffs 4 times/d for exacerbations. Beclomethasone can be increased from 160 μ g administered as 2 puffs 2 times/d to 160 μ g administered as 4 puffs 4 times/d.^{2,23} Treatment should be started before the patient becomes too ill to manage their disease at home. Inhaled therapy reduces the risk of unwanted side effects associated with SCS treatment, such as insomnia, increased appetite, hyperactivity, psychosis, and effects on bone metabolism and other organ systems. ICSs are less likely to be effective in patients with upper respiratory tract infections or those who are overusing β_2 -agonists. An OCS, with instructions for its use, should be prescribed as a backup treatment regimen so that the patient, family, or both understand when to start it. They should also have immediate access to a physician, other health care professional, or both until the asthma exacerbation is resolved.²³⁻²⁵ When an ICS is prescribed for mild asthma and is not effective, OCSs are indicated, regardless of their potential side effects. Glucocorticoid-induced psychosis, hypertension, and other side effects should be concomitantly treated until the OCS is tapered and no longer necessary for treatment.

Short courses of OCSs are effective to establish control of flare-ups of asthma or during a period of gradual deterioration of asthma not responding to increased doses of an ICS. Treatment should be continued until the patient is well or achieves a PEF of 80% of personal predicted best. Improvement can be seen between 5 and 14 days, although patients whose asthma is corticosteroid resistant might take several weeks to respond. It is not necessary to taper OCSs after 3 weeks or less of treatment, but when used for longer than 3 weeks, it is advisable to taper the medication over 1 to 2 weeks to decrease withdrawal side effects, such as fatigue, myalgias, nausea/vomiting, abdominal pain, decreased appetite, and joint pain.^{11,25}

CORTICOSTEROIDS: TREATMENT IN THE ACUTE SETTING

There are no substantial data to indicate that SCSs are immediately helpful in the acute asthma setting because the onset of action does not occur for hours after administration. However, SCSs are the best medications available to reduce airway inflammation and should be used immediately until the attack has abated, as evidenced based on their clinical response or by the PEF and FEV₁ returning to near-baseline levels.¹¹

Intramuscular or intravenous corticosteroids can be used in the initial treatment of acute asthma; however, there is no evidence that these routes have a more rapid onset of action or are more effective than oral administration.¹¹

CORTICOSTEROIDS: TREATMENT AFTER DISCHARGE FROM THE HOSPITAL

After discharge from the hospital, approximately 10% to 20% of patients treated for acute asthma will relapse within 2 weeks. This might be due to unresolved inflammation associated with asthma. As a result, EPR-3 encourages treatment with OCSs after emergency department discharge. ICS therapy should be resumed or short/long-term ICS therapy initiated to reduce the chances of a relapse. When the patient's asthma is stable, the ICS dose should be incrementally reduced to maintain an asymptomatic state and a PEF at a personal best level. A combination of a long-acting β_2 -agonist and an ICS can be considered to achieve the lowest ICS dose possible.^{11,26-28}

MAGNESIUM SULFATE

Magnesium sulfate has both immediate bronchodilator and mild anti-inflammatory effects. Intravenous magnesium is a safe and effective treatment and can be considered in patients presenting with severe life-threatening asthma exacerbations (FEV₁ <25% of predicted value) and those who remain in the severe category after 1 hour of intensive conventional treatment.^{2,11}

HELIOX-DRIVEN ALBUTEROL

The role of heliox-driven albuterol in the treatment of acute exacerbations is controversial. Despite these uncertainties, heliox-driven albuterol can be considered in both children and adults who exhibit severe life-threatening exacerbations and those who remain in the severe category after 1 hour of intensive conventional therapy.^{11,29}

HOSPITALIZATION

Failure to respond to treatment necessitates hospitalization. The patient's fluid status should be assessed, and oral or intravenous hydration therapy should be administered, as indicated. Hydration in young infants and children might be essential because these patients are at increased risk for dehydration because of poor oral intake and an increased respiratory rate. Oxygen can be administered at 2 to 4 L/min through a nasal cannula or mask, whichever is better tolerated, to maintain an arterial oxygen saturation of 90% or greater. In pregnant patients and those with underlying cardiac disease, an arterial oxygen saturation of 95% or greater is recommended. The patient should be monitored continuously with pulse oximetry and telemetry. Blood gases should be obtained until the patient is stable. The patient should be treated with continuous nebulized albuterol or levalbuterol, with or without ipratropium bromide, and a corticosteroid. Viral respiratory tract infections are more common in patients with acute asthma exacerbations, and therefore antibiotics should be reserved for patients who present with evidence of a coexisting bacterial infection (ie, pneumonia, bronchitis, and sinusitis). EPR-3 does not recommend the use of methylxanthines, mucolytics, sedation, or chest physiotherapy for the treatment of acute asthma.^{2,11,26}

IMPENDING RESPIRATORY FAILURE

The use of NPPV in the treatment of severe acute asthma can be tried in patients who are at increased risk of respiratory failure,

can safely cooperate with NPPV treatment, and do not require emergency intubation.¹¹ A review article by the Cochrane Reviews Group carried out a search of randomized controlled trials of adults with severe acute asthma who presented to the emergency department or were admitted to the hospital. Studies in the article were included if the intervention was usual medical care for the management of severe acute asthma plus NPPV compared with usual medical care alone. All 6 studies that were reviewed concluded that NPPV might be beneficial. The results did not show a clear benefit for NPPV use for its primary outcomes (ie, mortality rate and tracheal intubation). However, NPPV use did show favorable outcomes in many secondary objectives, such as number of hospital admissions, length of intensive care unit stay, length of hospital stay, and improvement in lung function parameters (PEF; forced vital capacity; FEV₁; and forced expiratory flow, midexpiratory flow).

Study quality of the evidence was an issue in this review because all 6 studies included had at least 1 identifiable source of unclear or high risk of bias. Because only 6 studies were reviewed by the Cochrane Reviews Group, no guidelines or implications for current practice can be made. Randomized controlled trials with a large sample size, good methodological design, and minimizing the risk of bias are needed to answer the question of the use of NPPV in patients with acute asthma.³⁰

The EPR-3 recommends that intubation should not be delayed in a patient once it is deemed necessary. Patients who present with apnea or coma should be intubated immediately. Persistent or increasing hypercapnia, exhaustion, and mental status changes strongly suggest the need for mechanical ventilation. Intubation is difficult in patients with acute asthma and should be performed, where possible, by a physician who has extensive experience in airway management. Ventilator management by a physician expert is important because ventilation of patients with severe acute asthma is complicated. An important issue to consider at the time of intubation is intravascular volume, which must be maintained or replaced, because hypotension commonly accompanies the introduction of positive pressure ventilation. In addition, high ventilator pressures should be avoided, where possible, because of their associated risks of barotrauma. "Permissive hypercapnia" or "controlled hypoventilation" is the preferred ventilator strategy because this provides adequate oxygenation and ventilation without the risks of barotrauma associated with high ventilator pressures. SABAs should be continued in ventilated patients, although no randomized controlled trials provide evidence to support their use.

CONCLUSION

Asthma affects approximately 300 million people in the world and accounts for 1 in every 250 deaths. The World Health Organization recognizes asthma as a major global health issue affecting all age groups in all countries. All patients presenting with an asthma exacerbation should be triaged and evaluated immediately. Treatment should be based on recognition of a moderate, severe, or life-threatening exacerbation. Clinicians should recognize the symptoms, signs, and risk factors (including comorbidities) for severe and life-threatening exacerbations. Primary treatment includes oxygen administration, SABAs, and SCSs. If the patient cannot tolerate SCSs, high-dose ICSs can be initiated in selected patients. For patients who do not respond to

primary treatment and show worsening signs of ventilation, secondary treatment options can be used. These include epinephrine, magnesium sulfate, heliox-driven albuterol, intubation and mechanical ventilation, and NPPV.

At the time of discharge, education on self-management of asthma can reduce the frequency of emergency department visits. Physicians and other health care professionals should assess inhaler techniques for all prescribed medications and reinforce correct technique. Patients should be referred for a follow-up appointment with a primary care physician or asthma specialist within 1 to 4 weeks.

Key points

- Asthma exacerbations are avoidable with appropriate therapy and patient education.
- Asthma remains a global health issue with significant morbidity and mortality.
- The primary treatment for acute asthma includes SABAs, SCSs, and oxygen administration.
- For patients unresponsive to primary treatment, secondary measures, such as epinephrine, magnesium sulfate, heliox-driven albuterol, NPPV, and intubation, can be considered.
- After discharge, education on self-management of asthma should be prioritized to reduce the frequency of exacerbations. Patients should be referred to a primary care physician or asthma specialist on being discharged.

REFERENCES

1. Masoli M. The global burden of asthma: executive summary of the GINA dissemination committee report. *Allergy* 2004;59:469-78.
2. Camargo CA, Rowe BH. Asthma exacerbations. In: Barnes PJ, Drazen J, Rennard S, Thomson N, editors. *Asthma and COPD: basic mechanisms and clinical management*. 2nd ed. San Diego: Elsevier; 2009. pp. 775-91.
3. Schatz M, Rosenwasser L. The allergic asthma phenotype. *J Allergy Clin Immunol Pract* 2014;2:645-9.
4. Nelson R, DiNicolo R, Fernández-Caldas E, Selezniuk MJ, Lockey RF, Good R. Allergen-specific IgE levels and mite allergen exposure in children with acute asthma first seen in an emergency department and in nonasthmatic control subjects. *J Allergy Clin Immunol* 1996;98:258-63.
5. Lockey RF, Ledford DK, in collaboration with the World Allergy Organization, editors. *Asthma, comorbidities, co-existing conditions, and differential diagnoses*. New York: Oxford University Press; 2014. pp. 231-367.
6. Holguin F, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Erzurum SC, et al. Obesity and asthma: an association modified by age of asthma onset. *J Allergy Clin Immunol* 2011;127:1486-93.e2.
7. Ledford DK, Lockey RF. Asthma and comorbidities. *Curr Opin Allergy Clin Immunol* 2013;13:78-86.
8. Blake K, Teague WG. Gastroesophageal reflux disease and childhood asthma. *Curr Opin Pulm Med* 2013;19:24-9.
9. Gibson PG, Henry RL, Coughlan JL. Gastro-oesophageal reflux treatment for asthma in adults and children. *Cochrane Database Syst Rev* 2003;(1):CD001496.
10. Global Initiative For Asthma (GINA) Website. Available at: <http://www.ginasthma.com/>. Accessed March 15, 2015.
11. Camargo CA, Rachelefsky G, Schatz M. Managing asthma exacerbations in the emergency department: summary of the National Asthma Education and Prevention Program Expert Panel Report 3 guidelines for the management of asthma exacerbations. *Proc Am Thorac Soc* 2009;6:357-66.
12. Hasegawa K, Sullivan A, Tsugawa Y, Turner S. Comparison of US emergency department acute asthma care quality: 1997-2001 and 2011-2012. *J Allergy Clin Immunol* 2014;135:73-80.e7.
13. Waseem M, Leber MJ, Wasserman EJ, Sullivan AF, Camargo CA Jr, Hasegawa K. Factors associated with concordance with the non-level-A guideline recommendations

- for emergency department patients with acute asthma. *J Allergy Clin Immunol* 2015;3: 618-20.e2.
14. British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. *Thorax* 2014;69(suppl 1):1-192.
 15. Patel M, Pilcher J, Reddel H, Qi V. Predictors of severe exacerbations, poor asthma control, and beta-agonist overuse for patients with asthma. *J Allergy Clin Immunol* 2014;2:751-8.e1.
 16. Rodrigo GJ, Rodrigo C. Elevated plasma lactate level associated with high dose inhaled albuterol therapy in acute severe asthma. *Emerg Med J* 2005;22:404-8.
 17. Bloom BM, Grundlingh J, Bestwick JP, Harris T. The role of venous blood gas in the emergency department: a systematic review and meta-analysis. *Eur J Emerg Med* 2014;21:81.
 18. Goodacre S, Bradburn M, Cohen J, Gray A, Bengier J, Coats T, et al. Prediction of unsuccessful treatment in patients with severe asthma. *Emerg Med J* 2014;31:e40-5.
 19. Camargo CA Jr, Spooner CH, Rowe BH. Continuous versus intermittent beta-agonists for acute asthma. *Cochrane Database Syst Rev* 2003;(4):CD001115.
 20. Cates CJ, Crilly JA, Rowe BH. Holding chambers (spacers) versus nebulizers for beta-agonist treatment of acute asthma. *Cochrane Database Syst Rev* 2006;(2): CD000052.
 21. Hasegawa K, Sullivan AF, Tovar Hirashima E, Gaeta TJ, Fee C, Turner SJ, et al. A multicenter observational study of US adults with acute asthma: who are the frequent users of the emergency department. *J Allergy Clin Immunol* 2014;2: 733-40.e3.
 22. Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. *Thorax* 2005;60:740-6.
 23. Osborne J, Mortimer K, Hubbard RB, Tattersfield AE, Harrison TW. Quadrupling the dose of inhaled corticosteroid to prevent asthma exacerbations: a randomized, double-blind, placebo-controlled, parallel-group clinical trial. *Am J Respir Crit Care Med* 2009;180:598-602.
 24. Beckhaus AA, Riutort MC, Castro-Rodriguez JA. Inhaled versus systemic corticosteroids for acute asthma in children. A systematic review. *Pediatr Pulmonol* 2014;49:326-34.
 25. Krishnan J, Nowak R, Davis S, Schatz M. Anti-inflammatory treatment after discharge home from the emergency department in adults with acute asthma. *J Allergy Clin Immunol* 2009;124(suppl):S29-34.
 26. Thomas AO, Lemanske RF Jr, Jackson DJ. Infections and their role in childhood asthma inception. *Pediatr Allergy Immunol* 2014;25:122-8.
 27. Gibson PG, Powell H, Coughlan J, Wilson AJ, Abramson M, Haywood P, et al. Self management education and regular practitioner review for adults with asthma. *Cochrane Database Syst Rev* 2003;(1):CD001117.
 28. Kang MG, Kim JY, Jung JW, Song JW, Cho SH, Min KU, et al. Lost to follow up in asthmatics does not mean treatment failure: causes and clinical outcomes of non-adherence to outpatient treatment in adult asthma. *Allergy Asthma Immunol Res* 2013;5:357-64.
 29. Chaudry RQ, Weinstein ME, Petrova A. Efficacy of inhaled compared to oral corticosteroids for acute asthma exacerbation in children [abstract]. *J Allergy Clin Immunol* 2010;125:AB69.
 30. Lim WJ, Mohammed Akram R, Carson KV, Mysore S, Labiszewski NA, Wedzicha JA, et al. Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma. *Cochrane Database Syst Rev* 2012;(12):CD004360.