Respiratory System Disease

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KEYWORDS

• Cystic fibrosis • Bronchiectasis • Lung disease • CFTR • Pulmonary exacerbation • Lung function

KEY POINTS

- Defects in the cystic fibrosis transmembrane regulator (CFTR) lead to airway surface liquid depletion, abnormal pH, inflammation, and chronic infection, causing the pulmonary symptoms/signs of cystic fibrosis (CF).
- Patients with CF are living longer, although respiratory disease remains as the leading cause of mortality; survival bias exists owing to those with "milder" mutations.
- Early lung disease occurs in children with minimal or absent symptoms; the ideal combination of monitoring with lung function, imaging, and bronchoscopy is controversial.
- Pulmonary exacerbations are a major cause of morbidity and expense, although the definition is debated.
- Chronic treatments with physiotherapy, mucolytic, antiinflammatory, and antimicrobial agents are recommended; CFTR potentiators and correctors may change the face of the disease.

Video content accompanies this article at http://www.pediatric.theclinics.com.

PATHOPHYSIOLOGY

Cystic fibrosis (CF) is an autosomal recessive disease occurring in approximately 1 in 3500 people and 70,000 people worldwide.[1] The gene for CF was discovered in 1989[2] and encodes the cystic fibrosis transmembrane regulator (CFTR) protein. As of 2015, there are nearly 2000 identified mutations in CFTR, approximately 200 of which are disease causing (see www.CFTR2.org). The cascade of events by which CFTR defects lead to irreversible airway wall damage is shown in **Fig. 1**. Lack of chloride and bicarbonate secretion through CFTR and excessive sodium absorption through the epithelial sodium channel leads to airway surface liquid (ASL) depletion.[3] Deficient

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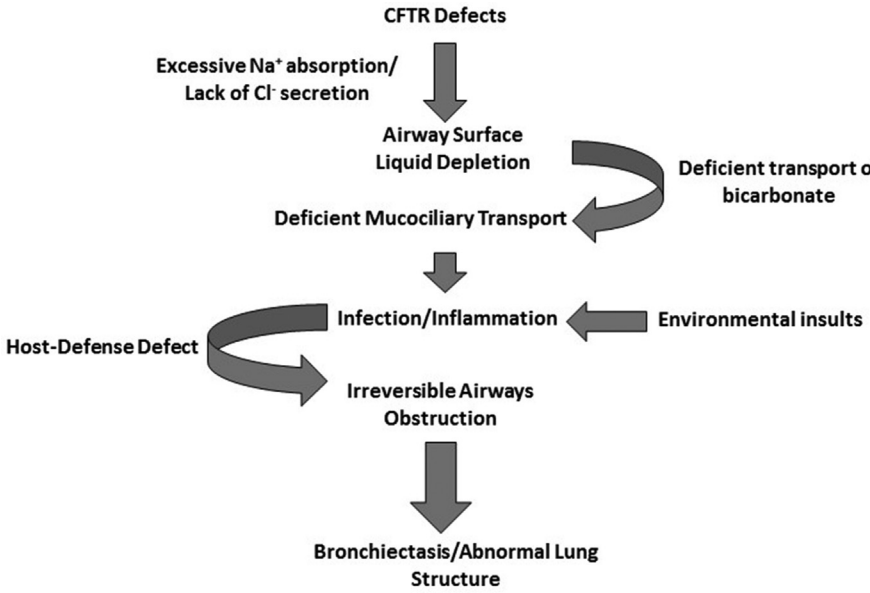

Fig. 1. CFTR defects lead to airway damage and bronchiectasis.

transport of bicarbonate and abnormal pH prevent proper antimicrobial function. The pH in the nasal ASL is lower in CF infants compared with normal infants; in older children and adults, the correlation of pH and genotype is variable, possibly owing to secondary effects of infection and/or inflammation.[4] ASL depletion and abnormal pH contribute to impaired mucociliary clearance. Recent data have suggested that mucociliary transport in piglets with CF is abnormal not only owing to ASL depletion, but also to abnormal adherence of mucus to the submucosal glands[5] and increased mucus viscosity, owing to bicarbonate secretion abnormalities.[6] Reduced MCC effectiveness, amino acid–rich and iron-rich sputum, as well as reduced antimicrobial activity allow typical CF-associated bacteria to grow.[4,7]

Airway inflammation adds to the cycle of excessive mucus production and infection. Neutrophil elastase, a protease released from neutrophils, causes neutrophil transmigration into the airways, mucus secretion, goblet cell hyperplasia, and CFTR degradation.[5] Other proteases such as cathepsins and matrix metalloproteases are involved in the inflammatory cascade. Irreversible airways obstruction leads to bronchiectasis, resulting in loss of lung function. See Video 1 from the CF Foundation (CFF) website demonstrating normal versus abnormal ciliary movement: https://www.youtube.com/watch?feature=player_embedded&v=YzjnxegMWfk.

Lung Disease, Mortality, and Determinants of Lung Disease Severity

The median predicted age of survival in people with CF has steadily increased over the last 25 years from approximately 28 to 39 years of age.[8] These data do not reflect the new corrector/potentiator therapies (see Ong T, Ramsey BW: New Therapeutic Approaches to Modulate and Correct CFTR, in this issue), but reflect earlier diagnosis by newborn screening. In 2014, 64% of new CF diagnoses in the United States were detected by newborn screening.[8] The Wisconsin newborn screening cohort showed that the significant determinants of lung disease were genotype, poor growth, hospitalizations, meconium ileus, and infection with mucoid *Pseudomonas aeruginosa*.[9]