inhaled corticosteroids on mortality rates in COPD is controversial. A meta-analysis and several retrospective studies suggest a mortality benefit, but in a recently published randomized trial, differences in mortality rate approached, but did not reach, conventional criteria for statistical significance. A trial of inhaled glucocorticoids should be considered in patients with frequent exacerbations, defined as two or more per year, and in patients who demonstrate a significant amount of acute reversibility in response to inhaled bronchodilators.

Oral Glucocorticoids The chronic use of oral glucocorticoids for treatment of COPD is not recommended because of an unfavorable benefit/risk ratio. The chronic use of oral glucocorticoids is associated with significant side effects, including osteoporosis, weight gain, cataracts, glucose intolerance, and increased risk of infection. A recent study demonstrated that patients tapered off chronic low-dose prednisone (~10 mg/d) did not experience any adverse effect on the frequency of exacerbations, health-related quality of life, or lung function. On average, patients lost ~4.5 kg (~10 lb) when steroids were withdrawn.

Theophylline Theophylline produces modest improvements in expiratory flow rates and vital capacity and a slight improvement in arterial oxygen and carbon dioxide levels in patients with moderate to severe COPD. Nausea is a common side effect; tachycardia and tremor have also been reported. Monitoring of blood theophylline levels is typically required to minimize toxicity. The selective phosphodiesterase 4 (PDE4) inhibitor roflumilast has been demonstrated to reduce exacerbation frequency in COPD patients with chronic bronchitis and a prior history of exacerbations; its effects on airflow obstruction and symptoms are modest.

Antibiotics As outlined below, there are strong data implicating bacterial infection as a precipitant of a substantial portion of exacerbations. Early trials of prophylactic or suppressive antibiotics, given either seasonally or year round, failed to show a positive impact on exacerbation occurrence. More recently, a randomized clinical trial of azithromycin, chosen for both its anti-inflammatory and antimicrobial properties, administered daily to subjects with a history of exacerbation in the past 6 months demonstrated a reduced exacerbation frequency and longer time to first exacerbation in the macrolide-treated cohort (hazard ratio, 0.73).

Oxygen Supplemental O_2 is the only pharmacologic therapy demonstrated to unequivocally decrease mortality rates in patients with COPD. For patients with resting hypoxemia (resting O_2 saturation ≤88% or <90% with signs of pulmonary hypertension or right heart failure), the use of O_2 has been demonstrated to have a significant impact on mortality rate. Patients meeting these criteria should be on continual oxygen supplementation because the mortality benefit is proportional to the number of hours per day oxygen is used. Various delivery systems are available, including portable systems that patients may carry to allow mobility outside the home.

Supplemental O_2 is commonly prescribed for patients with exertional hypoxemia or nocturnal hypoxemia. Although the rationale for supplemental O_2 in these settings is physiologically sound, the benefits of such therapy are not well substantiated.

Other Agents *N*-acetyl cysteine has been used in patients with COPD for both its mucolytic and antioxidant properties. A prospective trial failed to find any benefit with respect to decline in lung function or prevention of exacerbations. Specific treatment in the form of IV α_1AT augmentation therapy is available for individuals with severe α_1AT deficiency. Despite sterilization procedures for these blood-derived products and the absence of reported cases of viral infection from therapy, some physicians recommend hepatitis B vaccination prior to starting augmentation therapy. Although biochemical efficacy of α_1AT augmentation therapy has been shown, a randomized controlled trial of α_1AT augmentation therapy has not definitively established the efficacy of augmentation therapy in reducing decline of pulmonary function. Eligibility for α_1AT augmentation therapy requires a serum α_1AT level <11 μ*M* (approximately 50 mg/dL). Typically, Pi^Z individuals will qualify, although other rare types associated with severe deficiency (e.g., null-null) are also eligible. Because only a fraction of individuals with severe α_1AT deficiency will develop COPD, α_1AT augmentation therapy is not recommended for severely α_1AT-deficient persons with normal pulmonary function and a normal chest CT scan.

NONPHARMACOLOGIC THERAPIES

General Medical Care Patients with COPD should receive the influenza vaccine annually. Polyvalent pneumococcal vaccine is also recommended, although proof of efficacy in this patient population is not definitive. Similar recommendations and limitations of evidence also exist for vaccination for *Bordetella pertussis*.

Pulmonary Rehabilitation This refers to a treatment program that incorporates education and cardiovascular conditioning. In COPD, pulmonary rehabilitation has been demonstrated to improve health-related quality of life, dyspnea, and exercise capacity. It has also been shown to reduce rates of hospitalization over a 6- to 12-month period.

Lung Volume Reduction Surgery (LVRS) Surgery to reduce the volume of lung in patients with emphysema was first introduced with minimal success in the 1950s and was reintroduced in the 1990s. Patients are excluded if they have significant pleural disease, a pulmonary artery systolic pressure >45 mmHg, extreme deconditioning, congestive heart failure, or other severe comorbid conditions. Patients with an FEV_1 <20% of predicted and either diffusely distributed emphysema on CT scan or diffusing capacity of lung for carbon monoxide ($D_{L_{CO}}$) <20% of predicted have an increased mortality rate after the procedure and thus are not candidates for LVRS.

The National Emphysema Treatment trial demonstrated that LVRS offers both a mortality benefit and a symptomatic benefit in certain patients with emphysema. The anatomic distribution of emphysema and post-rehabilitation exercise capacity are important prognostic characteristics. Patients with upper lobe–predominant emphysema and a low post-rehabilitation exercise capacity are most likely to benefit from LVRS.

Lung Transplantation **(See also Chap. 320e)** COPD is currently the second leading indication for lung transplantation (Fig. 314-4). Current recommendations are that candidates for lung transplantation should have severe disability despite maximal medical therapy and be free of comorbid conditions such as liver, renal, or cardiac disease. In contrast to LVRS, the anatomic distribution of emphysema and the presence of pulmonary hypertension are not contraindications to lung transplantation.

EXACERBATIONS OF COPD

Exacerbations are a prominent feature of the natural history of COPD. Exacerbations are episodes of increased dyspnea and cough and change in the amount and character of sputum. They may or may not be accompanied by other signs of illness, including fever, myalgias, and sore throat. Self-reported health-related quality of life correlates with frequency of exacerbations more closely than it does with the degree of airflow obstruction. Economic analyses have shown that >70% of COPD-related health care expenditures go to emergency department visits and hospital care; this translates to >$10 billion annually in the United States. The frequency of exacerbations increases as airflow obstruction increases; patients with moderate to severe airflow obstruction (GOLD stage III or IV; Table 314-1) on average have one to three episodes per year. However, some individuals with very severe airflow obstruction do not have frequent exacerbations; the history of prior exacerbations is a strong predictor of future exacerbations. Recently, an elevated ratio of the diameter of the pulmonary artery to aorta on chest CT has been associated with increased risk of COPD exacerbations.

The approach to the patient experiencing an exacerbation includes an assessment of the severity of the patient's illness, both acute and chronic components; an attempt to identify the precipitant of the exacerbation; and the institution of therapy.