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EDITOR

Thomas Ciesielski

SERIES EDITOR

Thomas M. De Fer

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Editor

Thomas M. Ciesielski, MD
Instructor in Medicine
Division of Medical Education
Washington University School of Medicine
St. Louis, Missouri

Series Editor

Thomas M. De Fer, MD
Professor of Medicine
Division of Medical Education
Washington University School of Medicine
St. Louis, Missouri

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Asthma

11

Jaimie E. Bolda and Walter B. Gribben

GENERAL PRINCIPLES

Worldwide, ~300 million people suffer from asthma; the highest prevalence is in developed countries. About 11% of the US population has asthma. Prevalence, hospitalization rates, morbidity, and mortality attributable to asthma have all increased significantly over the last few decades. Factors conjectured to be causative for the increased prevalence include exposure to tobacco smoke and air pollution, dietary influences, obesity, and lack of exposure to infections and microbial products early in life. Hospital admission rates are higher in nonwhites. In the United States, there are approximately 5000 deaths due to asthma per year. Many of these deaths are likely preventable. Death rates are higher among African Americans, Hispanics, those with lower levels of education, inhabitants of large cities, and the poor. The economic burden of asthma is enormous.[1]

Definition

- The National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 (EPR3) defines asthma as “a common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation.”[2]
- The more descriptive definition from the prior NAEPP EPR2 (1997) still remains entirely valid. “Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. In particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and

coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli. Reversibility of airflow limitation may be incomplete in some patients with asthma."[3]

Classification

The **classification of the severity of asthma** in adults who are not currently taking long-term control medications is presented in Table 11-1. Specific forms of asthma include four types:

TABLE 11-1 Classification of Asthma Severity in Adults

	Mild Intermittent	Mild Persistent	Moderate Persistent	Severe Persistent
Symptoms	≤2 days per week	>2 days per week but not daily	Daily	Throughout the day
Nighttime awakenings	<2 per month	3–4 per month	More than once a week but not nightly	Often seven times a week
Short-acting β_2-agonist use for symptom control	≤2 days per week	>2 days per week but not more than once a day	Daily	Several times a 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 > 60% but <80% predicted	FEV_1 < 60% predicted
	FEV_1 > 80% predicted FEV_1/FVC normal	FEV_1/FVC normal	FEV_1/FVC reduced 5%	FEV_1/FVC reduced >5%
Recommended step at which to initiate treatment	Step 1	Step 2	Step 3	Step 4 or 5

Adapted from National Asthma Education and Prevention Program Expert Panel. *Report 3 (EPR3): Guidelines for the Diagnosis and Management of Asthma. Full Report 2007. National Institutes of Health. Publication No. 08-4051*. Bethesda: National Heart, Lung, and Blood Institute, 2007.

- **Cough-variant asthma**, where coughing is the predominant or sole symptom; the diagnosis is confirmed by resolution of the cough with antiasthmatic treatment.[4,5]
- **Exercise-induced bronchoconstriction (EIB) or asthma** describes patients with bronchoconstriction primarily or solely in association with exercise (generally after exercise). Such patients should derive benefit from

pretreatment with a β2-agonist. About 10% of the general population has EIB. However, it is important to note that EIB occurs in up to 90% of all asthmatics and is, therefore, a strong trigger for symptoms.[6]

- **Occupational asthma** consists of bronchoconstriction, bronchial hyperresponsiveness, and airway inflammation caused by exposure to workplace asthmagens. Triggers may be immunogenic or nonimmunogenic. In the latter situation, the condition may be referred to as **reactive airways dysfunction syndrome (RADS)** or **irritant-induced asthma**. There are hundreds of known stimulants and occupations at risk. Preexisting asthma worsened by the patient's occupation without clear substantiation for a diagnosis of independent occupational asthma is sometimes called **work-aggravated asthma**.[7]
- **Nocturnal asthma** is the nighttime worsening of asthma symptoms and is relatively common among asthmatics. Its occurrence is associated with inadequate control and increased morbidity. It is unclear if nocturnal asthma is a clinically distinct diagnosis or merely a marker for uncontrolled or more severe asthma.[8]

Pathophysiology

Airflow limitation is caused by multiple factors in the airways, including the following:

- Bronchoconstriction (bronchial smooth muscle contraction)
- Airway edema
- Excessive secretion of mucus and plugging
- Airway hyperresponsiveness (excessive bronchoconstrictor response to stimuli)
- Airway remodeling (subepithelial fibrosis, thickening of the subbasement membrane, smooth muscle hypertrophy/hyperplasia, blood vessel proliferation/dilation, and mucous gland hyperplasia)
- **Airway inflammation** appears to be a crucial underlying aspect of asthma pathophysiology.
    - Multiple **inflammatory cells** participate: eosinophils, mast cells, lymphocytes (particularly Th2 cells), neutrophils, dendritic cells (important antigen-presenting cells), macrophages, smooth muscle cells, and epithelial cells.
    - A wide array of **inflammatory mediators** contribute to the

inflammatory response: chemokines (e.g., eotaxin), cytokines (e.g., the interleukins IL-1β, IL-4, IL-5, and IL-13; tumor necrosis factor α [TNF-α]; and granulocyte–macrophage colony-stimulating factor [GM-CSF]), leukotrienes, and nitric oxide.
    - **Immunoglobulin E** (IgE) is also important in the pathophysiology of asthma. High-affinity IgE receptors are found on mast cells, basophils, dendritic cells, and lymphocytes. When mast cells are activated, they release many mediators that cause bronchoconstriction and promote inflammation.
- The factors that render certain individuals susceptible and those that initiate and perpetuate the inflammatory process are not precisely known. It does appear, however, that the interactions of environmental exposures at crucial times during immune development and host characteristics are particularly important. There are clearly aspects of asthma that are inheritable, and multiple genes have been associated with asthma. Obviously, though, asthma is not a single gene-related disease. Airborne allergens (e.g., dust mites and cockroaches) and viral infections are also thought to play key roles in the pathogenesis of asthma, especially when exposure occurs at vulnerable times in immunologic development. Precise mechanisms are not known, and some data are conflicting.[2,9]

Risk Factors

Risks for the development of asthma include the following factors:

- In childhood, male sex; in adulthood, female sex
- Family history (i.e., genetic susceptibility)
- Airway hyperreactivity
- Atopy and allergies
- Obesity
- Environmental exposures (i.e., allergens, pollution, cigarette smoking and exposure to secondhand smoke, infections, occupational exposures)[2]

DIAGNOSIS

Clinical Presentation

History

- The quintessential symptoms of asthma are wheezing, chest tightness, breathlessness, and coughing.
- In determining the severity of asthma, pertinent history includes the frequency of symptoms and use of a rescue metered-dose inhaler (MDI), presence of nocturnal symptoms, peak expiratory flow rates (PEFs), and degree to which everyday activities are limited (see Table 11-1).
- The patient should also be questioned regarding how well rescue MDIs work and how well controlled his or her asthma has been, if at all. Other factors include a history of frequent emergency department (ED) visits, prior admissions to an intensive care unit (ICU) and/or prior mechanical ventilation, recent oral corticosteroid therapy, and history of psychosocial problems, including medical noncompliance.
- It is important to identify aggravating factors or "triggers" for asthma. A careful allergy history should be obtained, including the presence of atopy, pets, active or passive smoke inhalation, and home/work/school environments. Be aware of the common allergens in your geographic area during each season.[2,10]

Physical Examination

The physical examination should focus on the patient's vital signs, general appearance, and pulmonary system. Between exacerbations, the exam may be completely normal.

- Check vital signs, which may reveal tachypnea and tachycardia (often from high doses of β2-agonist). A decreasing respiratory rate may indicate respiratory muscle fatigue rather than improvement in airway obstruction.
- Watch for decreasing mental status, which may represent hypercarbia or hypoxia.
- Examine the head, ears, eyes, nose, and throat to assess for signs of chronic allergic disease, including conjunctivitis, nasal polyps, rhinorrhea, and sinus tenderness.
- Observe for signs of respiratory fatigue or failure. These include inability to speak (words, phrases, sentences), inability to lie down, accessory muscle

use, paradoxical abdominal movements, and pulsus paradoxus.

- Auscultate for inspiratory/expiratory wheezing, prolonged expiratory phase, and diminished general air movement. In patients with audible inspiratory/expiratory wheezes over the upper airways or neck, rule out other causes of airway obstruction, including vocal cord dysfunction, foreign bodies, and upper airway tumors.
- Beware of the patient with no wheezing and poor air movement, as these findings may signify severe asthma and respiratory failure.
- Assess for signs of chronic corticosteroid use such as thin skin, easy bruising, cushingoid facies, central obesity, and proximal muscle weakness.

Differential Diagnosis

The differential diagnosis of asthma could potentially include all differential items for dyspnea, cough, wheezing, and chest tightness. A more limited differential diagnosis is presented in Table 11-2.

TABLE 11-2 Differential Diagnosis of Asthma in Adults

Laryngopharyngeal Causes	Small Airway[a]/Parenchymal Causes
Upper airway cough syndrome (UACS, previously known as postnasal drip syndrome)	Postinfectious cough
	Acute bronchitis
	Chronic bronchitis without COPD
Postinfectious cough	Chronic obstructive pulmonary disease (COPD)
Gastroesophageal reflux disease (GERD)	Congestive heart failure (CHF)
Laryngopharyngeal reflux (LPRD)	Pulmonary embolism (PE)
Tonsillar hypertrophy	Bronchiectasis
Peritonsillar abscess or mass	Bronchiolitis
Retropharyngeal abscess or mass	Nonasthmatic eosinophilic bronchitis (NAEB)
Vocal cord dysfunction syndrome	
Laryngocele	Pulmonary infiltration with eosinophilia (PIE)
Vocal cord paralysis	
Cricoarytenoid arthritis (e.g., rheumatoid arthritis)	Respiratory bronchiolitis–interstitial pneumonia (RB-ILD)
Epiglottitis	
Laryngostenosis	Interstitial lung disease (ILD)
	Chronic fungal and mycoplasmal infections
Large Airway[a] Causes	Other Causes
Foreign bodies	Drug-induced cough (e.g., secondary to angiotensin-converting enzyme inhibitors)
Tumors (malignant and benign and intrinsic and extrinsic)	Carcinoid syndrome
Tracheal stenosis	"Ear cough" (Arnold reflex)
Tracheomalacia	Deconditioning
Tracheobronchitis (e.g., herpetic)	Psychogenic
Goiter	
Acute bronchitis	
Postinfectious cough	

[a]The distinction between large and small and upper and lower airways is not always precise.

Diagnostic Testing

Diagnostic Procedures

- In stable patients, the diagnosis and severity of asthma are confirmed by **pulmonary function tests** (PFTs). In general, there is evidence of obstructive lung disease with a reduced forced expiratory volume in 1 second (FEV_1) and FEV_1/forced vital capacity (FVC) ratio. In addition, a postbronchodilator improvement in FEV_1 by at least 12% and 200 mL should be seen, indicative of reversible airway disease. Lung volumes will often show increased residual volume and a normal diffusion capacity of CO. The latter differentiates asthma from chronic obstructive pulmonary disease (COPD). Some asthmatics will have normal PFTs between attacks. During acute exacerbations, PEF should be routinely checked before and 15–20 minutes after administration of bronchodilators to assess the efficacy of therapy.[2,11]
- **Bronchial challenge testing** can be used to identify patients with abnormal airway hyperresponsiveness. Pharmacologic testing using methacholine has varying sensitivity and specificity based on the state of symptoms at the time of testing. In general, a positive test is indicated by a reduction in the FEV_1 of 20% or by a reduced specific airway conductance of 35–45% from baseline. This test simply indicates airway hyperresponsiveness, but does not give information about the etiology (i.e., COPD, cystic fibrosis, etc.). Many asthmatics have exercise-induced airway changes, even in the absence of exercise-induced symptoms. PFTs obtained before and after treadmill testing may therefore reveal the variability in FEV_1.[2,12]
- **Allergy testing**: Skin allergy testing can be considered for patients with persistent asthma and those who are exposed to indoor allergens.

Laboratories

- **For acute asthma exacerbations**, measurement of **arterial blood gases** (ABGs) is not routinely indicated in every acute exacerbation.
    - However, ABGs should be strongly considered in patients who fail to

respond to initial therapy with persistently diminished PEF and/or $FEV_1 \leq 25\%$ of predicted and those in severe respiratory distress or suspected of hypoventilation.
    - During the course of an exacerbation, tachypnea usually results in a below-normal $PaCO_2$. The presence of normal or increased $PaCO_2$ may indicate impending respiratory failure.[13]
- **For chronic asthma, in vitro allergy testing** can be considered for patients with persistent asthma and those who are exposed to indoor allergens.

Imaging

Chest radiography is not routinely needed but should be obtained if there is a suspicion of conditions such as congestive heart failure, pneumonia, pneumothorax, or pneumomediastinum.[2]

TREATMENT

The NAEPP EPR3 provides detailed treatment guidelines for asthma exacerbations and the chronic management of asthma.

Treatment of Acute Exacerbations of Asthma

- All patients should be taught to recognize the early warning signs of worsening asthma and have an **asthma action plan** for home management of asthma exacerbations. Patients should monitor their symptoms and PEFs. Exacerbations should be treated as early as possible. All patients should attempt to remove environmental factors that may be precipitating or contributing to the exacerbation.
- Patients with severe symptoms, those with PEF < 50% of predicted or personal best, and those at high risk for death should simultaneously initiate treatment with a short-acting β_2-agonist (SABA) and seek immediate medical attention. Risk factors for death from asthma include the following:
    - Prior severe exacerbations
    - Two or more asthma admissions in the previous year
    - Three or more ED visits for asthma in the previous year

    - Admission or ED visit for asthma in the previous month
    - Use of more than two MDIs of SABA a month
    - Low socioeconomic status
    - Inner-city dwelling
    - Illicit drug use
    - Major psychosocial issues, or major comorbidities (cardiovascular, pulmonary, and psychiatric)[2]
- **Mild and some moderate exacerbations** may be manageable at home per the patient's asthma action plan. A **moderate exacerbation** is indicated by FEV_1 and/or PEF 40–69% with moderate symptoms. Initial treatment should be SABA (e.g., albuterol MDI 4–8 puffs or 2.5–5 mg by nebulizer), up to two treatments 20 minutes apart.
    - If the symptomatic response is **good** and the PEF is ≥80%, the patient may continue SABA q3–4 hours for 24–48 hours. A short course of oral systemic corticosteroids can be considered. The patient should contact the physician for further instructions.
    - If the response is **incomplete** (PEF still 50–79%, the patient still dyspneic and/or wheezing), SABA (e.g., albuterol MDI 4–8 puffs q20 minutes up to 4 hours or 2.5–5 mg by nebulizer q20 minutes for a total of three doses, then q1–4 hours) should be continued and oral systemic corticosteroids started (e.g., prednisone 40–60 mg daily for 5–10 days). The physician should be urgently contacted for instructions.
    - If the response is **poor** (PEF < 50%, marked dyspnea and/or wheezing), SABA should be repeated, oral systemic corticosteroids started, and immediate medical attention sought.[2]
- **More significant moderate and all severe exacerbations** should be managed in the ED. A **severe exacerbation** is indicated by FEV_1 and/or PEF < 40%, severe symptoms at rest, accessory muscle use, high-risk patients (see above), and no improvement after initial treatment. Such patients should receive O_2, nebulized SABA, ipratropium every hour, and oral corticosteroids (if not already done). Adjunctive therapies such as magnesium sulfate (2 g IV) and heliox may be considered. If there is any evidence of impending or actual respiratory failure, the patient should be immediately intubated, mechanically ventilated, and admitted to the ICU. It is better to err on the side of caution in this context, as patients can deteriorate very rapidly. A rapid initial assessment should include a brief history and physical and an objective measurement of lung function (e.g., PEF and/or FEV_1) if possible. Pulse oximetry is indicated for patients in

severe distress or those with a PEF and/or FEV_1 < 40%. Serial oximetry is superior to a one-time SaO_2 measurements.[2]

- SABA is recommended for all patients and supplemental O_2 for most patients (to maintain $SaO_2 \geq 90\%$, 95% in patients with coexisting cardiac disease or pregnancy). Repetitive doses of SABA may be given by MDI or nebulizer q20 minutes.[2] MDIs are preferred to nebulizers due to the relatively inefficient delivery system of the nebulizer device. MDIs with spacers require much lower doses of SABA to achieve a comparable improvement in lung function.[14,15]
- Inhaled ipratropium bromide may also be added (MDI 8 puffs q20 minutes up to 3 hours or 0.5 mg by nebulizer q20 minutes for three doses, then as needed). The evidence regarding ipratropium in asthma exacerbations is mixed. Use of anticholinergic therapy is typically reserved for the most severe exacerbations, and therapy is generally stopped upon hospital admission with a few exceptions (e.g., refractory asthma requiring ICU admission, patients on monoamine oxidase inhibitor therapy, and asthma that has been triggered by β-blocker therapy).[2]
- Systemic corticosteroids should be given (e.g., prednisone 40–80 mg daily or equivalent doses of IV methylprednisolone); however, the optimal dose is unknown. The effects of comparable doses of oral and intravenous glucocorticoids are nearly identical. Intravenous steroids should be given to patients with impending respiratory arrest or intolerance for oral agents; otherwise, oral steroids are just as effective. Severe exacerbations requiring hospitalization generally require 5–14 days of therapy. Tapering is not necessary if the duration of treatment is less than a week and probably not necessary for courses <10 days. ICS may be started at any time and are indicated for all hospitalized patients after discharge.[2]
- Intravenous magnesium sulfate can be used in severe exacerbations; however, routine use of this agent in mild to moderate exacerbations does not confer a significant benefit.[2,16–18] Its benefit in severe exacerbations is thought to be related to its inhibition of calcium influx leading to bronchodilation.[19] It is contraindicated in renal insufficiency.
- Other interventions such as methylxanthines, antibiotics, aggressive hydration, chest physiotherapy, mucolytics, and sedation are generally

not recommended. Heliox may be considered in extremely severe exacerbations progressing toward intubation.[2,20]
    - If mechanical ventilation is necessary, permissive hypercapnia is recommended.[2]
- A reassessment should be performed after initial treatment (after one dose of SABA with a severe exacerbation and after three doses in all patients), including an assessment of symptoms, a repeat physical exam, PEF and/or FEV_1, and SaO_2. The patient's response to initial treatment, rather than his or her condition immediately on presentation, is more predictive of the subsequent need for hospitalization.
    - A **good response** is indicated by FEV_1 and/or PEF ≥ 70%, no distress, a normal exam, and the response sustained for 60 minutes. Such patients may be discharged to home. A short course of oral corticosteroids should be continued (e.g., prednisone 40–80 mg daily for 5–10 days). Consideration should be given to initiating an inhaled corticosteroid (ICS).
    - An **incomplete response** is indicated by FEV_1 and/or PEF 40–69% and continued mild to moderate symptoms. Determination of the disposition of these patients should be individualized. Those sent home can be treated as above; the others are admitted to the non-ICU hospital ward. There they should be treated with O_2, continued SABA, and systemic corticosteroids (oral or IV). Vital signs, SaO_2, and FEV_1/FVC should be monitored.
    - A **poor response** is indicated by FEV_1 and/or PEF < 40%, PCO_2 ≥ 42 mm Hg, continued severe symptoms, and drowsiness/confusion. These patients should be admitted to the ICU and intubation/mechanical ventilation considered. They continue to receive SABA and systemic corticosteroids (oral or IV).[2]

Treatment of Chronic Asthma

NAEPP EPR3 and the Global Initiative for Asthma (GINA) recommend a stepwise approach to the management of chronic asthma, depending on asthma severity (Table 11-1). There are substantive differences between them, but on the whole, the approaches are similar. Importantly, both emphasize the importance of ICS as the mainstay of treatment for patients with persistent symptoms and the advice that all patients should have SABA available for quick relief. The

recommendations presented here are somewhat more reflective of the EPR3. The recommended therapies by step are shown below.

- **Step 1**: SABA PRN. Appropriate only for intermittent asthma.
- **Step 2**: Low-dose ICS (Table 11-3). Less preferred alternatives include mast cell stabilizers (e.g., cromolyn or nedocromil), leukotriene modifiers (LMs) (e.g., montelukast or zileuton), and theophylline.
- **Step 3**: Low-dose ICS + long-acting β_2-agonist (LABA) or medium-dose ICS. Less preferred alternatives include low-dose ICS + either LM or theophylline.
- **Step 4**: Medium-dose ICS + LABA. Less preferred alternatives include medium-dose ICS + either LM or theophylline.
- **Step 5**: High-dose ICS + LABA. The anti-IgE agent omalizumab may be considered for those with allergies.
- **Step 6**: High-dose ICS + LABA + oral corticosteroid (lowest possible dose). The anti-IgE agent omalizumab may be considered for those with allergies.[2,10]
- Therapy should "step up" to achieve control. Once control has been achieved for at least 3 months, an attempt can be made to "step down."
- It is always valuable to remember the importance of adherence to therapy, inhaler technique, and control/elimination of environmental triggers.
- Consultation with an asthma specialist should be considered for patients requiring step 4 or higher treatment to achieve/maintain adequate control.
- The use of LABAs (e.g., salmeterol and formoterol) should be considered carefully owing to an increased risk of adverse outcomes.[21]
- The addition of desensitization immunotherapy should be considered for those with allergic asthma as an adjunct to step 2–4 therapy. Desensitization and omalizumab should be administered only by clinicians with specific knowledge who are equipped to treat anaphylaxis.[22–24]
- All patients should have an asthma action plan (see above) to deal with exacerbations and have SABA readily available for this purpose.

TABLE 11-3 Inhaled Corticosteroid Dosing

Drug	Low Dose (mcg/d)	Medium Dose (mcg/d)	High Dose (mcg/d)
Triamcinolone MDI (75 mcg/puff)	300–750	>750–1500	>1500
Beclomethasone HFA (40, 80 mcg/puff)	80–240	>240–480	>480
Budesonide DPI (90, 180 mcg/inhalation)	180–600	>600–1200	>1200
Flunisolide MDI (250 mcg/puff)	500–1000	>1000–2000	>2000
Flunisolide HFA (80 mcg/puff)	320	>320–640	>640
Fluticasone HFA (44, 110, 220 mcg/puff)	88–264	>264–440	>440
Fluticasone DPI (50 mcg/ inhalation)	100–300	>300–500	>500
Mometasone DPI (220 mcg/dose)	220	440	>440
Budesonide/formoterol HFA (80/4.5, 160/4.5 mcg/puff)	160/9–320/18	320/18–640/18	640/18
Fluticasone/salmeterol HFA (45/21, 115/21, 230/21 mcg/puff)	90/42–180/84	180/84–460/84	460/84–920/84
Fluticasone/salmeterol DPI (100/50, 250/50, 500/ 50 mcg/inhalation)	200/100	500/100	1000/100

MDI, metered-dose inhaler; HFA, hydrofluoroalkane; DPI, dry powder inhaler.

Adapted from National Asthma Education and Prevention Program Expert Panel. *Report 3 (EPR3): Guidelines for the Diagnosis and Management of Asthma. Full Report 2007. National Institutes of Health. Publication No. 08-4051*. Bethesda: National Heart, Lung, and Blood Institute, 2007.

REFERENCES

1. Braman SS. The global burden of asthma. *Chest* 2006;130:S4–S12.

2. National Asthma Education and Prevention Program Expert Panel. *Report 3 (EPR3): Guidelines for the Diagnosis and Management of Asthma. Full Report 2007. NIH Publication No. 08-4051*. Bethesda: National Institutes of Health, National Heart, Lung, and Blood Institute, 2007.
3. National Asthma Education and Prevention Program Expert Panel. *Report 2 (EPR2): Guidelines for the Diagnosis and Management of Asthma. Full Report 1997. NIH Publication No. 97-4051*. Bethesda: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, 1997.
4. Antoniu SA, Mihaescu T, Donner CF. Pharmacotherapy of cough-variant asthma. *Expert Opin Pharmacother* 2007;8(17):3021–8.
5. Dicpinigaitis PV. Chronic cough due to asthma: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129:75–9.
6. Parsons JP, Mastronarde JG. Exercise-induced bronchoconstriction in athletes. *Chest* 2005;128: 3966–74.
7. Beach J, Russell K, Blitz S, et al. A systematic review of the diagnosis of occupational asthma. *Chest* 2007;131:569–78.
8. Calhoun WJ. Nocturnal asthma. *Chest* 2003;123:399S–405S.
9. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006;355:2226–35.
10. Global Initiative for Asthma (GINA). *Global Strategy for Asthma Management and Prevention*. 2007.
11. Wagers S, Jaffe EF, Irvin CG. Development, structure, and physiology in normal and asthmatic lung. In: Adkinson, NF Jr, Busse WW, Yunginger JW, et al., eds. *Middleton's Allergy Principles and Practice*. 6th ed. St Louis, MO: Elsevier, 2003.
12. Birnbaum S, Barreiro TJ. Methacholine challenge testing: identifying its diagnostic role, testing, coding, and reimbursement. *Chest* 2007;131:1932–5.
13. Martin TG, Elenbaas RM, Pingleton SH. Use of peak expiratory flow rates to eliminate unnecessary arterial blood gases in acute asthma. *Ann Emerg Med* 1982;11:70.
14. Cates CJ, Welsh EJ, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. *Cochrane Database Syst Rev* 2013;(9):CD000052.
15. Newman KB, Milne S, Hamilton C, Hall K. A comparison of albuterol administered by metered-dose inhaler and spacer with albuterol by nebulizer in adults presenting to an urban emergency department with acute asthma. *Chest* 2002;121:1036.
16. Cheuk DK, Chau TC, Lee SL. A meta-analysis on intravenous magnesium sulphate for treating acute asthma. *Arch Disease Child* 2005;90:74–7.
17. Kew KM, Kirtchuk L, Michell CI. Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department. *Cochrane Database Syst Rev* 2014;(5):CD010909.
18. Silverman RA, Osborn H, Runge J, et al. IV magnesium sulfate in the treatment of acute severe asthma: a multicenter randomized controlled trial. *Chest* 2002;122:489–97.
19. Skobeloff EM, Spivey WH, McNamara RM, Greenspon L. Intravenous magnesium sulfate for the treatment of acute asthma in the emergency department. *JAMA* 1989;262:1210.
20. Ho AM, Lee A, Karmakar MK, et al. Heliox vs air-oxygen mixtures for the treatment of patients with acute asthma: a systematic overview. *Chest* 2003;123:882.
21. Salpeter SR, Buckley NS, Ormiston TM, et al. Meta-analysis: effect of long-acting beta-agonists on severe asthma exacerbations and asthma-related deaths. *Ann Intern Med* 2006;144:904–12.
22. Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2003;(4):CD001186.
23. Marcus P. Incorporating anti-IgE (omalizumab) therapy into pulmonary medicine practice: practice management implications. *Chest* 2006;129:466–74.
24. Strunk RC, Bloomberg GR. Omalizumab for asthma. *N Engl J Med* 2006;354: 2689–95.