Colonization and infection with multidrug-resistant organisms such as the *Burkholderia cepacia* complex may occur in advanced CF, creating challenging management issues. Most patients die of respiratory failure.

Clinical Presentation

Neonatal screening programs for CF exist nationwide in the United States to identify infants with possible CF who should undergo further testing (e.g., genotyping). Infants with CF may have meconium ileus or failure to thrive with steatorrhea. Salty-tasting skin may be noticed by caregivers. Patients with CF typically have chronic cough with thick sputum production, wheezing, and dyspnea. Pancreatic insufficiency and diabetes are common, and male patients have azoospermia. Nasal polyps are often present, and clubbing is typical.

CF should be considered in the differential diagnosis of patients with unexplained chronic sinus disease, bronchiectasis, male infertility associated with absence of the vas deferens, pancreatitis, or malabsorption. Pulmonary function tests demonstrate hyperinflation and obstruction; a bronchodilator response may be present. Chest imaging studies show hyperinflation, bronchial wall thickening, and bronchiectasis.

Diagnosis and Differential Diagnosis

Measurement of the concentration of chloride in sweat (sweat test) is used to diagnose CF. The diagnosis is considered definitive if the clinical picture is consistent with CF and if the chloride concentration measured in a certified laboratory is greater than 60 mEq/L on at least two occasions. Genotyping can also confirm the diagnosis if known mutations are identified in both gene alleles and may be used if sweat testing is equivocal.

Treatment

The treatment of CF currently relies on supportive measures such as aggressive airway hygiene, nutritional support including pancreatic enzyme replacement, antibiotics, and bronchodilators. Aerosolized recombinant human deoxyribonuclease I (Dornase alfa) decreases sputum viscosity, improves lung function, and reduces exacerbations in CF (level 1 evidence). Inhaled hypertonic saline helps to hydrate secretions, allowing them to be coughed out more easily, and also improves pulmonary function, although likely to a lesser extent than Dornase alfa (level 2). Inhaled tobramycin provided twice daily every other month is indicated for patients with moderate to severe CF who have pseudomonal infections (level 1). Inhaled aztreonam also appears to be beneficial in this patient group (level 2). Anti-inflammatory therapy with ibuprofen and azithromycin may be helpful in certain patients with CF (level 2 for both). However, chronic inhaled and oral corticosteroids are not beneficial and should not be used (level 1).

Specific treatments to improve the function of the defective CFTR chloride channel in CF are under investigation. Recent studies have shown ivcaftor to have positive benefits on CFTR function and FEV_1 in patients with a specific CF mutation (G551D) (level 1 evidence). As with other obstructive lung diseases, the ultimate therapy for patients with CF and end-stage lung disease is lung transplantation. Bilateral lung transplantation is preferred in this condition.

Prognosis

CF is ultimately a fatal disease, although supportive care measures have led to considerable improvement in median survival time. There clinical course of may be variable, in part related to the underlying mutations in the *CFTR* gene.

ASTHMA

Definition and Epidemiology

Asthma is described by the Global Initiative for Asthma as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to 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 within the lung that is often reversible either spontaneously or with treatment."

The incidence of asthma is highest in children, but it affects all ages and occurs worldwide, with a preponderance of the disease in developed industrialized countries. Asthma affects millions of individuals worldwide. In the United States in 2008, 8.2% of the population (approximately 24,000,000 persons) were estimated to have asthma based on survey data, an increase from 7.3% in 2001. The prevalence of asthma has increased markedly over recent decades. Nevertheless, after rising in the late 20th century, the number of deaths from asthma has declined since 2000; in 2010, there were 3404 deaths from asthma in the United States, compared with 5637 deaths in 1995. Asthma death rates are higher in older age groups, females, and blacks.

Pathology

Underlying chronic airway inflammation is considered to be a major pathogenic feature of asthma. Patients with asthma have higher numbers of activated inflammatory cells within the airway wall, and the epithelium is typically infiltrated with eosinophils, mast cells, macrophages, and T lymphocytes, which produce multiple soluble mediators such as cytokines, leukotrienes, and bradykinins. Airway inflammation in asthma is typified by a type 2 helper T-cell (T_H2) response with predominantly eosinophilic inflammation, but some patients with severe asthma exhibit neutrophilic airway inflammation and cytokine production more characteristic of T_H1 inflammation.

The hallmark of asthma is airway hyperresponsiveness—a tendency of the airway smooth muscle to constrict in response to levels of inhaled allergens or irritants that would not typically elicit such a response in normal hosts. Inhaled allergens provoke airway mast cell degranulation by binding to and cross-linking IgE on the mast cell surface. Mast cell degranulation leads to the release of chemical mediators, which cause acute bronchoconstriction and thus increased airway resistance and wheezing as well as mucus hypersecretion (E-Fig. 16-11). Disruption of the continuity of the ciliated columnar epithelium and increased vascularity and edema of the airway wall also follow antigen exposure. In addition to allergens, factors such as stimulation of irritant receptors, respiratory tract infections, and airway cooling can provoke bronchoconstriction in asthmatic individuals.