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Handbook of Cystic Fibrosis

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Abbreviations

ABPA	Allergic bronchopulmonary aspergillosis
ALT	Alanine aminotransferase
ASL	Airway surface liquid
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BAL	Bronchoalveolar lavage
BMI	Body mass index
BOS	Bronchiolitis obliterans syndrome
CF	Cystic fibrosis
CFA	Cystic fibrosis-related arthropathy
CFLD	Cystic fibrosis-associated liver disease
CFRD	Cystic fibrosis-related diabetes
CFSPID	Cystic fibrosis screen positive, inconclusive diagnosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CFTR-RD	CFTR-related disorder
Cl	Chloride
CRMS	CFTR-related metabolic syndrome
CT	Computed tomography
CXR	Chest radiograph
DEXA	Dual-energy X-ray absorptiometry
DIOS	Distal intestinal obstruction syndrome
ENaC	Epithelial sodium channel
ESCF	Epidemiological Study of Cystic Fibrosis
FE	Fecal elastase
FEF_{25-75}	Forced expiratory flow between 25 and 75 %
FESS	Functional endoscopic sinus surgery
FEV_1	Forced expiratory volume in 1 second

FVC	Forced vital capacity
GERD	Gastroesophageal reflux disease
GGT	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
HbA1c	Hemoglobin A1c
HD-Ibu	High dose ibuprofen
HNE	Human neutrophil elastase
HPOA	Hypertrophic pulmonary osteoarthropathy
ICM	Intestinal current measurement
ICS	Inhaled corticosteroid
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IRT	Immunoreactive trypsinogen
LCI	Lung clearance index
MABSC	*Mycobacterium abscessus* complex
MAC	*Mycobacterium avium* complex
MBL	Mannose-binding lectin
MBW	Multiple breath washout
MESA	Microsurgical epididymal sperm aspiration
MI	Meconium ileus
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-sensitive *Staphylococcus aureus*
MVCC	Mutations of varying clinical consequences
NBS	New born screening
NG	Nasogastric
NPD	Nasal potential difference
NTM	Non-tuberculous mycobacteria
NTM-PD	Non-tuberculous mycobacteria pulmonary disease
OP	Oropharyngeal
PEG	Polyethylene glycol
PERT	Pancreatic enzyme replacement therapy
PI	Pancreatic insufficiency
PIVKA	Protein induced by vitamin K absence
PMN	Polymorphonuclear neutrophil
ROS	Reactive oxidant species
RV	Residual volume
TGF-β	Transforming growth factor beta

Chapter 1
Introduction and Epidemiology of Cystic Fibrosis

1.1 Introduction

Cystic fibrosis (CF) is an autosomal recessive condition caused by mutations in the gene encoding the CF transmembrane conductance regulator (CFTR) protein [1]. CFTR plays a central role in the regulation of ion transport across the cell membrane. CF affects multiple organ systems, although, gastrointestinal and pulmonary complications are responsible for the vast majority of morbidity and mortality associated with this disease. When CF was initially described in the 1930s, patients rarely survived beyond infancy or early childhood [2]. Since then advances in care have resulted in marked improvements in survival. The development of patient registries and quality improvement initiatives has led to more consistent care; the results of which can be tracked on a regular basis. Today, half of all patients with CF in the US are adults, and estimated median survival is >40 years [3]. The future of CF care has become even brighter with the development of CFTR modulators; medications that can target the underlying defect causing CF. Currently available CFTR modulators target only a small proportion of patients with CF or lack potency, although, newer more effective compounds are under development. At the same time, there are large numbers of patients with CF that will continue to require close monitoring and treatment of ongoing CF issues.

Advances in understanding the genetics of CF and the spread of CF newborn screening have also affected how patients with CF are diagnosed. For all of these reasons, this handbook is very timely and will be a valuable resource for clinicians caring for patients with CF. In this handbook we will review the genetics and diagnosis of CF, the clinical manifestations and pathophysiology of CF, and monitoring and treatment of the disease.

1.2   Epidemiology

CF is the most common life-limiting genetic condition in the Caucasian population [4], but the disease has been diagnosed in all racial and ethnic groups. Table 1.1 shows the reported prevalence of CF by race [5]. Given an autosomal recessive inheritance pattern and a prevalence of CF in the Northern European population of 1 in 2500–3000, the carrier rate in this population is about 1 in 20–30 individuals. This is a high carrier rate for a condition that until recently was fatal in infancy. As far as can be determined CF carriers are unaffected. Several hypotheses of potential survival benefits associated with CF carrier status have been proposed, but the evidence to support any of them is inconclusive.

The appreciation of CF as a distinct disease entity dates back at least to medieval times, when German folk tales described infants with salty tasting skin as destined to have a hard and short life. Throughout the eighteenth and nineteenth centuries,

TABLE 1.1 Prevalence of cystic fibrosis by race [5]

Racial/ethnic group	Birth prevalence (affected/number of live births)
Non-hispanic white	1/3200
Hispanic	1/9200
African American	1/15,000
Asian American	1/31,000

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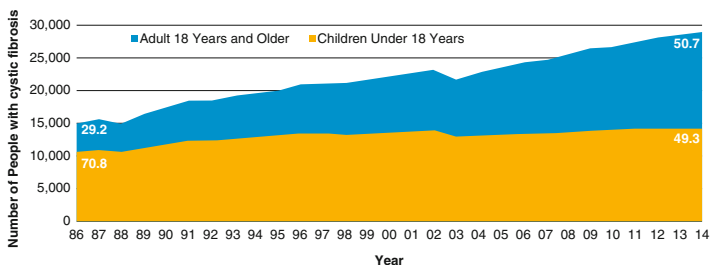
FIGURE 1.1 The number of children and adults in the US with cystic fibrosis, 1986–2014 [6]

case reports were published that in retrospect described patients with clinical features of CF. However, the first complete pathologic description of CF in the English literature is generally attributed to Dorothy Anderson in 1938 [2].

In the 1930s, when CF was initially described, most patients died in infancy. However, improvements in care as a result of increased understanding of the clinical manifestations and pathophysiology of the disease have resulted in steady improvements in survival. Landmark achievements, such as the identification of the *cftr* gene [1], have led to the development of disease-specific therapies targeting specific areas of the pathophysiologic pathway. The use of quality improvement initiatives to ensure consistent implementation of therapies and practices proven to result in better outcomes has also contributed to longer survival [6]. As of 2013, the estimated median survival of patients with CF in the US was 40.7 years [3], and in 2014, the number of adults with CF was similar to that of children with CF (50.7 % and 49.3 % of the CF population, respectively) [7] (Fig. 1.1).

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Chapter 2
Pathophysiology of Cystic Fibrosis

2.1 CFTR Structure and Function

Cystic fibrosis transmembrane conductance regulator (CFTR) is a transmembrane protein that belongs to the family of adenosine triphosphate (ATP) binding cassette proteins. It is expressed in multiple tissues throughout the body, where it plays a key role in the regulation of ion transport across cell membranes in mucosal surfaces [1]. CFTR conducts chloride (Cl) and bicarbonate (HCO_3-), and it also appears to reduce sodium (Na) transport through inhibition of the epithelial sodium channel (ENaC). In the absence of CFTR function the loss of ion transport has different effects on different tissues. In the sweat duct, CFTR serves to resorb NaCl from sweat, and in its absence there is excessive salt loss through sweat. In organs such as the pancreas and the liver, loss of ion transport results in viscous mucus secretions and ductal obstruction.

The mechanisms by which CFTR dysfunction leads to lung disease are not totally clear and several hypotheses have been proposed. The low volume hypothesis posits that under normal conditions CFTR-mediated Cl transport, coupled with ENaC inhibition, maintains salt transport to the periciliary layer of airway epithelial cells [2]. Water is passively transported because of the gradient created by this salt transport, thus creating an airway surface liquid (ASL) layer in which the cilia

can function. In the absence of CFTR ASL is depleted and ciliary function is impaired. This allows mucus to accumulate on the epithelium to create plaques and areas where bacteria can grow. More recent data using the cystic fibrosis (CF) pig model have suggested other pathogenic mechanisms [3]. The loss of CFTR-mediated HCO_3^- (bicarbonate) transport can lead to a shift in ASL from its normally neutral pH to an acidic one, which impairs innate bactericidal activity. Another finding in the CF pig model is that mucus globules frequently do not break free from the submucosal glands, which also reduces mucociliary clearance [3]. The development of animal models of CF that more accurately mimic the lung disease seen in humans will allow future research and development of therapeutics targeted at these different mechanisms.

2.2   CFTR Mutation Classes

After the discovery of the *cftr* gene in 1989 [4], it quickly became apparent that a variety of different mutations in the gene could affect CFTR function and result in CF disease. These mutations can be categorized into six different classes (Fig. 2.1) [5, 6]. They span the range from premature stop

	Normal	I	II	III	IV	V	VI
CFTR defect		No functional CFTR protein	CFTR trafficking defect	Defective channel regulation	Decreased channel conductance	Reduced synthesis of CFTR	Decreased CFTR stability
Type of mutations		Nonsense; frameshift; canonical splice	Missense; aminoacid deletion	Missense; aminoacid change	Missense; aminoacid change	Splicing defect; missense	Missense; aminoacid change
Specific mutation examples		Gly542X Trp1282X Arg553X 621+1G→T	Phe508del Asn130Lys Ile507del Arg560Thr	Gly551Asp Gly178Arg Gly551Ser Ser549Asn	Arg117His Arg347Pro Arg117Cys Arg334Trp	3849+10kbC→T 2789+5G→A 3120+1G→A 5T	4326delTC Gln1412X 4279insA

FIGURE 2.1 Cystic fibrosis transmembrane conductance regulator mutation classes [6] (Reproduced with permission from © Elsevier)

codons and abnormal protein folding to impaired function or activation. Knowledge of the mutation class is important for designing therapies that can reverse the effects of specific mutations, and recently such therapies have been developed (see Chap. 6).

2.3   Relationship Between CFTR Mutations and Clinical Phenotype

CF is an autosomal recessive condition and CFTR mutations are well established and accepted as the cause of CF, although there is a wide range of phenotypes of disease expression. In general, class I, II, and III mutations are considered 'severe', and patients with two copies of these mutations usually have almost no residual CFTR function. In contrast, patients with class IV, V, and VI mutations may have some residual CFTR function, although not enough to prevent all the consequences of CFTR dysfunction. In general, patients with these so called 'mild' mutations have better outcomes and survival than patients with 'severe' mutations. It is important to note that many other factors can affect clinical outcomes, and that even patients with 'mild' CFTR mutations can have severe clinical disease.

Clinical outcomes can vary even in patients with the same mutations. This observation has led to a search for modifier genes or epigenetic changes that might account for this variability. Early studies focused on genes involved in pathways presumed to be important in the pathogenesis of CF lung disease, such as ion transport genes, or genes related to the inflammatory response. Through this effort polymorphisms in the genes for mannose-binding lectin (MBL) and transforming growth factor beta (TGF-β) were linked to more severe outcomes [7, 8]. More recently, a non-biased approach through genome wide association studies has been undertaken [9]. The results of these studies have identified several potential gene modifiers, and work is underway to confirm these findings. Another approach to identifying rare variants is to

study extremes of phenotypes. Using this method, variants in the *DCTN4* gene in patients with CF have been shown to be associated with early *Pseudomonas aeruginosa* infection, a pathogen known to be associated with worse outcomes [10].

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Chapter 3
Clinical Features and Complications of Cystic Fibrosis

Cystic fibrosis (CF) is a multisystem disease, and its clinical features reflect the broad impact that loss of cystic fibrosis transmembrane conductance regulator (CFTR) function has on multiple organs (Fig. 3.1). However, pulmonary and gastrointestinal disease account for the vast majority of morbidity and mortality in CF.

3.1 Pulmonary Disease and Complications

3.1.1 *Pathophysiology of Cystic Fibrosis Lung Disease*

The pathophysiologic hallmarks of CF lung disease are chronic airway infection and inflammation [2]. The key steps in the pathogenesis of CF lung disease are shown in Fig. 3.1. CFTR dysfunction leads to loss of the airway surface liquid (ASL) layer, ASL acidification, and impaired mucociliary clearance, which in turn result in chronic bacterial airway infection. The chronic presence of bacteria in the airways of patients with CF elicits an intense neutrophilic inflammatory response. The release of proteolytic enzymes, such as human neutrophil elastase (HNE), and other inflammatory mediators, such as reactive oxidant species (ROS), causes airway damage and injury. HNE contributes to maintaining the inflammatory process by
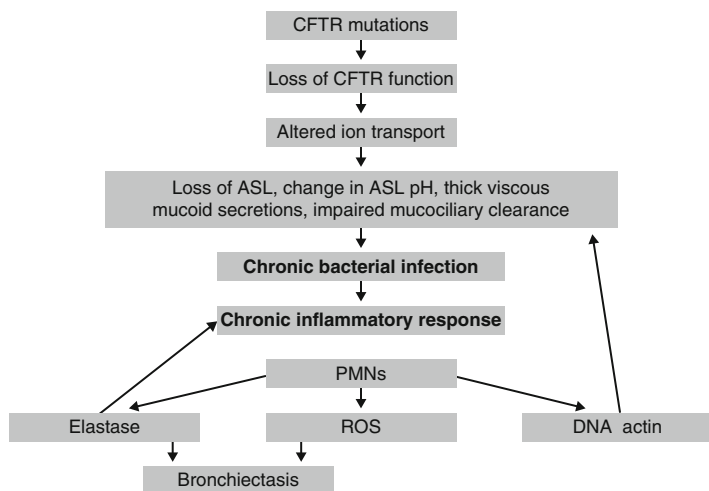
FIGURE 3.1 Pathogenesis of cystic fibrosis lung disease. *ASL* airway surface liquid, *PMNs* polymorphonuclear neutrophils, *ROS* reactive oxidant species

inducing the expression of neutrophilic chemokines by airway epithelial cells. DNA and actin released by neutrophil nuclei and cytoskeletons, respectively, further contribute to impaired mucociliary clearance by increasing sputum viscosity. Over time the presence of chronic neutrophilic airway inflammation results in bronchiectasis. This process of infection and inflammation occurs shortly after birth in infants with CF. Despite early diagnosis through newborn screening (NBS), up to 30 % of infants with CF have radiographic evidence of bronchiectasis by 1 year of age and the presence of free HNE in the bronchoalveolar lavage fluid of infants with CF is associated with persistent bronchiectasis [3, 4]. Lung function measures are also abnormal by the first year of life [5].

Early in the course of CF lung disease there are little to no clinical symptoms or signs of airway inflammation or bronchiectasis. However, over time, patients with CF progress from a frequent intermittent cough to a chronic daily cough [6]. As bronchiectasis progresses and mucopurulent secretions accumulate in the lower respiratory tract,

patients begin to produce daily sputum. Similar to clinical symptoms there are few signs of early disease progression in CF. Over time crackles and rhonchi can be heard, reflecting the presence of focal areas of bronchiectasis. Wheezing is another physical exam finding and results from mucus obstruction of airways. With increasing airway obstruction, due to bronchiectasis, gas trapping leads to thoracic expansion and a 'barrel chest' appearance. Digital clubbing is another sign that bronchiectasis has progressed, although there is a poor correlation between the degree of clubbing and the degree of lung disease. Lung function testing reveals an obstructive pattern, with decreased forced expiratory volume in 1 s (FEV_1), low ratio of FEV_1 to forced vital capacity (FEV_1/FVC), and increased residual volume (RV) and total lung capacity. Flows at mid-volume, such as the forced expiratory flow between 25 and 75 % FVC (FEF_{25-75}), are also reduced.

Radiographic imaging, especially with computed tomography (CT), detects bronchiectasis long before the development of clinical signs. The key features seen on imaging in patients with CF are [7]:

- air trapping/hyperinflation;
- bronchiectasis;
- peribronchial/airway wall thickening;
- mucus plugging; and
- parenchymal opacities or atelectasis.

As disease progresses these changes often correlate with clinical features, particularly lung function. Air trapping is the most common structural abnormality seen in CF, followed by bronchiectasis and mucus plugging. In early disease these changes are not apparent with plain chest radiography (CXR), but in contrast, chest CT is very sensitive at detecting early structural lung disease, even in infants.

Air trapping is characterized on CT images by mosaicism with hypoattenuation in the areas with gas trapping, compared to normal lungs, which have increased density on expiratory images. Diaphragm contour, retrosternal lucency, and cardiac position are signs of air trapping on CXR.

Bronchiectasis is defined as a bronchus that has a larger diameter than its accompanying artery or a bronchus that does not taper. It can be seen in up to 60 % of CT images, even in the first 3 years of life [4], but may be more variable early on, becoming irreversible over time. Bronchiectasis is only apparent on CXR when it is very advanced or extensive. The extent of bronchiectasis has been shown to correlate with reduced survival in CF [8]. Neutrophilic inflammation and pulmonary infection are risk factors for the development and progression of bronchiectasis, as well as decline in lung function and nutritional status [4]. Mucus plugging is present when the bronchi are filled or opaque and tends to have a lower lobe predominance. The thickness of airway walls is defined based on location, with the hilar region having thicker walls compared to more peripheral airways. Atelectasis is frequently related to mucus plugging and can range from lobar to subsegmental in nature. Small areas of mucus plugging can be identified through chest CT, whereas CXR will only demonstrate larger areas of atelectasis.

3.1.2   Pulmonary Exacerbations

In addition to the chronic endobronchial infection and inflammation with progressive decline in lung function, CF is characterized by episodic acute increases in respiratory symptoms. These flares are often referred to as pulmonary exacerbations, and in general, refer to change from baseline respiratory symptoms necessitating increased airway clearance and antibiotic treatment. The pathophysiology of CF pulmonary exacerbations is not well understood, although they are associated with an increase in airway inflammation [9]. A consensus definition of exacerbations is also lacking, although several sets of diagnostic criteria have been developed. Most include features of increased cough and sputum production, new crackles, decline in lung function, fatigue or decreased exercise tolerance, and weight loss. Rabin et al. [1] used data from the Epidemiological Study of Cystic Fibrosis (ESCF) to develop criteria based on age, suggesting that features of a pulmonary exacerbation may change with age and disease progression (Table 3.1). Fuchs

Table 3.1 Symptoms and signs used by cystic fibrosis clinicians to diagnose pulmonary exacerbation

Age group (years)			
<6	6–12	13–17	≥18
New crackles	Decline in FEV_1 (% predicted)	Decline in FEV_1 (% predicted)	Decline in FEV_1 (% predicted)
Increased cough	Increased cough	Increased cough	New crackles
Decline in weight for age percentile	New crackles	New crackles	Hemoptysis
Increased sputum	New *Pseudomonas aeruginosa*	Hemoptysis	Increased cough

The four clinical characteristics most associated with treatment for pulmonary exacerbation are shown by age group [1]. Reproduced with permission from © John Wiley and Sons

et al. [10] defined a standardized definition of an exacerbation based on treatment with intravenous antibiotics for any 4 of 12 signs or symptoms. Signs and symptoms include:

• change in sputum;
• new or increased hemoptysis;
• increased cough;
• increased dyspnea;
• malaise, fatigue, or lethargy;
• temperature above 38 °C;
• anorexia or weight loss;
• sinus pain or tenderness;
• change in sinus discharge;
• change in physical examination of the chest;
• decrease in pulmonary function by 10 % or more from a previously recorded value; or
• radiographic changes indicative of pulmonary infection.

The European based EuroCareCF Working Group has endorsed the criteria outlined by Fuchs et al. as the best defi-

nition of an exacerbation [11]. Pulmonary exacerbations have been associated with a more rapid decline in lung function and reduced quality of life.

3.1.3   Hemoptysis

Despite early diagnosis, improved treatment options, and aggressive management of pulmonary exacerbations, as CF lung disease advances, more severe pulmonary complications, including hemoptysis, pneumothorax, and ultimately respiratory failure may be seen. Small volume hemoptysis is relatively common in CF and is generally associated with infection or pulmonary exacerbation. Massive hemoptysis is more common in patients with advanced lung disease with FEV_1 <40 % predicted, although patients with normal lung function or mild obstruction account for 20 % of those with massive hemoptysis [12]. Risk factors for major hemoptysis include *Staphylococcus aureus* infection, pancreatic insufficiency (PI), and CF-related diabetes. In patients with CF, massive hemoptysis is generally arterial in origin, most commonly from the bronchial arteries (which are enlarged and tortuous).

3.1.4   Pneumothorax

Pneumothorax is another complication seen in patients with end-stage CF lung disease, generally with FEV_1 <30 % predicted. It occurs when the pressure in the alveoli is elevated, usually due to mucus plugging of the airways. When the pressure exceeds interstitial pressure air leaks out and may enter the pleural space. Colonization with *P. aeruginosa* or *Burkholdaria cepacia*, allergic bronchopulmonary aspergillosis (ABPA), and prior massive hemoptysis are risk factors for pneumothorax in CF [13]. Approximately 3 % of patients with CF will experience a pneumothorax during their lifetime. Having a pneumothorax is a poor prognostic sign with almost 50 % mortality within 2 years [12].

3.1.5   Respiratory Failure

The natural history of CF is that of worsening airflow obstruction, eventually leading to respiratory failure. Patients generally develop hypoxemia (with the need for supplemental oxygen), hypercapnia, and ultimately, pulmonary hypertension. Some patients will choose to pursue lung transplantation, while others will choose a palliative approach. Focus should be on relieving symptoms, such as dyspnea, and keeping the patient comfortable. Non-invasive positive pressure ventilation may be helpful in these situations, but intubation is discouraged unless it is being used as a bridge for a transplant that is expected to occur soon [12]. This is because outcomes in patients with end-stage CF lung disease who received prolonged mechanical ventilation are poor [12].

3.1.6   Allergic Bronchopulmonary Aspergillosis

ABPA is a hypersensitivity reaction with allergic features to airway colonization with *Aspergillus fumigatus* and is generally seen in patients with asthma or CF [14]. The prevalence of ABPA in asthma is 1–2 % and ranges from 2 to 9 % in the CF population [15]. Clinical manifestations include wheezing, pulmonary infiltrates, bronchiectasis, and fibrosis. Other clinical features include fever, malaise, and production of brown colored sputum. Immunologic findings include:

- peripheral blood eosinophilia (generally >500 cells/μliter);
- elevated total serum immunoglobulin E (IgE) (generally >1000 IU/mL);
- precipitating antibodies to *A. fumigatus*;
- immediate skin test positivity to *A. fumigatus*;
- and specific IgE and immunoglobulin G (IgG) antibodies to *A. fumigatus* on immunoassay.

It can be difficult to make a diagnosis of ABPA in a patient with CF as the symptoms and radiographic findings are also consistent with a pulmonary exacerbation of CF, and

TABLE 3.2 Diagnostic criteria and minimal diagnostic criteria for classic allergic bronchopulmonary aspergillosis

Diagnostic criteria for classic allergic bronchopulmonary aspergillosis
Major criteria
Asthma
Pulmonary infiltrates on chest radiography
Immediate skin test reactivity to *Aspergillus fumigatus* (or equivalent positive serum test)
Eosinophilia
Precipitating antibodies (IgG) to *A. fumigatus*
Elevated total serum IgE >1000 IU/mL
Central bronchiectasis
Elevated specific serum IgE and IgG to *A. fumigatus*
Minor criteria
Presence of *Aspergillu*s in sputum
Expectoration of brownish black mucus plugs
Delayed skin reaction to *Aspergillus* antigen
Minimal diagnostic criteria
Asthma
Immediate cutaneous hyperreactivity to *Aspergillus* antigens
Transient pulmonary infiltrates on chest radiograph
Elevated IgE
Raised *A. fumigatus*-specific IgG and IgE

Adapted from Stevens et al. [14]
IgE immunoglobulin E, *IgG* immunoglobulin G

bronchiectasis is a common finding in CF lung disease. A US Cystic Fibrosis Foundation ABPA Consensus Conference resulted in the development of diagnostic criteria for classic ABPA as well as minimal diagnostic criteria (Table 3.2).

3.1.7   Asthma in Patients with Cystic Fibrosis

The diagnosis of asthma in patients with CF is poorly defined and controversial [16]. Wheezing occurs in ~60 % of children with CF in the first 6 years of life, and wheezing in early childhood is associated with lower lung function between 6 and 8 years of age [17]. About 20 % of children with CF have clinically diagnosed asthma [16]. A high proportion (30–50 %) of patients with CF demonstrate bronchial hyperresponsiveness, but whether this represents asthma or underlying CF lung disease is unclear. In summary, while the diagnosis of asthma may be difficult to establish in patients with CF, it is clear that some patients do display clinical features consistent with asthma and may benefit from asthma therapies.

3.2   Upper Airway Disease

Nasal and sinus disease is seen in almost all people with CF. Common symptoms and complaints are noted to include nasal obstruction (unilateral or bilateral), rhinorrhea, daily headache, morning cough, halitosis, and throat clearing. Those with nasal polyps are more likely to have hyposmia and widening of the nasal bridge. The prevalence of nasal polyps in CF is widely variable, ranging from 7 to 48 %, with most being small and only visible via endoscopy [18]. CT is the preferred method for imaging the sinuses, with hypoplasia of the frontal and sphenoid sinuses and panopacification of the sinuses being common findings in CF [19]. The bacteria isolated from the sinuses tend to be the same as those found in the lower respiratory tract, with *P. aeruginosa* the most common in older patients, while *S. aureus* and *Hemophilus influenzae* are more common in younger children. Fungal cultures are positive in about one third of samples and anaerobes may also be isolated. A number of medical and surgical treatment options have been used in the management of CF sinonasal disease but few randomized controlled trials exist. Nasal steroids have been shown

to reduce symptoms and polyp size in adults with CF [20]. Nasally inhaled dornase alfa has also been shown to reduce recurrence of nasal polyps following functional endoscopic sinus surgery (FESS) over a 3 year period and also demonstrated improvement in nasal symptoms in those without polyps following FESS [21, 22]. When to perform sinus surgery remains somewhat controversial but persistent nasal or anatomic obstruction, worsening or more frequent pulmonary exacerbations, and symptoms leading to poor quality of life are factors to consider when determining need for surgical intervention. The use of antibiotic sinus lavage with surgery may decrease the need for repeat sinus surgery, but recurrence remains frequent, with repeat surgical intervention often being necessary.

3.3   Microbiology

3.3.1   Microbiology in Early Life

Lung disease begins early in life for patients with CF. Infection and inflammation can be seen within the first few weeks of life [23]. Rosenfeld et al. [24] followed infants with CF, performing bronchoscopy with bronchoalveolar lavage (BAL) annually for the first 3 years of life. They found that most infants had at least one pathogen isolated in BAL fluid at each bronchoscopy [24]. *H. influenzae* was the most common CF pathogen found at 1 year of age, present in over one third of infants. *S. aureus* and *P. aeruginosa* were the other predominant pathogens noted in the first 3 years of life. While *H. influenzae* rates declined after the first year, the prevalence of *S. aureus* and *P. aeruginosa* increased, with *P. aeruginosa* being present in one third of children at 3 years of age [24]. The study also found that it was common to isolate more than one pathogen in a single BAL. The US Cystic Fibrosis Foundation annually tracks the prevalence of bacteria in the respiratory tract by age through the Cystic Fibrosis Registry; data from 2014 are shown in Fig. 3.2 [25].
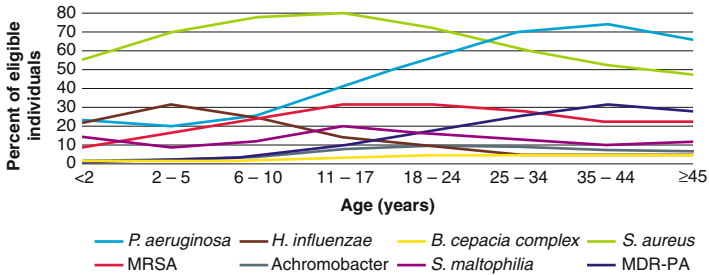
FIGURE 3.2   Prevalence of respiratory microorganisms by age [25]

3.3.2   *Staphylococcus aureus*

Young children with CF are usually initially infected with methicillin sensitive *S. aureus* (MSSA) (Fig. 3.2) [25]. There continues to be debate about the impact of *S. aureus* infection on CF lung disease and outcomes [26]. Epidemiologic studies of MSSA in CF have reached conflicting conclusions, probably because of the differences in patient population and clinical practices over time, as well as differences in data collection. In many countries, prophylaxis with antibiotics that are active against MSSA is a part of CF care. However, this is not common practice in the US, perhaps because of the results of a large clinical trial of cephalexin in young children with CF that showed an increased rate of *P. aeruginosa* infection in the treatment group [27].

In recent years, the prevalence of methicillin-resistant *S. aureus* (MRSA) has been rising in the CF population worldwide, but particularly in the US (the prevalence of MRSA in the 1999 and 2014 US Cystic Fibrosis Patient Registry was 4.2 and 25.9 %, respectively) (Fig. 3.3) [25].

The role of MRSA in CF pulmonary disease remains unclear. Observational studies have demonstrated an association between MRSA isolated in respiratory cultures and worse lung function as well as more frequent antibiotic use [28]. Analysis of data from the Cystic Fibrosis Foundation Registry has shown that the presence of MRSA in respiratory
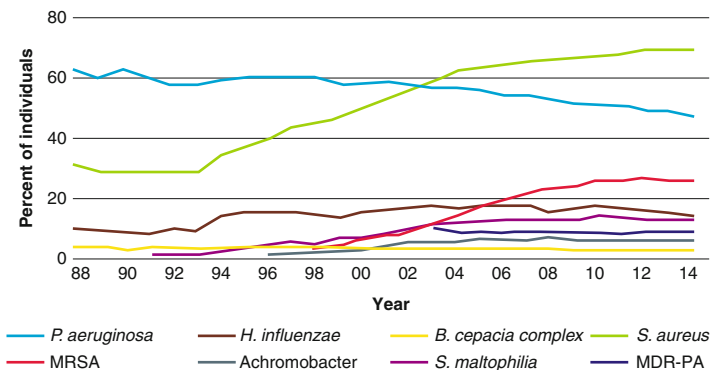
FIGURE 3.3 Prevalence of respiratory microorganisms, 1988–2014 [25]

cultures is associated with increased rate of lung function decline and mortality, even when controlling for baseline disease severity [29]. On the other hand, data from the ESCF did not show a significant change in lung function decline after acquisition of MRSA, suggesting that MRSA infection in CF is a marker of disease severity and more aggressive treatment, rather than having a causal effect on disease severity [30]. Sanders et al. [31] found that persistent MRSA infection was a risk factor for failure to return to previous lung function baseline following a CF pulmonary exacerbation. In contrast to eradication therapy for *P. aeruginosa*, eradication of MRSA remains controversial. A recent Cochrane review determined that although eradication of MRSA may be possible, there are not enough data to provide recommendations regarding management of MRSA infection in CF [32]. Studies are currently underway to understand better the pathophysiology of MRSA infections in CF and the role of eradication therapy.

3.3.3   *Pseudomonas aeruginosa*

Over time the predominant pathogen isolated from CF respiratory cultures is *P. aeruginosa* (Fig. 3.2). The reasons for why

P. aeruginosa has a predilection for infecting the CF airway is unclear, but chronic infection with *P. aeruginosa* is one of the hallmarks of CF lung disease. *P. aeruginosa* infection is associated with worse clinical outcomes, including a faster rate of decline in lung function, increased hospitalizations, and earlier mortality [33, 34]. Although studies have shown that *P. aeruginosa* infection is associated with an increased and prolonged airway inflammatory response in patients with CF, the precise mechanism remains unclear. *P. aeruginosa* that is isolated from initial infections in the CF airway display a phenotype similar to those isolated from non-CF patients. However, over time, *P. aeruginosa* in the CF airway develops a mucoid phenotype, which is also associated with a shift toward growth in a biofilm. Once *P. aeruginosa* is growing in a biofilm it cannot be eradicated, although the progression to chronic infection can be delayed through surveillance cultures and eradication of initial infection. The long-term benefit of eradication therapy has not been demonstrated in randomized controlled trials, however, the US Cystic Fibrosis Foundation has recommended treatment of initial or new growth of *P. aeruginosa* from a respiratory culture [35]. Management of *P. aeruginosa* infections is discussed further in the treatment section of this book (Chap. 6).

3.3.4   *Burkholderia cepacia Complex*

B. cepacia complex is a Gram-negative bacillus that has been shown to be an opportunistic pathogen in patients with CF. Patients with CF and chronic *B. cepacia* complex infections have demonstrated worsening decline in lung function and increased mortality [36]. The complex is made up of at least nine genomovars. The clinical course of *B. cepacia* complex infection is variable, ranging from asymptomatic, to worsening decline in lung function, to rapid fatal deterioration with bacteremia, with data suggesting that the course may vary based on the genomovar causing the infection [36]. *Burkholderia cenocepacia* is associated with a more rapid decline in lung function compared to *Burkholderia*

multivorans or *P. aeruginosa*. Additionally, *B. cenocepacia* is more often associated with cepacia syndrome, with higher mortality, as well as with worse outcomes following lung transplant [37, 38]. Strict infection control policies are recommended to help prevent patient to patient transmission [36].

3.3.5   Other Cystic Fibrosis-Associated Microorganisms

Stenotrophomonas maltophilia and *Achromobacter xylosoxidans* are two non-lactose fermenting Gram-negative rods that can be recovered occasionally (<10 %) in respiratory cultures from patients with CF [39]. Although their pathogenicity is still unclear, they do not appear to have as adverse an impact on clinical outcomes as *B. cepacia* [39]. Fungi, such as *Candida* species, can also be found in CF respiratory cultures, but they are not considered pathogenic. Anaerobes and small colony variants are two other classes of microorganisms that can be found in CF respiratory cultures, but whose contribution to disease pathogenesis is not well defined [39, 40].

3.3.6   Nontuberculous Mycobacteria

Nontuberculous mycobacteria (NTM) are found throughout the environment, and can cause chronic infection with progressive lung damage. NTM pulmonary disease (NTM-PD) is not unique to CF, however, the presence of structural lung disease with impaired mucociliary clearance is a risk factor for developing NTM-PD [23]. Interestingly, mutations in CFTR may be a predisposing factor for NTM infection, as 30–50 % of patients without CF who develop NTM lung disease have been reported to be carriers of CFTR mutations [41]. The prevalence of NTM infection in patients with CF increases with age, and detection rates of NTM in patients with CF have also been increasing worldwide [42]. Although a definitive reason for this increase is not clear, several theories have been proposed, including increased environmental exposure, spread

through person-to-person transmission, increasing use of intensive antibiotics, and the use of medications that may predispose to NTM infection (including corticosteroids, proton pump inhibitors, and azithromycin) [43, 44]. The Cystic Fibrosis Foundation and European Cystic Fibrosis Society recently developed consensus guidelines for management of NTM in patients with CF [43]. The guidelines recommend using the American Thoracic Society/Infectious Disease Society of America criteria for NTM-PD to determine when treatment should be considered. These criteria include [45]:

1. ≥2 sputum samples (or a single bronchoscopic sample) to be NTM culture-positive;
2. radiological changes consistent with NTM infection; and
3. clinical features attributable to NTM.

The most common types of NTM found in patients with CF are the slow growing *Mycobacterium avium* complex (MAC), which includes *M. avium*, *Mycobacterium intracellulare* and *Mycobacterium chimaera*, and the fast-growing *Mycobacterium abscessus* complex (MABSC), which includes *M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *Bolletii*, and *M. abscessus* subsp. *Massiliense* [46]. Infection with *M. abscessus* complex is more likely to lead to NTM-PD in patients with CF [44]. Figure 3.4 shows the consensus guideline recommendations for evaluating patients with CF suspected of having NTM-PD [43].

3.4   Gastrointestinal and Nutritional Disease

3.4.1   Pancreatic Insufficiency

Damage to the pancreas begins in utero. Destruction of the pancreas is generally related to obstruction of the ducts and acini due to dehydrated material within the lumen. Zymogen within the material elicits an inflammatory response with ultimate loss of exocrine tissue and replacement with connective tissue [47]. PI is seen in approximately 85 % of patients
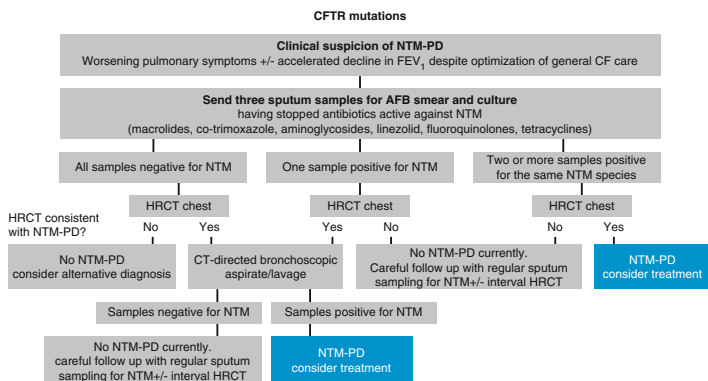
FIGURE 3.4 Recommended algorithm for evaluation CF patients with suspected nontuberculous mycobacteria pulmonary disease [43]. CF, cystic fibrosis; CT, computed tomography; FEV$_1$, forced expiratory volume in 1 s; HRCT, high resolution computed tomography; NTM, nontuberculous mycobacteria; NTM-PD, nontuberculous mycobacteria pulmonary disease. Reproduced with permission from © BMJ Publishing Group Ltd

with CF [48]. In infants diagnosed through NBS, PI is usually evident at the time of diagnosis, but in some cases it may take up to 3 years before the pancreas is completely insufficient [48]. The symptoms of malabsorption with steatorrhea become evident when pancreatic lipase secretion is less than 1–2 % of normal levels [48, 49]. Clinically, patients experience greasy stools, flatulence, bloating, and poor growth [50]. Gastric lipase production cannot compensate for the absence of pancreatic enzyme secretion, making fat the most sensitive nutrient to malabsorption. Pancreatic proteases, such as trypsin and chymotrypsin, are also likely seen in very low levels in patients with PI. Carbohydrate digestion is relatively spared as enzyme activity in other areas is sufficient to hydrolyze carbohydrate in the small intestine. Malabsorption of macronutrients leads to malnutrition with weight loss or poor weight gain as well as linear growth impairment. Protein loss can lead to hypoproteinemia and edema in undiagnosed infants with CF. Pancreatic enzyme replacement therapy

(PERT) has been shown to improve fat absorption and is routinely used in the management of patients with CF and PI.

3.4.2   Fat-Soluble Vitamin Deficiency

An additional consequence of PI is impaired absorption of the fat-soluble vitamins A, D, E, and K. Malabsorption of fat-soluble vitamins persists even with adequate treatment of PI with PERT [47]. This is further exaggerated in patients with CF-associated liver disease. Vitamin A includes the retinoids and beta-carotene (included in the vitamin A family as it is a precursor to retinol). Vitamin A is involved in vision, immunity, and epithelial cell proliferation and function and beta-carotene is an antioxidant. Vitamin A levels have been shown to decrease transiently as part of the acute phase response to inflammation [51]. Vitamin A deficiency is associated with night blindness and xerophthalmia.

Vitamin D is critical for calcium absorption and metabolism. It is important to the prevention of osteoporosis and bone fractures in patients with CF. The Cystic Fibrosis Foundation recommends maintaining 25-hydroxyvitamin D levels at ≥30 ng/mL [52]. Despite Vitamin D supplementation, maintaining target levels of Vitamin D in patients with CF is challenging.

Vitamin E has antioxidant properties. Deficiency in vitamin E can lead to hemolytic anemia and neuropathy. It is also important for early cognitive development in infants with CF.

Vitamin K plays a central role in the synthesis of several clotting factors. Vitamin K deficiency can lead to issues with bleeding (eg, uncontrolled bleeding). Another source of vitamin K is colonic bacteria; therefore, vitamin K can also be reduced acutely while taking oral antibiotics.

3.4.3   Meconium Ileus

Meconium ileus (MI) is the earliest gastrointestinal manifestation of CF. It is intestinal obstruction by meconium at the level of the terminal ileum. Approximately 10–20 % of newborns

with CF will present with MI [50]. While MI can be associated with other conditions, in full term infants, it is almost always due to CF. It is also highly correlated with more severe mutation classes, particularly in patients who are homozygous for F508del [50]. MI generally presents with failure to pass meconium within the first 48 h after birth. Simple cases can generally be treated with enemas, but more complex meconium ileus may be associated with intestinal atresia, microcolon, bowel necrosis, or perforation. These complications require operative intervention. Because the meconium is very thick and tenacious, surgical treatment can be challenging and is best performed by a surgeon skilled and experienced in management of MI. Prenatal ultrasound may demonstrate evidence of small bowel pathology including hyperechoic walls, calcifications, and luminal distension; newborns with these findings prenatally need further testing for CF.

3.4.4   Distal Intestinal Obstruction Syndrome

Distal intestinal obstruction syndrome (DIOS) may occur in patients with CF of any age but is more prevalent in adults compared to children [53]. DIOS is characterized by a fecal mass in the ileocecal region, abdominal pain or distension, and bilious emesis. Approximately 16–21 % of patients with CF experience DIOS, and 50 % of those with DIOS had MI at birth [50]. Over 90 % of patients with DIOS have PI, usually with more severe mutation classes [50]. Other risk factors include a prior episode of DIOS, dehydration, CF-related diabetes, and being post-lung transplant [54]. DIOS is caused by an accumulation of viscous fecal material and sticky intestinal contents adhering to the cells of the intestine. Secretion of chloride (Cl) and water into the intestinal lumen is impaired due to the faulty CFTR protein. Enhanced fluid uptake via epithelial sodium channels (ENaC) and decreased bile salt secretions may also be contributing factors. Additional factors that may predispose patients with CF to DIOS include impaired gut motility, enteric neuromuscular dysfunction, muscular hypertrophy, and fat malabsorption.

3.4.5 Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is identified in 25–80 % of patients with CF [55] and is 6–8 times more common in children with CF compared to healthy children [48, 50]. The exact mechanisms underlying the association between CF and GERD are unclear but likely multiple factors are involved, including [55]:

- increased frequency of lower esophageal sphincter relaxation;
- prolonged gastric transit time in CF;
- prolonged intraesophageal acidification related to issues with peristalsis;
- the effect of primary lung disease, cough, and wheeze leading to increased abdominal pressure;
- use of medications that increase GERD;
- effects of high fat diet recommended for patients with PI; and
- airway clearance regimens, particularly when performed after meals or in a head down position.

Both acidic and nonacidic GERD may contribute to symptoms in patients with CF, and 24 h mid-esophageal impedance/pH measurement is the most sensitive test to diagnose GERD [55].

3.4.6 Recurrent Pancreatitis

Pancreatitis is seen in 10–20 % of patients with CF who are pancreatic sufficient. It is seen in <1 % of patients with PI [48]. The risk of recurrent pancreatitis may relate to the balance between acinar pancreas function versus the extent of ductal plugging due to thick secretions. Development of pancreatitis may signal progressive decline in exocrine function and transition to PI [50]. Therefore, when a patient develops recurrent pancreatitis, testing of pancreatic function should be reassessed.

3.4.7 Rectal Prolapse

Rectal prolapse is when the rectum protrudes through the anal opening. In patients with CF it is usually related to either swings in intra-abdominal pressure due to coughing or to straining due to constipation. In some reports, over 20 % of patients with CF experienced rectal prolapse and it can also be an initial sole presenting sign of CF [56]. Rectal prolapse resolves in over 75 % of cases after PERT is initiated [56]. The widespread implementation of CF NBS has led to earlier diagnosis and treatment, therefore reducing the incidence of rectal prolapse. In a retrospective review over 10 years during the time of NBS, less than 5 % of patients experienced rectal prolapse [56].

3.4.8 Hepatobiliary Disease

CF-associated liver disease (CFLD) is the third leading cause of death in CF; 15–30 % of children with CF will demonstrate clinically significant manifestations of liver disease [48]. Survival is decreased in children who develop cirrhosis [48, 57]. CFTR is located in the membrane on the apical surface of cholangiocytes and drives hydration of bile. Abnormal CFTR function leads to thick inspissated secretions that, in turn, lead to biliary obstruction. CFTR dysfunction also influences digestive functions due to reduced alkalinization of bile. Accumulation of bile salts leads to hepatocyte injury, inflammation, and fibrosis. The clinical presentation of hepatobiliary disease is variable, but generally develops during childhood or adolescence. Asymptomatic hepatomegaly, associated with fibrosis, presents in 10–30 % of patients with CF as they enter puberty [57]. There are three stages to advanced disease seen in older children and adults:

1. hepatic steatosis;
2. focal biliary cirrhosis; and
3. multilobular cirrhosis.

Hepatic steatosis is the most common and seems to be more directly related to nutritional deficiencies rather than defective CFTR protein. Clinically, it presents with hepatomegaly and on

ultrasound imaging the liver tissue appears hyperechogenic. Transaminases are also elevated. Cirrhosis is irreversible liver damage and over time leads to jaundice, coagulopathy, ascites, and the development of portal hypertension. Portal hypertension is often accompanied by splenomegaly and thrombocytopenia as well as risk for bleeding from esophageal varices. Liver ultrasound imaging is the primary test when cirrhosis is suspected. The clinical course of CFLD is highly variable, but once cirrhosis and portal hypertension develop there tends to be slow progression of disease. In general, CFLD is seen in patients who are PI and it develops in childhood. New cases of CFLD are generally not detected after 20 years of age [48]. In one study, approximately 10 % of patients with CFLD either died from liver complications or needed liver transplant and 30 % developed varices over the follow-up period [58]. Patients with CFLD were also more likely to develop CF-related diabetes. There may also be extrahepatic abnormalities of the biliary tree, including the gallbladder [59]. Micro-gallbladder may be seen in up to one fourth of patients at autopsy and gallstones and biliary sludge are also common (seen in about 25 % of patients) [59].

3.4.9   Other Gastrointestinal Complications of Cystic Fibrosis

There is an increased incidence of almost all gastrointestinal disorders in patients with CF. This includes appendicitis, cholecystitis, and intussusception. For this reason, clinicians must be more circumspect and aggressive in evaluating CF patients with acute abdominal pain.

3.5   Endocrine Disease

3.5.1   Cystic Fibrosis-Related Diabetes

The prevalence of CF-related diabetes (CFRD) has increased with improved survival of patients with CF, and it is one of the most common complications seen in patients with CF [60].

The prevalence increases with age, with almost 20 % of adolescents being diagnosed with CFRD, and 40–50 % of adults with CF having CFRD [61]. As pancreatic damage progresses, eventually there is a critical proportion of islet cells that no longer function, leading to insulin insufficiency as well as a degree of insulin resistance. In this way, CFRD differs from either typical type 1 or type 2 diabetes. The diagnosis of CFRD is associated with decline in lung function, nutritional status, and increased mortality (particularly in women aged 30–39 years) [61, 62]. Unlike diabetes in individuals without CF, CFRD does not appear to increase the risk of atherosclerotic cardiovascular disease [60]. Diabetic retinopathy is seen in CFRD, most often after fasting hyperglycemia has developed, and is less common than in type 1 or type 2 diabetes. Mild diabetic neuropathy may also be seen [60, 61].

3.5.2   Bone Disease

CF-related bone disease is a common complication of CF; it affects approximately 11 % of patients with CF, although this may be an underestimation [63]. Many factors contribute to CF-related bone disease, including malabsorption of vitamins D and K, poor nutritional status, delayed pubertal maturation, and use of glucocorticoids. In addition, cytokines induced by chronic inflammation may also lead to increased bone resorption and reduced bone formation [64]. The key clinical manifestations of low bone mineral density or osteoporosis include an increased risk of fractures and an increased incidence of kyphosis in patients with CF. Not only do fractures and kyphosis lead to pain but this can in turn lead to reduced cough efficacy, chest wall abnormalities, and ultimately reduced lung volumes.

3.6   Urogenital Tract Disease

Obstructive azoospermia is found in over 95 % of men with CF, leading to infertility [65, 66]. The obstruction is due to a congenital bilateral absence of the vas deferens. The seminal

vesicles are also atrophic or absent. This may be due to obstruction by dehydrated secretions in the genital tract in utero or developmental abnormalities in the reproductive tract [67–69]. The diagnosis can be made when the vas deferens is not palpable on scrotal exam, or is not evident on ultrasound. Semen analysis reveals azoospermia and low semen volume.

3.7   Psychiatric Complications

Children with chronic illness and their parents/caregivers are at higher risk for anxiety and depression than the general population [70]. The International Depression/Anxiety Epidemiological Study was a multicenter and multinational effort to screen patients with CF and their parents/caregivers for depression and anxiety. The study found that symptoms of depression and anxiety were 2–3 times more common than in the general population. Procedural anxiety is particularly relevant to patients with CF. Prevalence of depression ranged from 10 % of adolescents to 37 % of mothers, and anxiety was reported by 22 % of adolescents and up to 48 % of mothers [71]. The presence of anxiety and/or depression has been associated with a variety of health-related issues in patients with CF, including decreased pulmonary function, lower body mass index, worse adherence to treatment regimens, worse health-related quality of life, more frequent hospitalization, and increased health care costs. Due to the importance of these issues to effective long-term treatment and management of CF, the US Cystic Fibrosis Foundation and European Cystic Fibrosis Society formed the International Committee on Mental Health in Cystic Fibrosis, and a consensus statement on screening and treatment of depression and anxiety in CF was published [71]. Recommendations include annual screening of adolescents and adults with CF as well as screening of at least one primary caregiver. They recommend a flexible stepped-care approach for evaluation and treatment of anxiety and depression.

3.8   Other Conditions Associated with Cystic Fibrosis

3.8.1   Hyponatremic Dehydration

Failure to resorb salt from the sweat ducts can result in hyponatremic dehydration. Indeed, it was the observation that large numbers of patients with CF required hospitalization for hyponatremia during a heat wave in New York City that led to the use of sweat Cl measurement as a diagnostic test for CF [72–75]. Hyponatremia is a greater problem in infants and young children, because infant formulas, breast milk, and baby foods typically are low in sodium, and these patients are unable to voluntarily increase their salt intake. For these reasons, salt supplementation is a part of CF infant care.

3.8.2   Drug Allergy

Drug allergy is not a direct complication of CF but due to the multiple courses of antibiotic therapy patients with CF receive over time drug allergy can frequently arise [74–76]. In one study 36 % of adult patients with CF had an antibiotic allergy and 19 % had allergies to multiple antibiotics. In addition to anaphylactic IgE-mediated drug allergy, patients with CF also develop serum sickness or Stevens-Johnson syndrome reactions [77]. Patients with CF with a suspected drug allergy should be seen by an allergist and appropriate testing should be conducted. If necessary, drug desensitization to anaphylactic IgE-mediated allergy can be performed using standard protocols.

3.8.3   Joint Disease

Arthritis is a relatively uncommon complication in CF, but when present, can cause significant morbidity. There are two different types of arthritis generally seen in patients with CF:

CF-related arthropathy (CFA) and hypertrophic pulmonary osteoarthropathy (HPOA) [78]. CF-related arthropathy generally presents as acute episodes of swollen, red, tender joints, often asymmetric in distribution and that causes significant pain. It may be accompanied by fevers or rashes, but is not generally associated with decline in lung function, pulmonary exacerbation, or change in gastrointestinal symptoms. Episodes generally last 7–10 days, and patients are often completely asymptomatic between flares. Symptoms can usually be treated with either non-steroidal or steroidal anti-inflammatory medications. [58, 59]. HPOA is less common than CFA and is characterized by periosteal proliferation of the long bones [78]. HPOA tends to be more chronic and causes symmetrical bone pain and pain in large joints. Unlike CFA, HPOA is associated with pulmonary exacerbations, as well as more severe lung disease and colonization with *P. aeruginosa*. Treatment is also with non-steroidal anti-inflammatories and analgesics [79].

3.8.4 Vasculitis

Vasculitis, or inflammation within the blood vessel walls, is another rare complication of CF. Vasculitis can develop as a result of a hypersensitivity reaction to a specific antigen, like in serum sickness, or it can be related to a connective tissue syndrome. CF vasculitis has some similarities to Henoch-Schönlein purpura, which is thought to be mediated by immunoglobulin A (IgA) [80]. Vasculitis can cause severe illness and may be somewhat unrecognized. It is unclear whether specific microorganisms may cause vasculitis in CF.

3.8.5 Dermatologic Manifestations

There are several cutaneous manifestations of CF that have been reported, including nutrient deficiency dermatitis of CF, increased prevalence of cutaneous atopy, more frequent drug hypersensitivity reactions, early aquagenic skin wrinkling, and cutaneous vasculitis [81]. Nutrient deficiency dermatitis of CF

can be life threatening and can be the presenting sign of CF. It tends to present in the first weeks to months of age with annular erythematous papules [82]. Associated symptoms may include hepatomegaly, failure to thrive, or periorbital and extremity edema [83]. Laboratory studies demonstrate anemia, abnormal liver function tests, and reduced zinc and Vitamin E levels. Aquagenic skin wrinkling is wrinkling of the palms and soles upon submersion in water. It generally appears within a couple of minutes of water submersion and symptoms may include pain or discomfort, itching, tingling, and associated hyperhidrosis [84]. Symptoms generally resolve within a few hours after removal from water.

3.8.6   Nephrolithiasis

Nephrolithiasis occurs in about 3–6 % of patients with CF [85]. Kidney stones in patients with CF tend to be made of calcium oxalate. They are thought to arise because fat malabsorption results in chelation of dietary calcium, resulting in increased absorption of dietary oxalate. Once in the bloodstream this oxalate can combine with serum calcium to form calcium oxalate that then precipitates in the kidneys. Other potential mechanisms include hyperuricosuria, loss of CFTR-mediated calcium transport, hypocitraturia, and lack of colonization with *Oxalobacter formigenes*, (an enteric oxalate-degrading bacterium).

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Chapter 4
Diagnosis of Cystic Fibrosis

4.1 Background and History

The approach to diagnosis of cystic fibrosis (CF) has evolved over the years as advances in CF genetics and pathophysiology have occurred. When CF was first described in 1938 it was primarily viewed as a gastrointestinal disease, and the diagnosis was made based on phenotypic features and demonstration of pancreatic insufficiency, eg, measurement of duodenal trypsin activity [1]. A major advance in the diagnosis of CF occurred when Dr Paul Di Sant'Agnese made the observation that children with CF were at increased risk of hyponatremic dehydration [2]. This led to the use of sweat chloride (Cl) concentration measurement (the sweat test) as a diagnostic test for CF [3]. More recently, the discovery of the *cftr* gene allowed genetic diagnosis of the disease and the implementation of newborn screening (NBS) has led to diagnosis at a younger age [4].

4.2 The Sweat Test

Cystic fibrosis transmembrane conductance regulator (CFTR) in the sweat duct serves to resorb Cl from sweat, and in the absence of CFTR function, sweat Cl is increased. Initial methods for sweat collection involved encasing patients in plastic and/or

Table 4.1 Interpretation of sweat chloride concentrations

Sweat chloride concentration (mmol/L)	Interpretation
<40[a]	Cystic fibrosis unlikely[b]
40–59	Intermediate
≥60	Consistent with cystic fibrosis

Adapted from Farrell et al. [7]

[a]In infants <6 months old, the cut-off is 30 mmol/L

[b]In rare instances, patients with cystic fibrosis may have a sweat chloride in the normal range

using a heated room, but these methods were cumbersome, associated with adverse events, and often required long collection times. In 1959, Gibson and Cooke developed a procedure using pilocarpine iontophoresis and this technique has become the standard method to perform sweat testing across the world [3]. The technique has remained remarkably unchanged since its original description. In brief, sweat production is stimulated by application of a mild electric current and the cholinergic agonist pilocarpine. The resulting sweat is collected on a gauze pad or microbore tubing and the Cl concentration is measured using a chloridometer. While simple in concept, accurate and reliable sweat testing requires strict and rigorous adherence to published standards [5, 6]. As part of the accreditation process for CF Care Centers in the United States the US Cystic Fibrosis Foundation requires annual documentation of the sweat testing protocol at each care center as well as reporting of quality metrics. The sweat test essentially serves as a biomarker of CFTR function and thresholds for normal and elevated sweat Cl have been established (Table 4.1). Sweat Cl increases with age so the threshold for a normal sweat Cl is lower in infants than in older children and adults. As with any biomarker there is an intermediate concentration that lies in between the normal and elevated thresholds. Some patients with intermediate sweat Cl concentrations will turn out to have CF and additional testing may be needed in order to make the diagnosis.

Sweat testing is a labor intensive procedure that requires specialized testing and therefore its availability is limited.

TABLE 4.2 Conditions that can cause falsely elevated sweat chloride	
	Eczema
	Addison's disease
	Ectodermal dysplasia
	Glycogen storage diseases
	Hypothyroidism
	Pseudohypoaldosteronism
	Vasopressin-resistant diabetes insipidus
	Mucopolysaccharidoses
	Fucosidosis

Adapted from Cotten et al. [8]

Sweat conductivity is another method to assess CFTR function in the sweat gland. However, because sweat conductivity represents nonselective ion measurement and is dependent upon the concentration of other ions present in sweat, it cannot be used as a diagnostic test for CF [5, 6]. Some diseases other than CF have been reported to be associated with an elevated sweat Cl concentration and could potentially result in false positive results (Table 4.2) [8]. In most cases these diseases can be readily distinguished from CF on clinical grounds. Edema and hypoproteinemia can potentially lower sweat Cl concentration and sweat testing is not recommended for infants in the first 48 h of life. A minimum amount of sweat is required in order to accurately measure Cl concentration and for this reason sweat testing patients <2 kg is usually not recommended as there will be insufficient sweat for analysis.

4.3   Genetic Testing

The discovery of *cftr* as the defective gene in CF led to the possibility of using genetic testing to diagnose CF. However, the use of CFTR mutation analysis to diagnose CF is complicated by the large number of mutations associated with a CF phenotype and

TABLE 4.3 Classification of cystic fibrosis transmembrane conductance regulator mutations in the CFTR2 database

Category	Definition	Examples
Cystic fibrosis-causing	Individuals with two copies on separate alleles will likely have cystic fibrosis (confirm with sweat test)	F508del, 3849 + 10 kb C>T
Mutations of varying clinical consequences (MVCC)	Mutations that in combination with a cystic fibrosis-causing mutation or another MVCC may result in cystic fibrosis	R117H, 5 T
Unknown/ unevaluated	Mutations that have not been evaluated by CFTR2 and may be disease-causing, MVCC, or benign	2789 + 2insA
Non cystic fibrosis-causing	Individuals with one or more of these mutations are unlikely to have cystic fibrosis	M470V, R75Q

Adapted from Castellani and CFTR2 team [10, 11]

the difficulty in assigning a pathogenic role to the mutation [9]. Over 2000 CFTR mutations have been associated with CF. In many cases patients do not have all the clinical features of CF or the mutation has been found only in a small number of related patients. While nonsense mutations containing a premature stop codon will clearly result in loss of CFTR function the vast majority of reported CFTR mutations are missense mutations, the impact of which is unclear. In only a small number of mutations has functional analysis been performed to demonstrate that they are truly disease-causing. The CFTR2 project is an international effort to classify CFTR mutations and define their disease liability [10, 11]. CFTR2 collects clinical data from patients around the world with different CFTR mutations and combines them with mutational and functional analysis to determine the likelihood that the mutation is disease causing. Mutations are categorized into one of four categories (Table 4.3). As of 2015, 276

CFTR mutations have been analyzed by CFTR2, and 242 have been categorized as CF-causing.

CFTR2 has been very valuable in helping determine the clinical relevance of CFTR mutations, although there will always be limitations to the use of genetic testing to diagnose CF. Not all reported CFTR mutations are in the CFTR2 database and many of these mutations are carried by only a few patients, reducing the robustness of the determination. Furthermore, for some mutations, the disease risk simply cannot be determined or they are associated with varying clinical consequences. Even complete sequencing of the entire coding region of the *cftr* gene may not identify all the mutations associated with CF since it will miss deep intronic mutations [12].

4.4   Newborn Screening

4.4.1   Newborn Screening Algorithms

Data from the US Cystic Fibrosis Patient Registry show that the median age at diagnosis is 6 months, but the mean age is 3 years, implying that there is an older cohort of patients diagnosed in later childhood or even in adulthood [4]. This observation, coupled with data showing the importance of early diagnosis in CF, has led to efforts to develop NBS for CF. Early attempts to find a suitable biomarker for CF NBS (eg, measurement of albumin in meconium) were unsuccessful due to low sensitivity and specificity, and difficulty in obtaining appropriate specimens. The observation that immunoreactive trypsinogen (IRT), a pancreatic proenzyme, is persistently elevated in newborns with CF allowed for a sensitive biomarker for CF that could easily be measured on a standard dried blood spot [13]. CF NBS is a locally administered program and the algorithm used to improve specificity varies by country and even by state in the US [14]. IRT levels vary throughout the year because of changes in ambient temperature and other factors, and the threshold cutoff is set by each state or country (eg, the top 3.5 % of IRT tests that day or that month).

Although neonatal IRT is a sensitive test for CF NBS, it is not specific. Some infants without CF will have transient elevation of IRT in the first few days of life. Preterm birth, perinatal stress, and African American race are also associated with higher IRT levels [15, 16]. Therefore, CF NBS algorithms must incorporate an additional step in the screening process to increase specificity [7, 17]. Figure 4.1 shows the two methods utilized to complete CF NBS. In most countries, the additional step is to perform DNA analysis on the dried blood spot (an IRT/DNA algorithm). Usually, a panel of CFTR mutations common to the region's CF population is screened, but in some parts of the world gene sequencing is performed. If no mutations are detected, the infant is considered screen negative and no further action is required. It is important to note that screen negative status does not rule out CF; the infant could still have two rare mutations that are not on the mutation panel. Therefore, diagnostic testing should be performed if the patient subsequently develops any clinical features concerning for CF. If two CF-causing mutations are detected (eg, two copies of F508del) a diagnosis
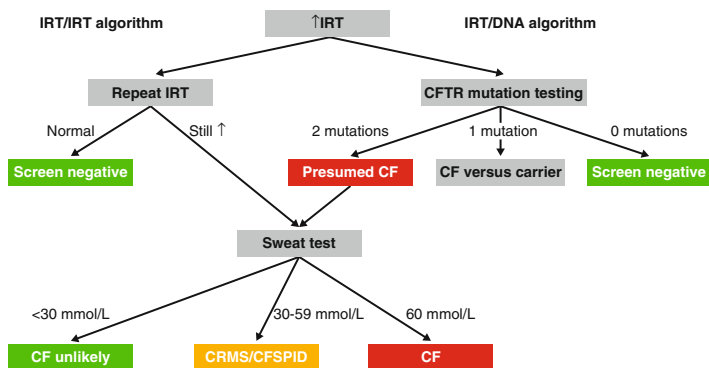
FIGURE 4.1 Cystic fibrosis newborn screening algorithms. *CF* cystic fibrosis, *CFSPID* cystic fibrosis screen positive, inconclusive diagnosis, *CFTR* cystic fibrosis transmembrane conductance regulator, *CRMS* CFTR-related metabolic syndrome, *IRT* immunoreactive trypsinogen

of presumptive CF is made and the infant should be seen as soon as possible at a qualified CF center for a confirmatory sweat test and initiation of CF treatment. If one mutation is detected the infant is either a CF carrier or has CF with a rare mutation not detected on the NBS panel; sweat testing should be performed to rule out CF. The IRT/DNA algorithm allows NBS to be performed from a single blood spot but detects many more carriers than affected infants. In some regions infants with very high IRT levels (eg, the top 0.5 %) are also considered screen positive and referred for sweat testing.

Another approach is to repeat the IRT 2–4 weeks later (the IRT/IRT algorithm), at which time infants with CF will still have elevated IRT but infants without CF have normal IRT levels. The IRT/IRT algorithm avoids detecting large numbers of carriers but requires that parents bring their newborn child back to a testing center again in the first few weeks of life. There is also some concern that the IRT/IRT algorithm is not as sensitive as the IRT/DNA algorithm at detecting newborns with CF [14].

In the last few years CF NBS has been embraced throughout the world and as of 2010 every state in the US offers CF NBS. It is important to note that CF NBS is only a screening test that identifies infants with an increased likelihood of having CF; a confirmatory diagnostic test must be performed. Conversely, a negative CF NBS test does not rule out CF and appropriate diagnostic testing should be performed if the infant develops any clinical features concerning for CF in later life.

4.4.2   Benefits of Newborn Screening

In the 1970s IRT was discovered as a biomarker for CF in newborns, despite this, CF NBS remained controversial due to limited data demonstrating its impact on long-term outcomes. During the 1980s and 1990s epidemiologic evidence of the benefits of CF NBS emerged [14]. Even stronger evidence came from the Wisconsin Cystic Fibrosis Neonatal Screening Project, a randomized trial of CF NBS in the state

of Wisconsin that was initiated in 1984 and is still ongoing. The results of this study, as well as many other epidemiologic studies, have demonstrated that infants diagnosed with CF through NBS have better nutritional outcomes, reduced pulmonary complications, and improved cognitive outcomes (through early correction of Vitamin E deficiency) [18–21]. Data from the US Cystic Fibrosis Foundation Patient Registry also suggest that NBS confers a survival benefit [21].

The benefits of CF NBS on lung disease have been more difficult to demonstrate. NBS diagnosis in the Wisconsin study did not lead to better lung function, but this result was confounded by a higher rate of infection with *Pseudomonas aeruginosa* (a pathogen known to be associated with worse pulmonary outcomes in CF) in the NBS group, highlighting the importance of good infection control practices in CF care [14]. Data from the Australian Respiratory Early Surveillance Team for Cystic Fibrosis study show both physiologic and structural abnormalities of the lung are present by 1 year of age despite diagnosis through NBS [22, 23]. These findings attest to the complexity of treating CF lung disease, the multiple factors involved in pulmonary outcomes, and the limitations of current therapies in affecting lung disease progression. However, the recent development of CFTR modulators that target the underlying defect in CF (see Chap. 6) offers the opportunity for early corrective therapy in infants diagnosed with CF through NBS and potentially preventing progression of lung disease.

4.4.3 CFTR-Related Metabolic Syndrome/Cystic Fibrosis Screen Positive, Inconclusive Diagnosis

In the vast majority of cases CF is either diagnosed or ruled out after a positive NBS test through a combination of sweat Cl concentration and/or genetic analysis. However, in some cases, sweat testing and genetic testing yield indeterminate results. In the US, infants with a positive NBS but

indeterminate diagnostic testing and no symptoms are classified as having CFTR-related metabolic syndrome (CRMS) [24]. CRMS was developed as a diagnostic code to allow care of these infants into the US health care system while avoiding the term CF in the diagnosis. In Europe, the analogous term is CF screen positive, inconclusive diagnosis (CFSPID) [25, 26]. An effort is underway to develop a single definition that can be applied by both terms. The term CRMS/CFSPID can be applied to an infant with a positive NBS and either a sweat Cl <30 mmol/L and 2 CFTR mutations, one of which has unclear phenotypic consequences, or a sweat Cl between 30 and 59 mmol/L and <2 CF-causing CFTR mutations. Infants with CRMS/CFSPID can only be identified through NBS.

Until recently, relatively little was known about the prevalence or outcomes of CRMS/CFSPID. The long-term outcomes remain unknown as children with CRMS/CFSPID have not yet been followed into adulthood. Table 4.4 summarizes the results of recent large cohort studies from multiple sites around the world that have helped shed light into the epidemiology and short term outcomes of CRMS/ CFSPID [27–30]. Differences in study populations and design make it difficult to compare results across studies but several general findings are apparent. The ratio of CF to CRMS cases ranged from 1.8:1 to 5.2:1 [28, 30]. In California, where extended gene analysis identifies numerous mutations with unclear phenotypic consequences, CRMS is actually identified more frequently than CF, with a CF: CRMS ratio of 0.65:1 [31]. In general, infants with CRMS are pancreatic sufficient and their nutritional indices are normal. However, the prevalence of oropharyngeal cultures positive for *P. aeruginosa* ranged from 10.7 to 78.4 %, and some studies have also reported respiratory cultures yielding other CF-related pathogens, such as *Stenotrophomonas maltophilia* [27–30]. In a study by Ooi et al. [28], 11 % of infants with CRMS were reclassified as having CF after additional study of their *cftr* mutations revealed that both were CF-causing. In 14–33 % of cases a repeat sweat test resulted

TABLE 4.4 Summary of recent studies of CFTR-related metabolic syndrome/cystic fibrosis screen positive, inconclusive diagnosis prevalence and outcomes [27–30]

	Ren et al. [28]	Ooi et al. [27]	Grove et al. [26]	Levy et al. [29]
Study design	Prospective cohort	Prospective case control	Retrospective case control	Prospective cross-sectional
Location	USA	Multi-national	Australia	USA
Duration of follow-up (years)	1	3	14[a]	20+
N with CF	1540	3101	225[b]	300
N with CRMS	309	82	29[c]	57
CF: CRMS ratio	5:1	1.8:1	7.8:1	5.2:1
N (%) converting from CRMS to CF	N/A	9[d](10.9)	14[e](48 %)	N/A
N (%) with sweat Cl^f to ≥60 mmol/L	N/A	3 (33 %)	4 (14 %)	N/A
% with *Pseudomonas* isolated from respiratory culture	10.7	14.6	78.6[g]	39

% with *Stenotrophomonas* isolated from respiratory culture	9.4	4.9	N/A	N/A
N (%) developing exocrine pancreatic insufficiency	14 (4.5 %)	0	4 (13.8 %)	0
N (%) with CF genotype F508del/R117H	26.1 %	19.5 %	4 (28.5 %)[g]	36 (63 %)

CF cystic fibrosis, *Cl* chloride, *CFSPID* cystic fibrosis screen positive, inconclusive diagnosis, *CRMS* CFTR-related metabolic syndrome; *N/A* not applicable

[a] 28 % lost to follow-up
[b] Estimated (not reported in the citation)
[c] CRMS definition was different than CRMS/CFSPID
[d] Diagnosed as CF through reclassification of CFTR mutations as CF-causing or increased sweat Cl concentration upon repeat testing
[e] Diagnosed through clinical signs and symptoms of respiratory disease (N=8) or exocrine pancreatic insufficiency (N=6)
[f] Sweat Cl to ≥60 mmol/L
[g] Denominator is 14

in a value ≥60 mmol/L [27, 28]. Grove et al. [27], in a 14-year retrospective study, found that 48 % of infants with CRMS were subsequently diagnosed as having CF, but the clinical features upon which this decision was made were not always specific for CF (eg, recurrent cough).

Sweat Cl concentration in the newborn period does not appear to be a predictor of which infants with CRMS will later develop clinical features of CF disease [29]. The rate of oropharyngeal cultures positive for *P. aeruginosa* was similar in infants with sweat Cl <30 mmol/L compared to infants with sweat Cl 30–59 mmol/L. The genotype F508del/R117H/7 T is commonly found in infants with CRMS, occurring in 23–63 % of patients in recent studies [27–30]. This is consistent with the classification of R117H without the 5 T polymorphism in *cis* as a mutation with varying clinical consequences [9, 32–34].

The US state of California, because of its diverse ethnic and racial population, incorporates gene sequencing in its NBS algorithm [35]. The California definition of a *cftr* mutation is very broad and includes poly T and TG repeats as well mutations with varying clinical consequences. As a result, their program detects 1.5 times as many CRMS cases as CF cases [31], although the majority of these infants appear to have benign outcomes [36].

In summary, although the vast majority of infants with CRMS/CFSPID remain well a small proportion may develop clinical features concerning for CF or even transition into a CF phenotype. Thus, these infants should be followed on a regular basis by clinicians trained in the care of children with CF, such as those at a Cystic Fibrosis Foundation-accredited care center [24]. Recent studies have provided us with more information regarding the prevalence and outcomes of CRMS and serial repeat sweat testing and extended genetic analysis appear to be useful in identifying infants with CRMS/CFSPID who will go on to develop CF. However, many questions remain unanswered, such as the long-term risk for development of CF and the optimal monitoring and management of these infants.

4.5   CFTR-Related Disorder

Inconclusive diagnostic testing can also arise in the evaluation of older patients who present with one or more clinical features associated with CFTR dysfunction but who do not meet the diagnostic criteria for CF. The term CFTR-related disorder (CFTR-RD) is used to describe this group of patients [37]. Patients with CFTR-RD have a single organ affected but they do not have all the clinical features of CF. Conditions associated with CFTR-RD include:

- bronchiectasis;
- chronic sinusitis;
- recurrent/chronic pancreatitis; and
- azoospermia/congenital absence of the vas deferens.

Patients with CFTR-RD, in contrast to infants with CRMS, are symptomatic (Table 4.5); the term should not be applied to infants identified through NBS. In both CRMS/CFSPID and CFTR-RD, diagnostic testing for CF is inconclusive. Similar to CRMS/CFSPID, CFTR-RD patients tend to have *cftr* mutations that result in diminished CFTR function or variable clinical consequences (eg, R117H), but not so reduced as to result in a full CF phenotype.

4.6   Other Diagnostic Tests of CFTR Function

The sweat test remains the most widely available and well-established test of CFTR function. However, sufficient CFTR function in the sweat gland may not always be enough to prevent the development of CF disease features in other organs, such as the lungs. Other diagnostic tests have been developed that target the respiratory or gastrointestinal tract [38], however, these tests are not widely available for clinical use and they require a high degree of expertise to perform properly. Therefore, the sweat test will remain the mainstay for CF diagnosis for foreseeable future.

Table 4.5 Signs and symptoms suspicious for cystic fibrosis

Respiratory manifestations

Recurrent pneumonia or bronchitis

Persistent or difficult-to-treat wheezing
Chronic atelectasis

Unexplained bronchiectasis

Chronic cough

Digital clubbing

Respiratory cultures positive for *Pseudomonas aeruginosa*

Hemoptysis

Nasal polyps

Chronic sinusitis

Gastrointestinal manifestations

Meconium ileus

Failure to thrive

Prolonged neonatal jaundice

Rectal prolapse

Recurrent intussception

Steatorrhea

Fat soluble vitamin deficiencies

  Hemolytic anemia (Vitamin E)

  Bulging fontanelle (Vitamin A)

  Petechiae or purpura (Vitamin K)

Unexplained liver failure

Chronic or recurrent pancreatitis

Other manifestations

Hyponatremic dehydration

TABLE 4.5 (continued)

Metabolic alkalosis

Salty tasting skin

Male reproductive tract abnormalities

Azoospermia

Absent vas deferens

Measurement of nasal potential difference (NPD) is a technique that assesses CFTR function in the nose [39]. In this technique, the nasal mucosa is perfused with a series of reagents designed to activate CFTR or detect its regulatory activity. Changes in NPD reflect CFTR-mediated ion flux. Since the nasal epithelium is part of the respiratory tract, NPD measurements may more accurately reflect CFTR function in the lower respiratory tract. There are several factors that limit the use of NPD measurements as a substitute for sweat testing; the test is more time consuming and expensive and it requires highly trained and skilled operators. Although standard operating procedures have been published standardization remains a challenge. The technique can be difficult to perform in infants and young children who may not cooperate with having their nasal mucosa perfused with fluids. NPD has been shown to be useful in establishing a diagnosis of CF in CRMS/CFSPID infants and older children with intermediate sweat Cl concentrations [40, 41].

Other diagnostic tests of CFTR function utilize intestinal mucosa. Intestinal current measurement (ICM) involves placing intestinal tissue obtained through rectal suction biopsies in an Ussing chamber and, in a manner similar to NPD, perfusing the tissue with different reagents to activate CFTR-mediated ion flux [42]. ICM does not require patient cooperation with the test, although local anesthesia and potentially sedation may be required for the rectal biopsy. However, the test is even less standardized than NPD and less widely available. Another approach to using intestinal tissue to assess CFTR function is to generate organoids from cells isolated from the rectal

biopsy [43]. CFTR activation results in swelling of the organoids, which can readily be observed and quantified by light microscopy. At time of writing, CFTR organoids have great potential and application as a cell-based assay system to test therapies that might restore or augment CFTR function. The procedure requires a highly skilled and experienced operator and it is not widely available for use on a clinical basis.

4.7   Patients with Clinical Features Suggestive of Cystic Fibrosis

In the non-screened population (older patients not screened and those with false negative NBS results) patients will present with clinical features suggestive of CF. The clinical features are wide and varied because CF affects multiple organ systems. Table 4.5 lists some of the signs and symptoms that might warrant diagnostic testing for CF. In many cases patients may present with only a single sign, eg, recurrent rectal prolapse. The best initial diagnostic test remains the sweat test and the overwhelming majority of patients with CF will have a sweat Cl ≥60 mmol/L. If sweat Cl is less than 40 mmol/L and clinical suspicion for CF is still present or the sweat Cl is between 40 and 59 mmol/L, then further genetic analysis and a search for clinical features of CF (eg, azoospermia) should be performed. Most commercial CFTR mutation panels test for CF-causing mutations associated with an intermediate or high normal sweat Cl (eg, $3849+10$ kb C→T). Complete sequencing of the coding region of the *cftr* gene can also be performed but if the results yield mutations with varying clinical consequence or unknown disease-causing potential the diagnosis of CF may still be unresolved.

4.8   Conclusion

As a result of advances in understanding CFTR genetics and the growth of CF NBS the US CF Foundation has held periodic diagnosis consensus conferences. The most recent

One or more of the following:
Clinical features suggestive of cystic fibrosis
Positive family history of cystic fibrosis
Positive newborn screen

AND

Sweat chloride ≥60 mmol/L on two or more occasions

OR

Two cystic fibrosis-causing CFTR mutations
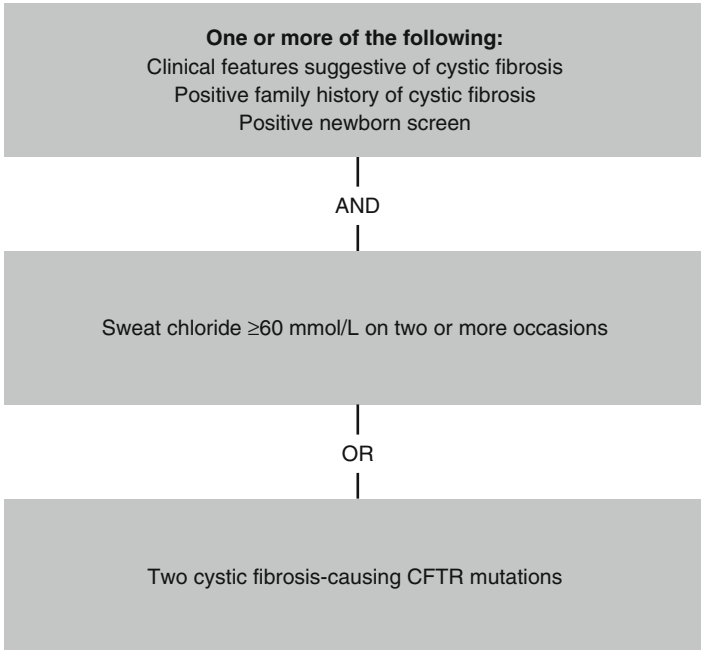
FIGURE 4.2 The US cystic fibrosis foundation criteria for diagnosis of cystic fibrosis (Adapted from Farrell et al. [7])

US Cystic Fibrosis Foundation consensus criteria from 2008 are summarized in Fig. 4.2. A conference to update these criteria was held in October 2015. The final document from that conference is still pending, but it is likely to incorporate updated information on CFTR genetics, CF NBS and CRMS/CFSPID, and diagnostic thresholds for sweat Cl.

Despite advances in our understanding of CFTR genetics and the development of CFTR functional assays other than sweat testing, there will always be some patients for whom the clinical, laboratory, and genetic data are still insufficient to definitively make the diagnosis of CF. In these cases, the diagnosis of CF must remain a clinical decision.

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Chapter 5
Monitoring and Evaluation of Patients with Cystic Fibrosis

5.1 Overview

The monitoring of individuals with cystic fibrosis (CF) has become increasingly complex, as the benefits of screening for complications and proactive early intervention have been realized. The era of newborn screening (NBS) has provided a wealth of information that has demonstrated the importance of optimal nutrition early in life. The prognosis of an individual patient is closely tied to his or her nutritional status and, therefore necessitates close attention to growth parameters. Lung disease is an overwhelming cause of morbidity and mortality, and monitoring of lung disease is an essential component of CF care.

5.2 Nutritional Status

The single most important factor for health maintenance in CF is the ability to achieve an adequate nutritional status [1]. This has been defined as a weight-for-length ≥ the 50th percentile and as a weight-for-age ≥ the 10th percentile in infants and children less than 2 years of age. A body mass index (BMI) percentile ≥ the 50th percentile for age is recommended for children and adolescents aged two through 20 years. An absolute BMI of ≥23 for men and ≥22 for women

is the target for adults with CF [1]. The US Cystic Fibrosis Foundation Infant Care Guidelines suggest monthly monitoring of infants diagnosed through NBS for at least the first 6 months [2]. Monitoring of children and adults may be spaced to quarterly visits in patients with adequate and stable nutritional status and lung disease. It is important to obtain a detailed diet history from patients on an annual basis, or more frequently for those with suboptimal nutritional status. It is important to track linear growth for infants and children, as it relates to predicted height.

Fat soluble vitamin deficiency is another manifestation of CF that requires regular monitoring. Levels of fat soluble vitamins should be checked within a few months of beginning treatment for CF, and these should be repeated on at least an annual basis. Vitamin A, vitamin E, and 25-hydroxyvitamin D levels should be measured. Vitamin K status can be monitored with coagulation studies (eg, prothrombin time), but this may be abnormal only in cases of severe deficiency; proteins induced by vitamin K absence (PIVKA) testing may provide a more accurate measure. Infants born with meconium ileus who have undergone extensive bowel resection, particularly the terminal ileum, should have vitamin B12 levels checked [3].

5.3   Gastrointestinal Disease

The majority of infants (nearly 60 %) with CF have evidence of exocrine pancreatic insufficiency (PI) shortly after birth. An additional 25 % will lose pancreatic function during the first few months or years of life [4]. It is important to obtain a stool specimen for the measurement of fecal elastase (FE) at diagnosis. If this is initially normal and growth proceeds normally, then annual monitoring is sufficient. Low values (<200 mcg/g stool) indicate the need for pancreatic enzyme replacement therapy (PERT) [2]. FE measures only human elastase, it is unaffected by PERT, and patients can be started on PERT for clinically diagnosed PI while obtaining FE to

confirm the diagnosis. Fecal fat measurements may also be obtained, but they are cumbersome to perform. In order to calculate an accurate coefficient of fat absorption, a detailed dietary history and stool collection should be performed over a 72 h period. In general measurement of FE is the simplest way to assess for PI, but measurement of fecal fat may be helpful to determine the adequacy of PERT. Cholecystokinin/secretin-stimulated pancreatic function testing may also be used to detect PI.

A detailed stool history is important both to assess adequacy of PERT as well as to ascertain the presence of constipation. Constipation is common and may be a precursor to distal intestinal obstruction syndrome (DIOS) [5], which can become a medical emergency. Gastroesophageal reflux disease (GERD), peptic ulcer disease, and recurrent pancreatitis are all complications that are common in the CF population, and clinicians screen for these conditions through obtaining appropriate patient history and performing diagnostic testing if a high index of suspicion develops [6, 7].

Cystic fibrosis-associated liver disease (CFLD) is common in CF, and may affect up to 10–20 % of individuals, although the true incidence of subclinical biliary tract abnormalities is unknown [8]. Manifestations may include focal biliary cirrhosis, large bile duct disease, cholelithiasis, and hepatic steatosis. Annual screening with laboratory studies, which may include alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), and alkaline phosphatase, is recommended. More frequent monitoring is recommended for persistently elevated levels. If values are elevated greater than 1.5–2 times of the upper limit of normal or physical examination findings suggest organomegaly then further evaluation with abdominal ultrasonography is indicated. Unfortunately, these laboratory studies are relatively insensitive at detecting early CFLD. Portal hypertension and cirrhosis may develop in a minority of individuals [8].

Screening for intestinal health may also be important for adults with CF. There may be an increased incidence of

malignancy [9]. The long-term use of high doses of PERT has also been linked to the development of fibrosing colonopathy [4].

5.4   Lung Disease

Monitoring for the development of respiratory disease is often difficult to elicit by history in the very young, and even in older individuals. Inflammation and infection may exist in the neonatal airway in CF in the absence of symptoms. A combination of radiographic, microbiologic, and lung function surveillance tools are recommended to detect respiratory disease and to direct appropriate management.

5.4.1   Chest Imaging

An annual chest radiograph (CXR) is usually performed to assess for progression of lung disease, although the sensitivity of CXRs for detecting small airway changes or early lung disease is poor. CXRs in asymptomatic individuals may appear normal or reveal air trapping, bronchial thickening, or evidence of mucous plugging. Chest computed tomography (CT) is more sensitive at detecting early lung disease, although most clinicians are reluctant to repeatedly expose patients to ionizing radiation, especially if they are young [10]. Additionally, the ability to perform CT scans in infants and young children in many instances is hampered by the need for sedation in order for them to lie still or to administer positive pressure ventilation. There are no data that demonstrate regular chest CT imaging results in improvement of pulmonary outcomes, and its role in routine monitoring is generally not recommended. Recently, the development of magnetic resonance imaging (MRI) techniques, using both traditional proton MRI as well as ultra-short echo time and hyperpolarized gas MRI, has raised the possibility of obtaining images equal to chest

CT while avoiding the ionizing radiation risk [11, 12]. However, at present MRI remains an investigational technique.

5.4.2   Physiologic Assessments

The measurement of lung function is a mainstay of pulmonary disease monitoring in CF and the most widely used and available method is spirometry. Infant pulmonary function testing may be performed in infants and children less than 2 years of age but it is not widely available due to the considerable resources required and the need for sedation. In patients with CF aged 6 years and older, spirometry should be performed at least quarterly and if the patient presents with increased respiratory symptoms or abnormal chest exam. Forced expiratory volume in 1 s (FEV_1) is the parameter that has the best predictive value for pulmonary health in CF. In many children the FEV_1 may be normal but small airway obstruction may be evident with a reduced FEV_1/forced vital capacity (FVC) ratio or forced expiratory flow between 25 and 75 % (FEF_{25-75}) and a concave shape of the flow volume loop. Traditionally, it was thought that reliable spirometric data cannot be obtained in children under 6 years of age, but spirometry has been successfully performed in 3–5 year olds with CF [13]. Most CF care centers begin attempting spirometry as early as 3 years of age in a cooperative child.

Full lung volume measurement by plethysmography may provide additional information regarding the degree of pulmonary impairment. Even early in the disease course with preservation of normal FEV_1, there may be an elevated residual volume that may indicate air trapping as a result of small airway obstruction. As CF lung disease progresses a reduction of vital capacity may become apparent on spirometry due to severe airflow limitation from advanced bronchiectasis and bronchomalacia. Lung volume may be further compromised by chronic atelectasis, inspissated secretions in the airways, and scarring.

Multiple breath washout (MBW) is a test for the detection of ventilation inhomogeneity and may be a more sensitive indicator of early CF lung disease when compared to spirometry [14, 15]. The MBW technique consists of patients breathing a mixture containing ambient air and a tracer gas (eg, sulfur hexafluoride) until the lungs are filled with the gas mixture ('wash in' phase). They then breathe ambient air until the fraction of tracer gas falls below a detectable level ('wash out' phase). Alternatively, instead of using a tracer gas, the resident nitrogen in the lungs can be washed out by breathing 100 % oxygen. The lung clearance index (LCI) may be derived from MBW and is a measure of the number of lung volumes equivalent to functional residual capacity that is needed to complete turnover of the resident gas in the lungs. In the setting of ventilation inhomogeneity the LCI is elevated. At time of writing, the routine clinical use of MBW in CF is still in evolution.

5.4.3   Assessment of Early Lung Disease

Research in recent years has shown that the process of infection, inflammation, and permanent lung damage begins early in infancy. Although FEV_1 has been the traditional method to assess CF lung disease, it is an insensitive measure early in the course of the disease. Even though median FEV_1 in children 6–12 years old with CF in the US is 97 % [16], extensive bronchiectasis can frequently be seen on chest CT imaging, and children with a normal FEV_1 can frequently have an elevated LCI [15, 17]. These observations have prompted investigators to search for better measures of early lung disease. As discussed above, MRI is an attractive alternative to chest CT because the lack of ionizing radiation makes it a safer alternative for repeated imaging. MBW is also a potential method to detect early changes in lung disease. LCI is elevated in a substantial number of young children with CF and an abnormal LCI at ages 3–5 years is predictive of abnormal FEV_1 by 6 years of age, suggesting that LCI is a physiologically

relevant measure [14]. There are some issues that need to be resolved before applying MBW in routine clinical care, including establishing a minimal clinically important difference in change after treatment or over time and standardization of equipment and technique for different age groups. Imaging and MBW may also offer complementary information regarding the nature of lung disease in individual patients. Further research is needed to develop these techniques as clinical tools and to define their role in routine monitoring of CF lung disease, especially in infants and young children.

5.5   Microbiology

The respiratory flora in CF may change with age, during illnesses, and with disease progression. Certain infections, eg, *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, and *Burkholderia cepacia* complex, have been associated with worse pulmonary disease or an accelerated decline of lung function [18]. Therefore, it is critical to detect infection with these organisms early and in some cases attempt eradication. Microbiologic surveillance may be performed with oropharyngeal (OP) swabs, expectorated sputum, or bronchoalveolar lavage (BAL). Infants and young children (as well as many adolescents and adults with better lung function) are unable to expectorate sputum. Some individuals may respond to sputum induction with hypertonic saline. BAL is not recommended for routine surveillance but may be considered if the individual with CF has an unexplained decline of health, new radiographic findings, or a failure to respond to treatment directed against organisms obtained by OP or sputum culture. A large Australian multi-center randomized trial failed to show a benefit of BAL-directed compared to standard therapy for infants and young children with CF [19]. Respiratory cultures should be obtained at least quarterly. In addition, it is important to routinely screen for non-tuberculous mycobacteria (NTM) in patients who

receive chronic macrolide therapy, as NTM infection is a contraindication to this treatment. Fungal disease may also occur in CF and should be considered if treatment directed against other organisms is unsuccessful. Although not a primary infection, allergic bronchopulmonary aspergillosis (ABPA) is a form of hypersensitivity pneumonitis with allergic features that occurs more frequently in the CF population. Screening for ABPA is done by measuring total serum IgE. An IgE >1000 ng/mL should prompt further diagnostic evaluation for ABPA, which consists of testing for precipitating antibodies and antigen specific IgE to *Aspergillus fumigatus*. IgE should be measured at least annually and if there is unexplained decline of lung function, refractory wheezing, new infiltrates on radiographic imaging, or peripheral eosinophilia [20].

5.6   Endocrine Disease

The development of CF-related diabetes (CFRD) may be a critical determinant of pulmonary prognosis in many individuals. CFRD incidence increases with age and has an overall prevalence of 35 % in the CF population, including a majority of people over 40 years of age [21]. Adequate glycemic control is essential to the preservation of both lung function and nutritional status and early recognition is considered important. Children and adults with CF are at increased risk for poor bone health and pre-adolescents have been found to have low bone density. The effects of corticosteroids, disease severity, delayed puberty, dietary factors, vitamin D and K status, and activity level may adversely affect bone health in CF.

5.6.1   *Cystic Fibrosis-Related Diabetes*

Routine glucose measurements should be obtained with annual laboratory studies for all individuals with CF. Any random value greater than 200 mg/dL warrants follow-up testing. Hemoglobin A1c (HbA1c) measurement is a poor

screening test in CF and is not recommended for those without impaired glucose tolerance or CFRD. Values for HbA1c may remain relatively normal in the presence of post-prandial hyperglycemia in the setting of impaired glucose tolerance. The gold standard for the diagnosis of CFRD is the 2 h oral glucose tolerance test; this test should be performed after fasting with an administered dose of 1.75 g/kg glucose. The US Cystic Fibrosis Foundation recommends that screening for CFRD should begin at 10 years of age [22]. A fasting value greater than 126 mg/dL (7 mmol/L) or a 2 h level greater than 200 mg/dL (11.1 mmol/L) is indicative of CFRD. A normal fasting glucose with a 2 h level between 140 and 200 mg/dL (7.8–11.1 mmol/L) demonstrates impaired glucose tolerance and warrants closer monitoring. In those patients with CF who have been diagnosed with CFRD, HbA1c monitoring is necessary with a goal of <6.5 %. Patients with CFRD should be monitored for microvascular complications of diabetes, including urine testing for microalbuminuria and ophthalmologic screening.

5.6.2   Osteopenia

Routine screening for decreased bone mineralization is controversial for the pediatric CF population. Although, children with poor nutrition, delayed puberty, history of bone fractures, or other risk factors (frequent or chronic corticosteroid use) should undergo an endocrinologic evaluation including bone densitometry. The US Cystic Fibrosis Foundation recommends screening with a dual-energy X-ray absorptiometry (DEXA) scan to measure bone mineral density at age 18 years [23]. If bone mineral density is normal scans should be repeated every 5 years. If the z-score is between −1 and −2, studies should be repeated in 2–4 years, and if −2 or less, treatment should be considered and the DEXA scan repeated annually. Aggressive nutritional support is imperative to maintain good bone mass and to prevent the development of CF-related bone disease.

5.7   Sinus Disease

Radiographic chronic pansinusitis is present in the vast majority of individuals with CF and nasal polyposis may occur in up to 50 % of individuals [24]. At this time there is no recommended surveillance for chronic sinusitis. Intervention and subspecialty referral to otorhinolaryngology is based on patient-reported symptoms in conjunction with physical exam findings.

5.8   Reproductive and Sexual Health

Genetic counseling should be provided to parents following the diagnosis of CF in their child in order to understand the implications for future pregnancies. Such counseling should be offered to adolescents and adults with CF as well. It is important to recognize that adolescents with CF face the same challenges with regard to sexual development, gender identity, and relationships as those without CF. Almost all males with CF have obstructive azoospermia (98 %) and congenital bilateral absence of the vas deferens. Semen analysis can be performed for adolescent and adult males to determine fertility status. While female fertility may be impaired to a lesser degree, some women may require further endocrinologic evaluation if they cannot conceive. Fertility issues notwithstanding, contraceptive options and prevention of sexually transmitted infections should be addressed [25].

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Chapter 6
Treatment of Cystic Fibrosis

The treatment of cystic fibrosis (CF) requires a multi-pronged approach to target dysfunction in a number of organ systems. Although the advent of cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies heralds a new era in CF care, their full impact on CF remains to be determined, and older patients with CF are likely to still have complications of CF that need to be addressed.

6.1 Gastrointestinal Disease and Nutrition

6.1.1 Pancreatic Enzyme Replacement Therapy

Approximately 85 % of patients with CF are pancreatic insufficient (PI), and pancreatic enzyme replacement therapy (PERT) is empirically prescribed for patients with PI genotypes or who present with clinical features suggestive of malabsorption [1]. Once the diagnosis of PI is confirmed the use of PERT is universally indicated. For most individuals, a lipase dose of 2000–2500 units of lipase per kg per meal is preferred and a maximum daily lipase dose of 10,000 units/kg should be maintained if possible [2]. There are differing clinical responses to various brand name enzyme preparations so close attention should be given to the medication that is dispensed. The use of acid blocking therapy, such as H2 receptor antagonists and

proton pump inhibitors, is common due to deficient bicarbonate secretion and altered intestinal pH that is associated with exocrine pancreatic failure [3]. These agents may help raise duodenal pH and improve the action of pancreatic enzyme supplements. Poor mealtime behaviors in some young children with CF may adversely affect caloric intake and cognitive behavioral therapy may be beneficial [4].

6.1.2   Caloric Supplementation

There is a well-established link between nutritional status and lung function (Fig. 6.1). Nutrition early in life is especially important, since poor nutrition in early childhood is associated with lower lung function in later childhood and decreased survival [5, 6].

Patients with CF have high caloric requirements; caloric supplementation is often required whether they are PI or not. Breast milk is the preferred source of nutrition for infants with CF and supplementation with fortifier, formula powder, and lipids may be necessary to achieve adequate growth. Infants should not be fed soy formula, since soy
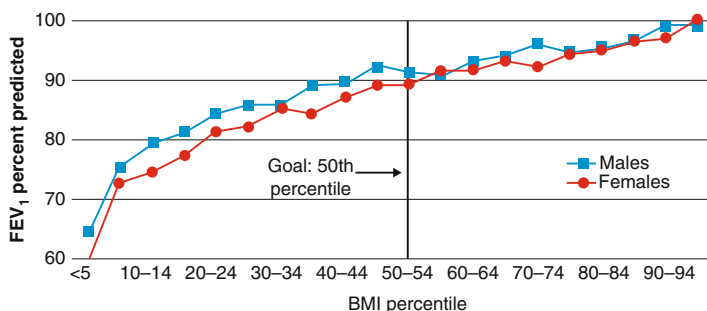

FIGURE 6.1   Median forced expiratory volume in 1 s predicted versus median body mass index percentile for children between 6 and 19 years old. The goal of the US Cystic Fibrosis Foundation is for all patients with cystic fibrosis to have a body mass index in at least the 50th percentile. *BMI* body mass index, *FEV1* forced expiratory volume in 1 s

protein appears to be have less bioavailablity compared to cow's milk or breast milk proteins. High fat diets are encouraged in children and adults. Commercial oral supplements are often used to bolster caloric intake. However, there are still many individuals that will have tremendous caloric needs that may necessitate consideration of gastrostomy tube placement, or in some cases jejunostomy tube placement, to provide enteral feeding. Supplemental enteral feedings have been demonstrated to improve nutritional outcomes in CF [7–9].

Poor appetite is reported by many patients and appetite stimulation may be attempted. Cyproheptadine may be an effective treatment for anorexia in CF and is most effective during the first few months of use. Cyprohepatidine may be preferable to megesterol or drorabinol, as the former has exogenous steroid effects that may be unacceptable [10].

6.1.3 Other Supplemental Therapy

Despite use of PERT, most patients with CF who are PI require supplementation of the fat soluble vitamins A, E, D, and K. Some individuals may require additional supplementation of individual vitamins depending on serum levels. Annual monitoring of vitamin levels is indicated, with more frequent follow-up of suboptimal levels after additional supplementation [2]. Salt supplementation is recommended during infancy, and a high salt diet is generally recommended in older children and adults. This is of particular importance for patients who incur high sodium losses through sweat, and are therefore at risk for the development of hyponatremic dehydration [11].

6.1.4 Hepatobiliary Disease

The management of hepatobiliary disease in CF can be challenging as it is often clinically silent [12–14]. Many individuals with elevated transaminases or ultrasonographic evidence of disease

may not develop progressive liver disease regardless of treatment. Ursodeoxycholic acid is frequently prescribed to improve bile flow in patients with chronic CF-related liver disease, although there are no data regarding its effectiveness in delaying the progression of CF liver disease. There is an increased risk for cholelithiasis and cholecystitis in CF that may require surgical management in symptomatic individuals. The need for liver transplantation due to CF-related hepatobiliary disease is uncommon and is reserved for those patients with recurrent variceal bleeding from severe portal hypertension or synthetic dysfunction due to end-stage cirrhosis and hepatic failure.

6.1.5   Intestinal Obstruction

Chronic constipation is a common complication in CF. The management of constipation in CF may include stool softeners and increased fluid intake. Polyethylene glycol (PEG) solutions have been advocated for treatment of CF-related constipation. Distal intestinal obstruction syndrome (DIOS) is a related gastrointestinal (GI) complication of CF that is thought to result from impaction of mucus and stool in the GI tract of patients with CF, leading to small bowel obstruction at the terminal ileum and ileocecal valve [15]. Initial treatment of DIOS is similar to management of any bowel obstruction. If the patient is vomiting, a nasogastric (NG) tube should be placed to decompress the stomach. Polyethylene glycol can then be administered either orally or via the NG tube, initially at low volume and then increasing until the bowels are cleared out of stool and mucus. N-acetylcysteine or gastrograffin enemas can also be used to relieve distal obstruction at the ileocecal valve. Surgical intervention is a last resort and usually not required.

6.2   Pulmonary Disease

Pulmonary disease and respiratory failure is the overwhelming cause of morbidity and mortality in CF. Treatment of CF lung disease has evolved from acute treatment focused on

Table 6.1 Chronic pulmonary therapies used in patients with cystic fibrosis. Therapies are grouped by class or mechanism of action

Chronic pulmonary therapies used in patients with cystic fibrosis
Airway clearance therapies
Manual chest percussion
High frequency oscillating chest wall devices
Hand-held oscillatory positive pressure devices
Autogenic drainage/active cycle of breathing techniques
Anti-infectives
Inhaled tobramycin[a]
Inhaled aztreonam[a]
Mucolytics
DNase[a]
Hydration therapies
Hypertonic saline[a]
Anti-inflammatory therapy
Oral corticosteroids
High dose ibuprofen
Low dose azithromycin[a]

[a]Denotes that the therapy has been shown to reduce the risk of pulmonary exacerbation

symptom relief to a chronic therapy approach to maintain pulmonary health and prevent exacerbations. Table 6.1 summarizes the chronic pulmonary therapies currently used in patients with CF. The number of therapeutic options has increased markedly in the last few years, and one of the challenges facing CF clinicians and their patients is balancing the potential benefits of multiple therapies with the increased treatment burden.

6.2.1   Airway Clearance Therapies

The mainstay of preventative pulmonary treatment is airway clearance, which is introduced at or shortly after diagnosis [16]. Airway clearance facilitates mucus transport and can alleviate bronchial obstruction by secretions [17]. There are various modalities that can be used, depending on age. Instruction on chest percussion with postural drainage is initially taught to parents of infants and young children with CF. High frequency oscillating chest wall devices are commonly prescribed as they are less labor-intensive and thus can be managed by one caregiver or by the patient without assistance. These devices consist of an inflatable vest that surrounds the thorax. The vest is connected via a hose to a compressor that generates low amplitude, high frequency pressure oscillations, which in turn create shear forces in the airway that help mobilize airway secretions. Hand-held oscillatory positive pressure devices are another option. These devices use the patient's own expiratory flow to generate intraluminal pressure oscillations. Autogenic drainage and active cycle of breathing are techniques that utilize inspiratory and expiratory maneuvers for airway clearance. There have been very few studies comparing the efficacy of one method over another and the US Cystic Fibrosis Foundation guidelines do not recommend a specific method [16], although they do note that individuals may respond better to one method than another so airway clearance therapy should be personalized for the patient [16].

Standard instruction involves performance of airway clearance twice daily, even in asymptomatic patients. During illness and for those with progressive bronchiectasis the frequency of airway clearance should be increased and the use of different modalities should be considered. An active lifestyle should be encouraged in children and adults with CF. A daily exercise program is considered an important adjunct for the maintenance of pulmonary health and can augment the benefits of airway clearance.

Exercise has also been associated with higher quality of life scores and less severe respiratory scores on validated questionnaires [18].

6.2.2   Bronchodilators

Bronchial hyperresponsiveness is present in more than 30 % of patients with CF [19] and bronchodilators have been recommended for routine use in the past, although evidence is lacking for their efficacy. The most recent version of the US Cystic Fibrosis Foundation clinical practice guidelines does not recommend for or against their use [20]. It remains common to prescribe bronchodilators in conjunction with airway clearance or prior to hypertonic saline (HS) administration. The latter therapy can sometimes be associated with bronchoconstriction, hence the rationale of pretreatment with a bronchodilator. In most cases, the bronchodilator used is a selective beta-2 agonist, such albuterol. However, there is some evidence to suggest that anticholinergics, such as ipratropium, may also be beneficial [21, 22].

6.2.3   Dornase Alfa

Dornase alfa (recombinant human DNase 1) is an endonuclease that cleaves long filamentous strands of DNA into shorter pieces. CF sputum contains copious amounts of DNA, primarily derived from neutrophils, and DNase can help markedly reduce sputum viscosity. Dornase alfa therapy has been demonstrated to increase lung function and decrease pulmonary exacerbations [23]. It is recommended for routine use once daily in children over 6 years of age and adults [20]. Its use in patients under 6 years of age has become increasingly common, particularly in those with chronic respiratory symptoms or other evidence of lung disease. Its use is recommended in children aged 2–5 years, depending on the child's symptoms or history [24]. The use of twice daily dornase alfa has been employed in more

advanced bronchiectasis, although there is no evidence to support this increased frequency.

6.2.4   Hypertonic Saline

HS is thought to help rehydrate the airway surface liquid (ASL) through increasing the tonicity and passively drawing in tissue water. Elkins et al. [25] demonstrated that chronic HS therapy resulted in increased forced expiratory volume in 1 s (FEV_1) and reduced pulmonary exacerbations in patients aged 6 years and older. A large randomized trial of HS in children younger than 6 years of age with CF failed to demonstrate an effect on its primary outcome measure, pulmonary exacerbation, although there were physiologic improvements [26]. The US Cystic Fibrosis Foundation currently recommends chronic HS therapy in patients ≥6 years old and its use can be considered for patients 2–5 years of age [20, 24].

6.2.5   Anti-inflammatory Therapies

With the increased understanding of the important role inflammation plays in the pathogenesis of CF lung disease clinicians and investigators have long sought safe, easily administered, effective anti-inflammatory therapies. Despite this, such a treatment is still not available. Caution regarding anti-inflammatory therapy has been raised. In a randomized trial of an oral leukotriene B4 receptor antagonist in CF there was a higher rate of pulmonary exacerbations in the treatment group, suggesting that excessive attenuation of the inflammatory response may have unwanted deleterious effects [27].

High dose ibuprofen (HD-Ibu) has been shown to inhibit neutrophil migration in rodent models of chronic *Pseudomonas aeruginosa* infection, and based on this observation a randomized clinical trial of HD-Ibu was conducted in patients with CF ≥5 years of age [28]. The results of this

study showed that the treatment group had a slower rate of decline in FEV_1 (-1.48 ± 0.69) compared to the placebo group (-3.57 ± 0.65) [26]. Children between 5 and 17 years of age had the greatest benefit, suggesting that the treatment is more effective in patients with less advanced or established bronchiectasis. The dose for HD-Ibu is 20–30 mg/kg twice daily, which is much higher than standard antipyretic or analgesic doses. Furthermore, individual pharmacokinetics must be performed on a biannual basis to ensure that an ibuprofen serum concentration of 50–100 mg/L is achieved. The need for individual pharmacokinetic studies and concern about potential adverse effects, such as gastrointestinal bleeding and renal disease, may be reasons why very few patients are on HD-Ibu [29]. Nonetheless, the data regarding HD-Ibu serve as important proof-of-concept evidence of the role of inflammation in the pathophysiology of CF lung disease and the therapeutic efficacy of anti-inflammatory therapy.

Macrolide antibiotics also appear to have an anti-inflammatory effect that is independent of their antimicrobial properties. Randomized clinical trials of azithromycin 250 mg (or 500 mg if weight is >40 kg) three times weekly have demonstrated improved FEV_1 in patients ≥6 years old who are chronically infected with *P. aeruginosa* [30] and a lower rate of pulmonary exacerbations in patients 6–18 years old without *P. aeruginosa* infection [31]. Based on these results the US Cystic Fibrosis Foundation currently recommends that chronic azithromycin therapy be considered in patients with CF ≥6 years of age [20]. Contraindications for this treatment include the presence of non-tuberculous mycobacterial (NTM) infections or severe liver disease.

Oral and inhaled corticosteroids have been studied in CF [32]. Alternate day prednisone can improve lung function, but at the cost of growth retardation, glucose intolerance, and cataract formation [33]. They are not recommended for routine use, although some clinicians may use them in severe or advanced lung disease, and they clearly have a role in treatment of allergic bronchopulmonary aspergillosis (ABPA). Inhaled corticosteroid (ICS) therapy has been associated with a lower rate of FEV_1 decline [34]. Although, there have

been no randomized clinical trials of ICS that demonstrate improvement in lung function or reduction in pulmonary exacerbation rates. The US Cystic Fibrosis Foundation currently recommends against routine use of ICS in the absence of a diagnosis of asthma [20]. Despite this recommendation approximately 50 % of patients with CF in the US are receiving ICS therapy [35].

6.2.6   Anti-Infective Therapy

Another hallmark of CF lung disease is chronic bacterial airway infection, and antibiotic therapy has a major role in the treatment of CF [36]. Antibiotics can be administered chronically and acutely, as well as via the oral, inhaled, and intravenous route.

The persistence of *P. aeruginosa* in CF respiratory cultures is associated with a more rapid deterioration of pulmonary function as well as increased mortality [37]. Surveillance for *P. aeruginosa* infection using oropharyngeal swab or sputum cultures has become standard of care in CF. Eradication of *P. aeruginosa* infection at first isolation can be achieved with the use of 28 days of inhaled tobramycin with or without the addition of ciprofloxacin. A culture based regimen, where respiratory cultures are obtained quarterly and antibiotics are only given if *P. aeruginosa* is cultured, is equally effective as a cycled treatment regimen, where antibiotics are given quarterly regardless of respiratory culture results [38]. Similar eradication regimens have been achieved with the use of colistimethate and aztreonam [39, 40].

Inhaled antipseudomonal antibiotics increase lung function and reduce pulmonary exacerbations in patients with chronic *P. aeruginosa* infection. The alternate month use of inhaled tobramycin solution twice daily, or inhaled aztreonam lysine three times daily, have both been studied and are effective regimens in improving lung function and reducing the risk of pulmonary exacerbations [41, 42]. Both treatment strategies have been demonstrated to reduce pulmonary exacerbations and improve lung function, even in patients

with mild disease [43, 44]. The use of inhaled vancomycin for individuals with methicillin-resistant *Staphylococcus aureus* (MRSA) is under investigation. A dry powder formulation of colistimethate sodium for inhalation is available in Europe for the treatment of patients with CF and *P. aeruginosa* infection, but this medication is not available in the US at time of writing.

With regard to chronic oral antistaphylococcal antibiotics, their routine use is not currently recommended by the US Cystic Fibrosis Foundation, although it is common practice in other countries [45]. While there is a decrease of staphylococcal burden with chronic antibiotic use the emergence of earlier *P. aeruginosa* infection has tempered antistaphylococcal use in the US.

6.2.7   Pulmonary Exacerbations

Treatment of pulmonary exacerbations remains highly variable and there is a paucity of high quality evidence to guide treatment. The Pulmonary Therapies Committee of the US Cystic Fibrosis Foundation has suggested guidelines for management of exacerbations, including recommendations regarding site of treatment (in hospital versus outpatient), number of antibiotics used and dosing of antibiotics targeting *Pseudomonas*, and synergy testing. They do not make specific recommendations regarding duration of treatment [46].

Early recognition of symptoms is imperative in order to treat an exacerbation and avoid hospitalization or parenteral antibiotics. Increasing airway clearance and the early use of oral antibiotics directed against the individual's microbiology are cornerstones of treatment. In individuals with more severe or rapidly progressive symptoms, or in those who fail to respond to first-line treatment, parenteral antibiotics and more aggressive airway clearance are used. Traditionally, the choice of antibiotics has been based on organisms that are recovered from respiratory cultures, although there is evidence to suggest that clinical response is not related to in vitro antibiotic sensitivities [47].

Monotherapy is often used for the treatment of methicillin-sensitive *Staphylococcus aureus* (MSSA) and MRSA, whereas a two drug regimen is typically used for patients with *P. aeruginosa* infections. An aminoglycoside (tobramycin or amikacin) in addition to a beta-lactam (ceftazidime, piperacillin/tazobactam, meropenem), monobactam, or quinolone is preferred. The duration of treatment is traditionally 14 days, although shorter duration of treatment may be effective in some individuals. Conversely, some patients may benefit from up to 21 days of therapy, although treatment beyond that duration is unlikely to provide additional benefit. Patients who received multiple courses of aminoglycoside as part of their pulmonary exacerbation treatment should be routinely screened for hearing loss and kidney injury. Treatment of *Burkholderia cepacia* complex infections is often more challenging due to antibiotic resistance. A variety of agents have been used including ceftazidime, meropenem, trimethoprim/sulfamethoxazole, and minocycline. The presence of other resistant Gram-negative rods, such as *Stenotrophomonas maltophilia* or *Achromobacter xylosoxidans*, can further complicate the clinical picture, however, the causative effect of these bacteria on exacerbations is not clearly understood.

Atypical infections are also encountered in the CF airway and may lead to worsening pulmonary disease. Fungal disease unrelated to ABPA may be targeted with antifungal treatment, based on sensitivities. Non-tuberculous mycobacteria (NTM) are seen with increasing prevalence as the CF population ages. *Mycobacterium avium* complex (MAC) infections are the most common, followed by 'rapid growers' such as *Mycobacterium abscessus* complex infections [48]. These latter organisms have been associated with severe lung disease in some cases. Treatment of mycobacterial infections is difficult and may require three or four agents for 9 months or longer. Recent consensus guidelines for management of mycobacterial infections have been published by the US Cystic Fibrosis Foundation and European Cystic Fibrosis Society [49].

6.2.8 Other Pulmonary Complications

ABPA is a hypersensitivity pneumonitis with allergic features that occurs more commonly in the CF population [50]. Treatment generally is with systemic glucocorticoids, and may also include antifungals or anti-immunoglobulin E (IgE) antibody therapy [51].

Hemoptysis and pneumothoraces are two other pulmonary complications that can occur in patients with CF. Hemoptysis can range from scant streaks of blood in sputum to massive, life-threatening hemorrhage. The US Cystic Fibrosis Foundation Pulmonary Guidelines recommend that for scant amounts of hemoptysis (<5 mL), airway clearance and nebulized therapies should be continued, but there is no consensus as to whether antibiotics need to be prescribed in the absence of other symptoms of an exacerbation [52]. In the case of major hemoptysis, intravenous antibiotics are indicated, with some clinicians advocating empiric coverage for *S. aureus* while awaiting culture results. Guidelines also recommend discontinuing chest physiotherapy, HS, and non-steroidal anti-inflammatories. When a patient is clinically unstable or when bleeding is persistent or recurrent bronchial artery embolization is recommended. It is successful in stopping bleeding in most cases but recurrence is relatively common, often requiring re-embolization. Surgical resection is generally reserved for times when all other options have been exhausted, with lobectomy being the most common procedure performed.

Pneumothoraces in patients with CF can similarly have a wide range of severity. Cystic Fibrosis Pulmonary Guidelines recommend that patients with larger pneumothorax should be admitted to the hospital and should have a chest tube placed for drainage [52]. Pleurodesis is recommended for patients who develop a recurrence of large pneumothorax. Recurrence is fairly common and is seen in over half of patients. A surgical pleurodesis is recommended over chemical pleurodesis [52]. The US Cystic Fibrosis Foundation Pulmonary Guidelines recommend that positive pressure,

such as continuous positive airway pressure or bilevel positive airway pressure, be withheld until the air leak has resolved. Patients should not perform spirometry, fly on a plane, or lift weights for at least 2 weeks following resolution of the pneumothorax.

6.2.9   Lung Transplantation

Patients who develop progressive loss of lung function with subsequent evidence of chronic respiratory failure, frequent pulmonary exacerbations, and poor quality of life may be candidates for bilateral lung transplantation [53]. A variety of risk models have been developed to identify patients who are more likely to benefit from lung transplant and should be listed [54]. Specific criteria for listing vary by transplant center and incorporate considerations of disease severity and adherence. Important predictors of success following lung transplantation include nutritional status, exercise tolerance, and microbiology. While 1 year post-transplantation survival statistics are favorable (around 90 %), 5-year outcome data continues to demonstrate survival at 50–60 % [55]. The main cause of long-term death is bronchiolitis obliterans syndrome (BOS). BOS is characterized by progressive narrowing and ultimately fibrosis of the small airways as a result of chronic graft rejection.

6.3   Cystic Fibrosis-Related Diabetes

Over time, progressive fibrosis of the pancreas in patients with CF results in the development of diabetes mellitus. Cystic fibrosis-related diabetes (CFRD) is a unique form of glucose intolerance that is different from type 1 and type 2 diabetes mellitus. Although insulin production is insufficient in CFRD, patients usually produce enough residual insulin to avoid diabetic ketoacidosis. The treatment of CFRD generally involves insulin therapy [56]. Oral hypoglycemic agents

are not typically effective in the setting of pancreatic destruction and limitation of caloric intake is discouraged. Rather, calculation of carbohydrate intake followed by administration of appropriate short-acting insulin coverage is preferred. Long-acting insulin has also been used successfully. A hallmark of CFRD is global islet cell destruction, which leads to both insulin and glucagon deficiency. Therefore, treatment for hypoglycemia may be necessary.

6.4   Sinusitis and Nasal Polyposis

Sinus disease may be a source of morbidity in CF. Inspissated mucus may lead to chronic infection and inflammation. The use of saline nasal sprays and rinses may be effective in clearing secretions. Nasal steroids and montelukast may also be effective to decrease nasal inflammation and reduce polyp formation. A longer (several weeks) duration of oral, nasal, or parenteral antibiotics may be used for the treatment of sinusitis. Failure of medical therapy may lead to endoscopic sinus surgery.

6.5   Other Cystic Fibrosis Therapies

Patients with CF are at increased risk for salt loss and hyponatremic dehydration. Breast milk and infant formulas tend to be low in salt, therefore salt supplementation is recommended for infants until they have transitioned to a primarily table food diet. Older patients with CF who are engaging in intense physical activity, especially during the summer, should also take salt supplements.

Males with CF have azoospermia due to atresia and obstruction of the vas deferens, although, using microsurgical epididymal sperm aspiration (MESA) and in vitro fertilization, they are able to father their own biologic children. CF clinicians should counsel their male patients during adolescence about the option of MESA.

6.6   CFTR Modulators

CFTR modulators are small molecules that can restore partial or complete CFTR function in defective CFTR proteins [57, 58]. CFTR modulators can be divided into two broad classes; CFTR potentiators and CFTR correctors. CFTR potentiators bind to CFTR and increase the open channel probability of the protein, thereby increasing chloride (Cl) conductance. CFTR correctors bind to mutant CFTR mRNA or proteins and correct their transcription or processing defects, increasing surface expression of the protein. Because CF is an autosomal recessive condition and carriers are known to be unaffected, correction of a single mutant allele in a patient with CF should be enough to prevent disease. In fact, studies of CFTR function in patients with CFTR-related disorder (CFTR-RD) suggest that as little as 20–30 % of wild type CFTR function is enough to prevent disease [59]. Potentiators and correctors are small molecules that were discovered by using high throughput screening to search large medicinal chemical libraries for compounds with potentiator or corrector capacity.

At present there is only one CFTR potentiator available for clinical use — ivacaftor. Ivacaftor is a CFTR potentiator that can increase Cl conductance in class III mutations. It was initially introduced into clinical use in 2012 for patients with at least one copy of the G551D mutation. Treatment with ivacaftor in patients with this mutation resulted in improvement of lung function, pulmonary symptoms, quality of life scores, nutritional status, and decreased sweat Cl values [60]. It has now been approved for use in CF for several other class III gating mutations and R117H (class IV mutation). Together, these mutations are present in about 10 % of the US CF population [35]. Currently, ivacaftor is indicated for patients with CF who are 2 years of age and older with G551D, R117H, and a small number of other gating mutations, and the US Cystic Fibrosis Foundation recommends its use in these patient populations [20].

The most common CF-causing mutation, F508del, results in a CFTR protein that folds improperly and has reduced Cl conductance. The former property leads to F508del CFTR being degraded in the golgi, and <1 % of the protein is expressed on the cell surface [61]. Due to this, F508del CFTR is not responsive to ivacaftor alone. Lumacaftor is a CFTR modulator that partially corrects the folding defect in F508del, increasing surface expression of the protein [62]. A combination of lumacaftor and ivacaftor has been shown in randomized clinical trials to improve FEV_1 and decrease the rate of pulmonary exacerbations [63], and lumacaftor/ivacaftor is currently approved by the US FDA for patients with CF who are homozygous for the F508del mutation and are ≥12 years old. In the US, these patients comprise approximately 45 % of the total CF population in the country [35, 63].

Ataluren is a small molecule that allows read-through of mutations with a premature stop codon (nonsense mutations/class I mutations). In patients with class I mutations, ataluren can improve CFTR-mediated ion flux and increase CFTR expression in airway epithelial cells [64]. Ataluren is currently preregistered in the EU and completing Phase III clinical trials in the US, and if the results are favorable it may be available for clinical use.

It remains unclear whether the use of CFTR modulators will decrease the treatment complexity for individuals with CF. Longer duration follow-up of adverse and clinical effects is necessary before it can be determined if these agents may be able to supplant any of the chronic therapies for CF, both for pulmonary complications as well as other organ systems affected by CF. The degree of pre-existing disease prior to starting CFTR modulators may also affect the need for continued CF maintenance therapies. More potent CFTR modulators are also currently under development, and they may have a greater impact on need for other chronic CF therapies.

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