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UPDATES ON THE MANAGEMENT OF SEVERE ASTHMA

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Asthma is a common chronic respiratory disease that affects 1% to 18% of the population worldwide. From 2001 to 2010, the age-adjusted prevalence of asthma in the United States alone increased from 7.3% to 8.4%. Asthma is responsible for nearly 4,000 U.S. deaths each year and is associated with an increase in cardiovascular disease risk; it is also an independent predictor of increased risk for coronary heart disease. In addition, chronic airway inflammation may contribute to systemic inflammation and can increase the risk of vascular disease. Conversely, prevention of asthma exacerbations can decrease cardiovascular morbidity.

The following 10 points reflect the latest strategies for managing severe asthma and provide an overview of appropriate treatment options for selected patients.

1. Cough, shortness of breath, and wheezing can be present in pulmonary edema, chronic obstructive pulmonary disease, vocal cord dysfunction, gastroesophageal reflux disease, bronchiectasis, hypersensitivity pneumonitis, and central airway obstruction. Always consider these conditions in the differential diagnosis of asthma (Table 1).
2. A small subset of asthmatic patients (5%-10%) continue to have symptoms despite maximal therapy. For these patients, limited treatment options result in uncontrolled disease and a significant increase in morbidity.^{1,2} Until recent therapeutic developments and advances, these patients experienced a severe decline in quality of life.
3. According to American Thoracic Society guidelines, "severe" asthma requires management with high-dose inhaled corticosteroids as well as a second asthma controller that potentially includes a systemic corticosteroid.² It is important to note that the definition of severe asthma does not include pulmonary function values (Table 2).
4. The goal of treatment is to use disease prevention strategies that help patients avoid serious exacerbations of acute asthma, improve daily symptoms, and improve quality of life.³
5. Allergen immunotherapy should be considered when maximum treatment with inhaled bronchodilators and corticosteroids is not effective in patients with significant environmental allergies.⁴
6. Patients with asthma can have elevated levels of immunoglobulin E (IgE); therefore, treatments that target IgE-mediated pathways are beneficial.⁵ Omalizumab is a recombinant monoclonal antibody that binds with free IgE to block its interaction with receptors on mast cells, basophils, and other cells.⁶ Omalizumab is approved for use in patients with moderate to severe persistent asthma whose symptoms are uncontrolled with inhaled corticosteroids, who have positive allergen testing, and whose total serum IgE concentration is between 30 to 700 IU/mL. A minimum of 12 weeks of therapy is required before determining therapeutic efficacy. In patients with uncontrolled asthma despite treatment with long-acting β_2 -agonists and high-dose inhaled corticosteroids, omalizumab was found to significantly reduce asthma exacerbations and decrease the need for corticosteroids.⁷
7. Interleukin-5 (IL-5) inhibitors reduce blood and airway eosinophil counts, improve asthma control, and decrease the rate of exacerbations.⁸ Randomized controlled trials showed that mepolizumab, an IL-5 inhibitor, improved asthma control and reduced the rate of exacerbations in patients with uncontrolled eosinophilic asthma (blood eosinophils > 150 cells per μ L).⁹⁻¹² Mepolizumab should be considered in patients with elevated eosinophils and frequent asthma exacerbations even with chronic oral corticosteroid use. Another IL-5 inhibitor, reslizumab, was shown to improve lung function, asthma control, and quality of life in patients who had inadequately controlled asthma on inhaled corticosteroids and a blood eosinophil count \geq 400 cells/ μ L. Reslizumab (3 mg/kg/mo intravenously) should be considered in patients with uncontrolled eosinophilic asthma.^{13,14}
8. Bronchial thermoplasty (BT) is an outpatient procedure that uses fiberoptic bronchoscopy to treat patients with severe asthma.¹⁵ Three separate bronchoscopies are performed over a 3-week period with the patient under moderate sedation. During the procedure, segmental and subsegmental bronchi are warmed to 65°C to reduce smooth muscle mass in the airway. This technique works by treating smooth muscle hypertrophy, thus attenuating bronchoconstriction and bronchial hyperreactivity.^{16,17}

- Pulmonary edema
- Chronic obstructive pulmonary disease
- Vocal cord dysfunction
- Gastroesophageal reflux disease
- Bronchiectasis
- Hypersensitivity pneumonitis
- Central airway obstruction

Table 1. Differential diagnosis of asthma.

Mild intermittent asthma	Symptoms < 2x/wk
	Nocturnal symptoms < 2x/mo
	FEV1 and PEFR > 80% predicted
	PEFR variability < 20%
Mild persistent asthma	Symptoms 2x/wk and < 1x/d
	Nocturnal symptoms > 2x/mo
	FEV1 and PEFR > 80% predicted
	PEFR variability between 20% and 30%
Moderate persistent asthma	Daily symptoms and daily use of rescue β -agonist
	> 2 exacerbations/wk and 1 nighttime exacerbation/mo
	FEV1 and PEFR between 60% and 80% predicted
	PEFR variability > 30%
Severe persistent asthma	Continuous symptoms
	Daily nocturnal symptoms
	Limited physical activity
	Frequent exacerbations
	FEV1 and PEFR < 60% predicted
	PEFR variability > 30%

Table 2. Classification of asthma severity, courtesy of the National Asthma Education and Prevention Program. FEV1: 1-second forced expiratory volume; PEFR: peak expiratory flow rate

- Randomized trials support the use of BT as a treatment for uncontrolled asthma, with efficacy and safety demonstrated for at least 5 years following the procedure.^{16,18-20} Patients who received BT for moderate-to-severe persistent asthma experienced fewer mild exacerbations, a marked decrease in emergency room visits, and an improvement in symptom-free days, asthma control, and quality of life.^{16,21} As a result, BT was approved by the FDA for use in adults with severe asthma who have uncontrolled symptoms despite treatment with inhaled corticosteroids and long-acting bronchodilators.
- Clinicians should make shared management decisions and take into account personal preferences when treating patients with severe asthma.

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