Chapter 47: Cystic Fibrosis

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KEY CONCEPTS

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1. Cystic fibrosis (CF) is caused by a functional loss of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This leads to reduced chloride and bicarbonate secretion and a buildup of thick mucus throughout the body affecting the lungs, pancreas, liver, intestine, and reproductive tract. Thus, CF is a multisystem disease with most patients experiencing a wide range of symptoms and diverse organ complications.

2. Three classes of CFTR modulators play an important role in the treatment of CF. Although there is no cure for CF, the CFTR modulator class of medications alleviates and corrects the underlying pathophysiology.

3. Infection is one of the main causes of morbidity and mortality in patients with CF and contributes to CF lung disease. Treating infections in CF involves not only antibiotics but chest physiotherapy and inhaled mucolytics play an important adjunction role. Strategies should be employed to prevent *Pseudomonas aeruginosa* acquisition including measures to prevent transmission between CF patients and early eradication of both *P. aeruginosa* and *Staphylococcus aureus* with appropriate treatment regimens. Chronic colonization with *P. aeruginosa* necessitates chronic treatment with inhaled antibiotics.

4. Pancreatic exocrine insufficiency occurs in CF patients as a result of pancreatic duct obstruction. If left untreated, pancreatic insufficiency leads to growth failure, weight loss, abdominal bloating, foul-smelling stools, or diarrhea. Pancreatic enzyme replacement therapy is the treatment of choice.

5. Dosing of antibiotics in CF patients can be a challenge to ensure adequate lung penetration and maximum bactericidal activity. In addition, the pharmacokinetics of antibiotics in CF patients differ compared to most other individuals. The volume of distribution and total body clearance is increased in CF patients for hydrophilic drugs such as aminoglycosides, penicillins, and cephalosporins. Specifically, the initial dose of aminoglycosides is higher in CF patients when compared to the general population and adjusted based on patient-specific pharmacokinetic parameters.

6. CF is a multi-system disease requiring a multimodal treatment approach administered through a multidisciplinary team to provide optimal care and the best patient outcomes. With the advancements in science and treatment options, not only is the quality of life for cystic fibrosis patients increasing but their lifespan is extending.

BEYOND THE BOOK

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1. Create a concept map that interlinks cystic fibrosis pathophysiology and its complications with appropriate medication regimens. This activity will help develop the learner's application of treatment strategies with the underlying pathophysiology and complications of the disease.
2. Review the case study "Cystic Fibrosis: Blood, Sweat, Lungs, and Gut Level III," by Novak, Kimberly J. in *Pharmacotherapy Casebook: A Patient-Focused Approach*, 11e Eds. Terry L. Schwinghammer, et al. McGraw Hill, 2020. Write a pharmacokinetic SOAP note based on the serum tobramycin concentrations obtained in the case. This activity will help develop the learner's application of pharmacokinetic principles and practice communication of recommendations based on patient-specific pharmacokinetic parameters.

INTRODUCTION

Cystic fibrosis (CF) is the most common autosomal recessive disease in the Caucasian population with a prevalence of approximately 1/3,500 live births.[1] First described in 1938, CF was initially thought to be a disease of malnutrition since malnutrition was the cause of death in these children in early childhood but is now known to be a genetic disorder.[2] Mutations of a gene that encodes the cystic fibrosis transmembrane conductance regulator (CFTR), a chloride-conducting transmembrane channel, impairs the regulation of chloride and other anion transport and results in thickened, viscous secretions in many organ systems, including the pulmonary, biliary, pancreatic, intestinal, and reproductive systems.[3] The resultant organ dysfunction not only encapsulated the initial findings of malnutrition due to maldigestion and malabsorption but also signifies the progressive lung disease that now highlights the major cause of morbidity and mortality in most patients.

CF currently affects more than 30,000 people in the United States and approximately 80,000 people worldwide. However, CF is no longer exclusively a childhood disease. Advancements in therapy have enabled most CF patients to live into adulthood.[2] More than half of the CF patients in the United States are adults.[4] The median predicted survival age has steadily increased over the past decade and was approximately 48 years in 2019. It is likely the median survival age will continue to increase as the impact of newer therapies such as the CFTR modulators are realized.

EPIDEMIOLOGY

Cystic fibrosis occurs in a classic single-gene (Mendelian) autosomal recessive pattern.[5,6] Autosomal recessive patterns of inheritance require both parents to be carriers of the gene. CF occurs most commonly in the populations of people of northern European ancestry where the predominant mutation is delta F508 (which is a deletion of phenylalanine at position 508 on the long arm of chromosome 7 also known as F508del).[5,6] This mutation accounts for approximately 70% of all mutations. The disease incidence in other populations is less defined but has been reported to be 1 in 17,033 live births for Black American patients, 1 in 12,000 in mixed-race South Africans, and 1 in 90,000 in Asian populations (Chinese, Japanese, and Filipino) living in Hawaii.[7] To date more than 2,000 gene variants have been identified many of which have been associated with disease causation.[8]

ETIOLOGY

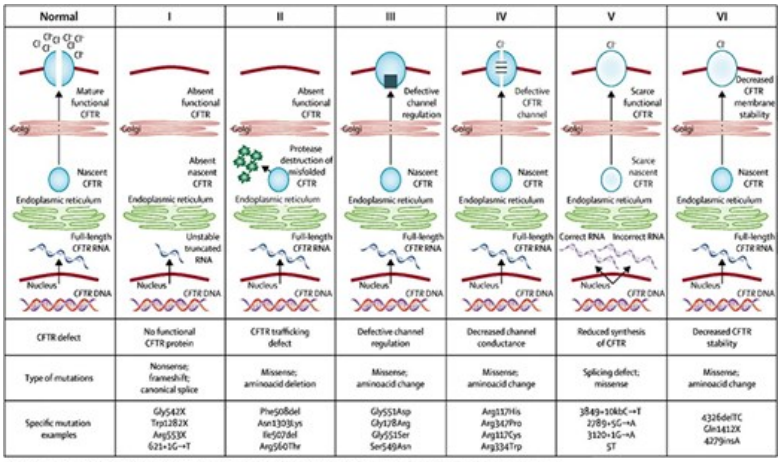
The gene for CF, localized to the long arm of chromosome 7, encodes a protein of 1,480 amino acids residues.[9] This CFTR protein is found in the apical membrane of epithelial cells and regulates the transepithelial transport of chloride, other ions, and water.

The CFTR mutations can be grouped into six classes (Fig. 47-1).[6,10] Classes 1 to 3 are known as minimal function mutations as they confer no, or hardly any, CFTR function. Class 1 mutations, referred to as protein production mutations, affect the transcription of CFTR by the formation of premature stop codons into the messenger RNA. This results in a total absence of the CFTR protein. Class 2 mutations, protein processing mutations, or trafficking defects, involve intracellular processing of the CFTR protein. CFTR protein is produced but is misfolded, making it unstable and leading to degradation. The most notable Class 2 mutation is delta F508. Class 3 mutations (defective channel regulation or gating mutations) alter the regulation of CFTR. While the CFTR is intact and incorporated into the cell membrane surface, this mutation affects channel activation, reducing its opening probability. Class 4 mutations, referred to as conduction mutations, affect the chloride conductance of CFTR. The CFTR protein channel can be activated to open and secrete chloride but the conductance is reduced. Class 5 mutations result in the production of CFTR protein with normal chloride

secretion but a decreased number of CFTR channels. Finally, Class 6 mutations result in an accelerated CFTR turnover from the cell surface resulting in decreased CFTR stability.

FIGURE 47-1

Mutations in the cystic fibrosis transmembrane conducatance regulator (CFTR) gene can be divided into six classes. Class I mutations result in no protein production. Class II mutations (including the most prevalent, Phe508del) cause retention of a misfolded protein at the endoplasmic reticulum, and subsequent degradation in the proteasome. Class III mutations affect channel regulation, impairing channel opening (eg, Gly551Asp). Class IV mutants show reduced conduction—ie, decreased flow of ions (eg, Arg117His). Class V mutations cause substantial reduction in mRNA or protein, or both, Class VI mutations cause substantial plasma membrane instability and and include Phe508del when rescued by most correctors (fPhe508del). *(Reproduced, with permission, from Boyle MP, De Boeck K. A new era in the treatment of cystic fibrosis: correction of the underlying CFTR defect. Lancet Respir Med 2013;1:158-163.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

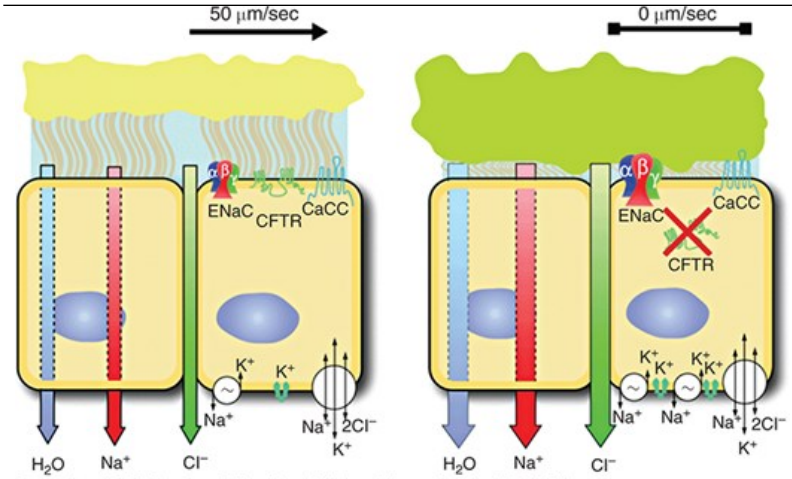
Patients with at least one mutation of class 4, 5, or 6 typically have a later onset of disease, lower sweat chloride values, slower decline in lung function, less chronic *Pseudomonas aeruginosa* infections, less CF-related diabetes, and lower treatment burden.[11] Together, these mutations are called residual function mutations.

PATHOPHYSIOLOGY

CF is caused by a mutation in the CF transmembrane conductance regulator gene.[12] The CFTR protein produced by this gene regulates the movement of chloride and sodium ions across epithelial cell membranes (Fig. 47-2). CFTR functions primarily as an apical anion channel of chloride and bicarbonate, rather than an active pump. Loss of apical CFTR leads to reduced chloride and bicarbonate secretion, resulting in a buildup of thick mucus throughout the body including in the lungs, pancreas, liver, intestine, and reproductive tract. This defect also leads to increased salt content in sweat gland secretions. Thus, cystic fibrosis is a multisystem disease with most patients experiencing a wide range of symptoms and diverse organ complications.

FIGURE 47-2

Illustration of the normal and abnormal movement of chloride and sodium ions across epithelial cell membranes. ENaC, amiloride sensitive epithelial Na+ channel; CFTR, cystic fibrosis transmembrane conductance regulator; CaCC, calcium-activated Cl− channels.



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Pulmonary Manifestations

Although CFTR mainly functions as an anion transporter, it also regulates numerous processes, including fundamental aspects of airway defense and inflammatory cell function.[13] The release of water and electrolytes onto the airway surface is driven in large measure by CFTR-dependent fluid secretion through both the sweat glands and the surface epithelia. A CFTR deficiency leads to diminished airway surface hydration, thickened mucus secretions, and accumulation that compromises the airway lumen, submucosal gland hyperplasia, and impaired mucociliary transport.[14,15] Airway disease likely begins in the small airways with the development of bronchiectasis whereby the walls of the bronchioles are thickened from infection and inflammation. This leads to irreversible changes that encourage continued infection, accelerate disease pathogenesis, and ultimately, obstructive pulmonary disease.[15]

The inflammatory response contributes to a pro-inflammatory state that sets up chronic infections and further tissue damage.[16] The massive influx of neutrophils to the airways further exacerbates inflammatory cell recruitment, perpetuating a cycle of inflammation and damage. In addition, in the CF airways, neutrophils undergo necrosis instead of apoptosis and clearance by alveolar macrophages that occurs in healthy lung tissue. This necrosis leads to the release of intracellular contents further eliciting a persistent inflammatory response. This exaggerated inflammatory process plays an essential role in the progression of airway wall remodeling, lung damage, and lung function decline in CF patients. With the colonization by bacterial pathogens, overly exaggerated protective mechanisms result in the release of proteases, reactive oxygen/nitrogen species, and proinflammatory chemokines. CFTR also regulates anion secretions through other chloride channels such as transmembrane member 16a (TMEM16a; also known as anoctamin-1) and contributes to airway pH regulation through chloride exchangers, such as anion exchanger type 2. Dysfunction of these mechanisms results in diminished or absent bicarbonate secretion leading to an acidic pH airway surface liquid in cystic fibrosis. This may lead to changes in the highly pH-sensitive innate defensins and defective bacterial killing.[17,18] CFTR also has a direct effect on neutrophil killing, as it affects degranulation by interfering with granule trafficking as peripheral neutrophils release fewer secondary and tertiary granule components compared with control cells. Activation of the low-molecular-mass GTP-binding protein Rab27a, involved in the regulation of granule trafficking, is also defective.

Chronic pulmonary infections adversely impact the quality of life and can lead to respiratory failure which is the leading cause of death in patients with CF.[19] The decreased airway surface liquid volume leads to a collapse of respiratory cilia, impaired mucociliary clearance, and mucus retention on the lower airways. Under these conditions, inhaled microorganisms cannot be efficiently cleared and this predisposes CF patients to chronic bacterial infection and recurrent pulmonary exacerbations. The most common microorganisms that cause chronic pulmonary infections are *P. aeruginosa*, *Staphylococcus aureus*, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia*. CF patients are not infected at birth but acquire these organisms over time. Viral infections such as Rhinovirus and Influenza A and B and fungal infections such as Aspergillus fumigatus are also prevalent in the population.

Finally, mucus accumulation in the lower airways is the main feature of CF lung disease. The major component of mucus in CF is not mucin from mucus-producing cells but rather a pus that includes viscous materials such as polymerized DNA from degraded neutrophils.

Upper Airway Manifestations

Due to the increased viscous mucus that accumulates in the sinuses, chronic rhinosinusitis is common and nasal polyposis is a complication noted in up to 45% of patients.[15] Imbalance of electrolyte transport from CFTR dysfunction reduces airway surface liquid depth and increases the viscosity of mucins in the airway 30 to 60 times higher than seen in patients without CF.[20] Tenacious secretions and tissue inflammation block sinus ostia, which results in hypoxia, mucosal edema, and additional impairment of mucociliary function.

Gastrointestinal Manifestations

Defective CFTR in the pancreatic epithelium results in proteinaceous secretions that block the exocrine ducts and ultimately cause acinar destruction.[14] Pancreatic insufficiency results when >95% of the total pancreatic exocrine function is lost. This then leads to nutrient loss due to the inability to break down nutrients as well as reduced fat-soluble vitamin absorption (Vitamins A, D, E, and K). The early recognition of nutritional deficits is vital. Poor growth and malnutrition adversely affect pulmonary function and can lead to premature death.

CFTR is also present in the GI epithelium and, like the lung, reduced chloride and fluid secretion lead to mucus buildup in the intestines resulting in obstruction of the intestines. Impaired bowel transit can lead to frequent gastro-esophageal reflux, distal intestinal obstruction syndrome, and constipation, depending on the site of obstruction.

Hepatic involvement is also common. Up to one in three patients have evidence of hepatic steatosis, cholelithiasis, ductal stenosis, or focal biliary cirrhosis due to the accumulation of viscous secretions that clog the biliary tract.[21] Biliary cirrhosis typically becomes evident in late childhood or early adolescence and leads to portal hypertension. Patients with liver disease may be classified into the following categories: (1) liver involvement with cirrhosis/portal hypertension or (2) liver involvement without cirrhosis or portal hypertension. Advanced liver disease may be found in patients with PI. Risk factors for advanced liver disease include male gender and the presence of alpha-1 antitrypsin Z allele. Typically, patients with a CFTR mutation that belongs to class I to III are more likely to have abnormalities of the hepatobiliary system.

Endocrine Manifestations

Cystic fibrosis-related diabetes (CFRD) is increasingly common as more patients with CF live longer. CFRD is clinically distinct from type 1 and type 2 diabetes mellitus. CFRD is thought to be related to loss of insulin-producing islet cells due to autolysis and fatty infiltration of the pancreas, pancreatic duct obstruction from the accumulation of viscous secretions, and decreased islet cell mass, all of which lead to both insulin and glucagon deficiency, altered intestinal motility, and delayed gastric emptying.[22] Unlike type 1 diabetes, the loss of islet cells in CFRD is not due to an autoimmune process.[23] The course is progressive in nature, and patients may move back and forth between an impaired state and CFRD. Uncontrolled CFRD may correlate with pulmonary function decline, weight loss, and *P. aeruginosa.*

Other endocrinological complications of cystic fibrosis include delayed menarche in malnourished adolescent females and reduced bone mineral density, increasing the risk of bone fractures. A bilateral absence of the vas deferens occurs in 98% of males with cystic fibrosis and results in azoospermia. Most males with CF are infertile.

Renal Manifestations

Nephrocalcinosis due to salt and water depletion can result in acute kidney injury and proteinuria.[14] Chronic kidney disease is more common in adult patients and risk factors for its development include diabetes, prior episodes of acute kidney injury, and immunosuppressive regimens associated with prior organ transplantation.

CLINICAL PRESENTATION

Clinical Presentation: Cystic Fibrosis[24–28]

General

- Typical respiratory manifestations include persistent productive cough, hyperinflation of the lung fields, and obstructive findings on pulmonary function tests. Other manifestations may include GI, endocrine, and renal abnormalities.

Diagnosis

- Two diagnostic components and a combination of criteria.[24]
- At least one clinical feature of the disease (such as failure to thrive, malabsorption, chronic sinopulmonary disease), a history of a sibling with the disease, or a positive neonatal screening test.
- The second diagnostic component is the demonstration of CFTR dysfunction which can be established either by sweat testing or by molecular genetic testing (Fig. 47-3).[25]
    - The demonstration of CFTR dysfunction using a “sweat test” requires high chloride values in sweat (≥60 mmol/L) in two independent measurements on the same day.[24] Values below 29 mmol/L make cystic fibrosis unlikely; values between 30 and 59 mmol/L require further diagnostic testing.
    - Infants identified at risk for CF through newborn screening who have an in-determinate sweat chloride (30-59 mmol/L) and less than two known disease-causing CFTR mutations are classified as having Cystic Fibrosis–Related Metabolic Syndrome (CRMS).[27]
    - CFTR-Related Disorder is used for patients who do not meet diagnostic criteria for CF but have clinical disease limited to an isolated CF-related condition or organ system, such as the congenital bilateral absence of the vas deferens (CBAVD).[28]

Signs and Symptoms

- Disease progression results in acute exacerbations with cough, tachypnea, dyspnea, increased sputum production, malaise, anorexia, and weight loss.
- Digital clubbing is often seen in advanced disease as well. Sinus involvement can present with chronic nasal congestion, headaches, cough, and sleep disturbance.
- Common signs and symptoms of pancreatic insufficiency include steatorrhea, poor weight gain, and failure to thrive.
- In CFRD, patients often do not present with the classic symptoms of diabetes such as polyuria and polydipsia.[23] There may be no symptoms, or there may be poor growth velocity, delayed progression of puberty, and unexplained chronic decline in pulmonary function.

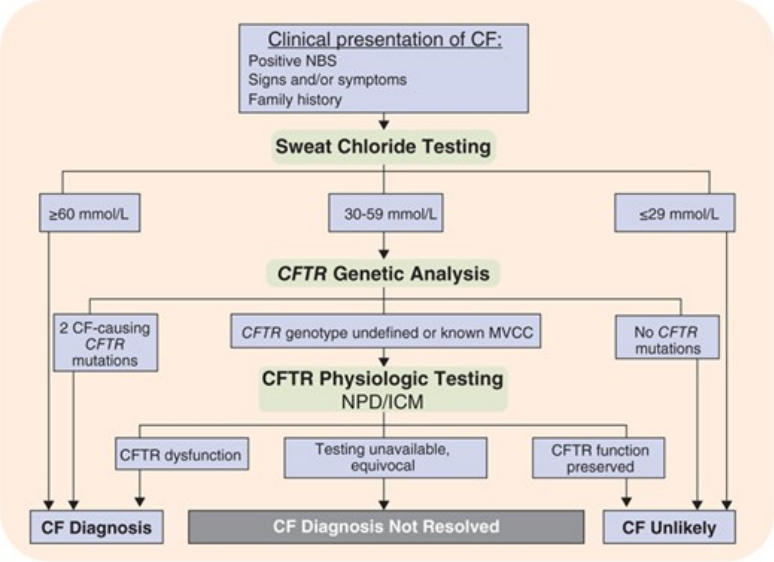
Historically, cystic fibrosis was diagnosed based on presenting symptoms such as meconium ileus, respiratory symptoms (persistent productive cough, wheezing, or any breathing difficulty), or failure to thrive. However, with the newborn screening programs now in place, the number of cases identified prior to presenting with symptoms has greatly increased.

The demonstration of CFTR dysfunction using a “sweat test” requires high chloride values in sweat (≥60 mmol/L) in two independent measurements on the same day.[24] Molecular genetic tests constitute the second stage of confirmatory diagnostic testing (see Fig. 47-3). This test also determines which mutations are present.

FIGURE 47-3

CFF diagnostic algorithm. (CFTR, cystic fibrosis transmembrane conductance regulator; ICM, intestinal current measurements; MVCC, mutation of

varying clinical consequence; NBS, newborn screen; NPD, nasal potential difference)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

All 50 states in the United States now require cystic fibrosis tests as part of newborn screening.[26] It is a screening test and not diagnostic. The first-tier screen in all state screening programs involves measuring immunoreactive trypsinogen (IRT), a marker of pancreatic injury. A second-tier test is needed to improve test specificity because the initial IRT can be increased due to perinatal stress, critical illness, CFTR mutation carrier status, and other causes. The second-tier test differs between state newborn screening programs and can include CFTR mutation analysis, measurement of pancreas-associated protein, or repeat IRT. The diagnosis must be confirmed by a positive sweat test or, alternatively, by genetic tests demonstrating two disease-causing mutations.

With the increase in newborn screening, new categories of infants who do not meet the classic definition of CF have arisen. Infants identified at risk for CF through newborn screening who have an in-determinate sweat chloride (30-59 mmol/L) and less than two known disease-causing CFTR mutations are classified as having Cystic Fibrosis–Related Metabolic Syndrome (CRMS).[27] An additional diagnostic category, CFTR-Related Disorder, is used for patients who do not meet diagnostic criteria for CF, but have clinical disease limited to an isolated CF-related condition or organ system, such as congenital bilateral absence of the vas deferens (CBAVD).[28] Many of these patients have mutations in the CFTR gene that are not considered the classic disease-causing mutations. For example, some patients with CFTR-Related Disorder have the 5T variant which is a common mild variant and causes abnormal splicing of the CFTR gene transcript. Most individuals with two copies of this variant are asymptomatic but some may have an absence of the vas deferens or bronchiectasis. Patients without a definitive diagnosis of CF are continued to be followed for symptom progression and potentially reclassification later in life.

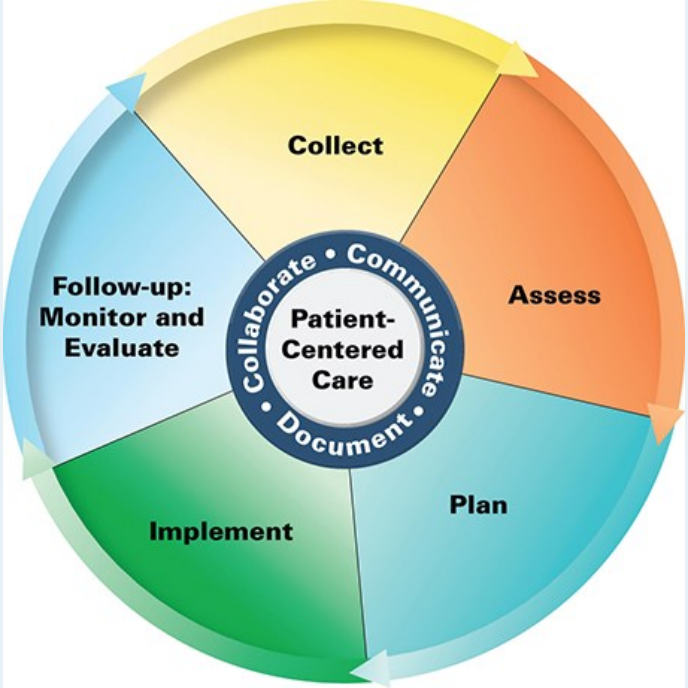
Diagnosis of liver disease can include a physical exam which may reveal ascites, palmar erythema, digital clubbing, scleral icterus, spider hemangiomas, and hepatosplenomegaly.[21] Additionally, evaluation of liver function panel and obtaining lab work for alpha-1 antitrypsin deficiency, Wilson disease, and hemochromatosis should be included. Imaging and a liver biopsy may also be performed to determine the extent of the liver disease and exclude other causes. There are annual labs that can identify CFLD early; these include complete blood count (CBC), prothrombin time, liver function panel, gamma-glutamyl-transferase (GGTP), albumin, cholesterol, and glucose.

In CFRD, patients often do not present with the classic symptoms of diabetes such as polyuria and polydipsia.[23] There may be no symptoms, or there may be poor growth velocity, delayed progression of puberty, and unexplained chronic decline in pulmonary function. Screening for CFRD should occur annually in patients aged 10 and older as recommended by the American Diabetes Association (ADA). Additionally, women with CF who are not previously known to have CFRD and who are contemplating pregnancy should be evaluated for CFRD utilizing a 2-hour, 75-g oral glucose tolerance test (OGTT). If screening has not occurred within the last 6 months, screening should occur in women prior to conception because women with CF are at higher risk for developing hyperglycemia. Screening is typically done as an OGTT for all patients with CF. An A1c reading of ≥6.5% (48 mmol/mol) may indicate CFRD; however, an A1c should be used in combination with an OGTT as a confirmation of CFRD. Fructosamine, urine glucose, and random

glucose levels have low sensitivity in patients with CF. The OGTT should be administered following stable baseline health for at least 6 weeks and patients should consume at least 150 carbohydrates for 3 days prior and fast for 8 hours prior to the OGTT.

PATIENT CARE PROCESS

Patient Care Process



Collect

- Patient characteristics
  - Age
  - Race/ethnicity
  - Sex assignment
  - Gender preferred pronouns
- Symptoms
  - Sputum production color and production
  - Cough
  - Shortness of breath
  - Stool frequency and description
- Diagnostic Screening
  - Newborn screening

- Genetic mutations
- Sweat test

- Patient history (past medical history, family history, birth history)
  - History of hospitalizations
  - History of infections (particularly resistant organisms)
  - Complications of CF (eg, CF renal disease, CF lung disease)
  - Past surgical history (eg, G-tube placement)
  - Reproductive history
- Social history
  - Home and work environment (infection control, dedicated space, and time for treatments)
  - Insurance status and income history may be used to qualify for grants
  - Eating habits
- Current medication and history of past medication use, herbals, dietary supplements, and over the counter products
- Objective data
  - Respiratory function (FEV1, oxygen saturation)
  - Nutritional status (height, weight, BMI)
  - Mental status (PHQ-9 and GAD-7)
  - Labwork: CBC, CMP, Lipids, Liver function, Vitamin D
- Immunization status and history

Assess

- Medication effectiveness and safety (reduction in symptoms, ADEs)
- Medication adherence to prescribed medications (schedule, costs, dietary supplements)
- Barriers to medication use
- Adherence to respiratory therapy (vest and technique)
- Nutritional status (BMI, calorie intake)
- Lung function (exacerbations)
- Emotional well-being of patient, family, and caregivers
- Exercise tolerance
- Comorbidities

Plan*

- Infection control and environmental modifications
- Medication plan (timing, order of medications, doses, route, formulation, frequency, duration)
- Labs
  - CBC and CMP yearly
  - Sputum culture quarterly
  - Liver panel quarterly for the first year of modulator therapy
  - 25-hydroxyvitamin D, retinol, alpha-tocopherol, prothrombin time, PIVKA II, and OGTT annually
- Referrals (endocrinology, urology, gastroenterology, ob-gyn, transplant, infectious disease, audiology, ophthalmology)

Implement*

- Patient/family education on the purpose of each medication
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Results of lab work and sputum cultures
- Medication access and adherence
- Medication changes based on results of lab work
- Sick visits to decrease the need for hospitalization
- Home infusions of antibiotics when necessary and available

***In collaboration with the patient, caregiver, and other healthcare professionals on the team (social worker, dietitian, respiratory therapist, pulmonologist, nurses).**

TREATMENT

Desired Outcome(s)

The overall goal of treatment is to enable each person with cystic fibrosis to live a full and productive life. Optimizing treatment to reduce pulmonary exacerbations, delaying colonization by pathogens, and maintaining lung health is key to improving survival. In addition, maximizing adequate nutrition with appropriate dosing of pancreatic enzymes and vitamin supplementation contributes to accomplishing the desired outcomes. Furthermore, with the development of the CFTR modulators and as other disease-modifying therapies become available, every patient should receive treatments that address the underlying pathophysiology of the disease.

General Approach to Treatment

Pulmonary and Sinus

The goal of treatment is to prevent and treat sinusitis and acute pulmonary exacerbations. Routine care goals are to maintain the FEV1 and promote optimal pulmonary function tests. Effective airway clearance is promoted with counseling on the use of appropriate medications and airway clearance

techniques (ACT) at least twice a day. Prevention and treatment of bacterial colonization with oral and inhaled therapies are also keys to maintaining lung function.

Gastrointestinal

Optimizing growth and nutrition is done primarily with the use of pancreatic enzyme supplementation. This in turn will promote healthy bowel habits and maintenance of appropriate fat-soluble vitamin levels (Vitamins A, D, E, and K). Vitamin levels are checked at least yearly and some such as Vitamin D can have seasonal variations. Evaluating and supporting needed caloric intake is important to promote good lung function and symptoms of malabsorption are evaluated at every clinic visit. Patients' weight for length or body mass index (BMI) should be maintained at or above the 50th percentile because it has been associated with the best lung functions.

Psychosocial

Each patient will need ongoing education and support to encourage adherence to pharmacological and nonpharmacological therapies. Counseling to help cope with a lifelong disease, as well as guidance to live a fulfilling life, are paramount to successful treatment. Once patients' mutations are determined by genetic testing, it is essential to provide appropriate genetic counseling at the time of diagnosis and periodically thereafter. As patients and significant others reach reproductive age it is key to offer both possible birth control methods and support couples in family planning with education and resources.

Nonpharmacologic Therapy

Exercise, infection prevention control, nutrition, and airway clearance are ways in which a patient with CF can improve mucous obstruction and avoid chronic infections. There is not a specified length of time in which exercise is recommended by the Cystic Fibrosis Foundation; however, the purpose is to loosen mucous and clear the airways.[29] Shorter exercises that are enjoyable and tolerated by patients are the best exercises. Sodium loss may occur during intense exercise, and repletion is necessary to avoid dehydration.

The Cystic Fibrosis Foundation sets forth several recommendations for infection prevention. Patients with CF should engage in regular hand hygiene throughout the day using an antimicrobial soap or alcohol-based hand rub. All patients with CF should adhere to the six-foot rule to reduce droplet transmission. Patients with CF should wear a surgical mask when in a healthcare setting to reduce transmission or acquisition of CF pathogens.[30]

Patients with CF often need 1.5 to 2 times the number of calories as patients without CF. Nutrition plays an essential role in pulmonary function and bone health. Weight for length is a measure that is used to track patients who are under the age of two and body mass index (BMI) is typically used after the age of two. The CF Foundation recommends that children younger than 2 should reach a weight-for-length >50th percentile by 2 years of age and children and adolescents 2- to 20 years old should be at or above the 50th percentile for BMI.[31] In adults, women should be encouraged to maintain a BMI of at least 22 and for men, a BMI of 23 is recommended.

Airway clearance techniques (ACT) include percussion and postural drainage, positive expiratory pressure (PEP), active-cycle-of-breathing technique, autogenic drainage, oscillatory PEP, high-frequency chest compression, and exercise. One way to facilitate airway clearance is through the use of a vest. A vest uses high-frequency chest wall oscillation that is performed by a machine. Use of the vest loosens and thins mucus. These sessions typically last about 20 to 30 minutes. Airway clearance may also be done manually by a parent or caregiver. The caregiver uses a variety of hand-to-chest techniques, typically lasting 3-5 minutes, to help loosen and drain the mucus. These techniques can include clapping with a cupped hand and creating vibration with a flattened hand. The best times to complete chest physical therapy (CPT) is before meals or one and a half hours to two hours after eating. CPT may be performed more frequently if the patient is congested or getting sick.

Pharmacologic Therapy

Genetic Therapies

CFTR Modulators

Understanding the defect with each class of mutations helps identify the role the three classes of CFTR modulators play in the treatment of CF.[32] Even though no cure to treat the underlying cause of cystic fibrosis currently exists, the CFTR modulator class of medications is used to alleviate and correct

part of the underlying pathophysiology.

The three classes of CFTR modulators include correctors, potentiators, and amplifiers. Correctors work by increasing the amount of functional CFTR at the cell surface. Medications labeled as correctors include lumacaftor, tezacaftor, and elexacaftor. There are a few additional correctors that are in the pipeline which include posenacaftor, dirocaftor, and ABBV-2222, which are currently in clinical trials. There is only one potentiator on the market, ivacaftor. The role of the potentiator is to keep the channel open to increase the transport of chloride in and out of the cell. VX-561 is deuterated ivacaftor meaning that it is more stable in the body than the current formulation of ivacaftor and would be able to be taken once daily. This agent is currently in phase 2 trial. The last class of CFTR modulators is the amplifiers which include one agent in the pipeline, nesolicafator. This class of medications works by increasing the amount of CFTR protein in the cell, which provides more CFTR for correctors and potentiators to act upon.

The CFTR modulators have mutation-specific and age-specific indications. General recommendations for the selection of a CF modulator are therefore based on the age of the patient and the mutation. For delta F508 homozygotes older than 6 years of age, elexacaftor/tezacaftor/ivacaftor combination is recommended. For delta F508 homozygous children between 2 and 5 years of age should be started on lumacaftor/ivacaftor combination. Patients can be transitioned from dual therapy to triple therapy as they increase in age. For delta F508 heterozygous patients who are 6 years of age or older, triple therapy is recommended. Tezacaftor/ivacaftor may be used for children 6 and older, whereas ivacaftor alone may be used in infants greater than 4 months old. As the FDA approves additional modulators and adjusts the age-specific labeling of current modulators, recommendations for a CF modulator will need to follow suit.

Even though adverse effects with the CFTR modulators are often mild, monitoring for the elevation of transaminases and cataracts is currently recommended. Assessments of transaminases (ALT, AST, and/or bilirubin) are recommended for all patients prior to initiating the currently approved CF modulators, every 3 months during the first year of treatment, and annually thereafter. In addition, baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with these agents. Of particular note, a subgroup of patients develops chest discomfort and dyspnea after initiating the combination of lumacaftor/ivacaftor.[33] These patients tend to have worse baseline lung function. Initiating treatment with a one-half dose for the first 1-2 weeks may help prevent treatment discontinuations in patients with severe lung disease.[34] However, there was no increase in chest discomfort, bronchospasm, dyspnea, or wheezing with tezacaftor as seen with lumacaftor/ivacaftor.[35,36]

Caution should also be used when CFTR modulator medications are used concomitantly with CYP3A4 inducers or inhibitors. Even though tezacaftor/ivacaftor are substrates of CYP3A and co-administration with strong CYP3A inducers is not recommended, texacaftor/ivacaftor combination appears to have fewer drug interactions than the lumacaftor/ivacaftor combination.

Current CFTR modulators are administered with a high-fat meal to improve absorption. Some examples of high-fat foods include eggs, peanut butter, avocado, butter, cheese pizza, and whole-milk dairy products.

CFTR Correctors

Lumacaftor

Lumacaftor is manufactured in combination with ivacaftor which works to potentiate and enhance chloride transport.[37] This combination product is currently approved for use in patients homozygous for delta F 508 for ages two and up. The formulation usually is dosed as two tablets of lumacaftor 200 mg/ivacaftor 125 mg every 12 hours with fat-containing food to help with medication absorption. See Table 47-1 for dosing and dosing formulations.

TABLE 47-1

Lumacaftor Dosing and Dosing Formulations

Dosage Form	Age	Recommended Dose	Counseling Points
Granules	2-5 years old	• <14 kg one packet lumacaftor 100 mg/ivacaftor 125 mg every 12 hours • >14 kg one packet lumacaftor 150 mg/ivacaftor 188 mg every 12 hours	• Take with fat-containing food • Shake the packet gently to settle the granules, after opening the packet, pour the granules into 1 teaspoon of soft food or liquid in a small container, food or liquid should be at or below room temperature, and once mixed should be given within 1 hour, the entire dose should be consumed
Tablets	6 years and older	• 6-11 years old • 2 tablets lumacaftor 100 mg/ivacaftor 125 mg every 12 hours • 12 years and older • 2 tablets lumacaftor 200 mg/ivacaftor 125 mg every 12 hours	

The outcomes that were studied when looking at the efficacy of lumacaftor/ivacaftor included FEV1, BMI, and exacerbations.[38] In homozygous delta F508 participants, clinical studies demonstrated statistically significant improvements in percent predicted FEV1 along with improvements in body mass index and quality-of-life measures at both low and high doses (400 or 600 mg of lumacaftor in combination with ivacaftor 250 mg every 12 hours for 24 weeks). In addition, pulmonary exacerbations were significantly reduced when compared to placebo. In heterozygous patients for the delta F508 mutation, lumacaftor/ivacaftor does not appear to have the same clinical benefits.[39]

Tezacaftor

Tezacaftor is additionally found in combination with ivacaftor.[36] It was previously approved in patients 12 and older but has now expanded to patients ages 6 and older. This combination is different from lumacaftor/ivacaftor due to it being indicated in patients that are homozygous for F508del or those who have at least one mutation that is responsive to tezacaftor/ivacaftor. At least 150 different mutations are eligible for tezacaftor/ivacaftor.

Weight-based dosing is used with recommendations made for those children greater than 30 kg and those children less than 30 kg. See Table 47-2 for dosing of tezacaftor/ivacaftor. The dosing is also twice daily, similar to lumacaftor/ivacaftor, and still needs to be taken with fat-containing food.

TABLE 47-2

Tezacaftor/Ivacaftor Dosing

Weight Based, Ages 6-11	Morning	Evening
<66 lbs or less than 30 kg	One tezacaftor 50 mg/ivacaftor 75 mg tablet	One ivacaftor 75 mg tablet
≥66 lbs or greater than 30 kg	One tezacaftor 100 mg/150 ivacaftor tablet	One ivacaftor 150 mg tablet
Patients who are greater than 12 years of age		
Ages greater than 12	One tezacaftor 100/ivacaftor 150 mg tablet	One ivacaftor 150 mg tablet

As with lumacaftor/ivacaftor trials, tezacaftor/ivacaftor also demonstrated improvements in FEV1, disease-related quality of life, and rate of pulmonary exacerbations when compared to placebo.[36] Additionally, it was found that BMI had improved slightly. These effects were seen in both delta F508 homozygous and heterozygous patients.

Elexacaftor

The newest approved CFTR modulator is the first triple combination that includes elexacaftor/tezacaftor/ivacaftor.[40] Elexacaftor and tezacaftor have slightly different mechanisms although both are still known as correctors. Elexacaftor corrects a flaw during the formation of the delta F508 CFTR protein that helps get more functioning CFTR proteins to the surface. This is known as a next-generation CFTR when compared to tezacaftor. Additionally, the triple combination only requires a single delta F508 mutation. Elexacaftor/tezacaftor/ivacaftor is currently only approved in those ages 6 and older. See Table 47-3.

TABLE 47-3

Elexacaftor Dosing

Age	Morning	Evening
6-12 years weighing less than 30 kg	Two tablets, each containing elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg	One tablet of ivacaftor 75 mg
6-12 years weighing more than 30 kg	Two tablets, each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg	One tablet of ivacaftor 75 mg
12 years and older	Two tablets, each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg	One tablet of ivacaftor 150 mg

Clinical trials, in both homozygous and heterozygous delta F 508 patients, evaluating the efficacy of the triple combination demonstrated an increase in percent predicted FEV1, a decrease in pulmonary exacerbations, and sweat chloride concentrations, and an improvement in respiratory symptoms as measured by a standardized questionnaire.[41,42] When compared to dual therapy, tezacaftor/ivacaftor, improvements were still noted in FEV1, sweat chloride concentrations, and respiratory symptoms.

Similar outcomes were noted in patients with advanced lung disease (<40% percent predicted FEV1).[41,43,44] These patients experienced an increase in FEV1, a decrease in chronic oxygen therapy and noninvasive ventilation, an increase in mean body weight, and a decrease in enteral feeding requirements.

CFTR Potentiator

Ivacaftor

Ivacaftor was the first medication approved for patients with CF that targeted the CFTR protein.[45] It is a CFTR potentiator that keeps the channels open at the cell surface to increase the transport of chloride in and out of the cell. Ivacaftor needs the CFTR protein to be present at the cell surface in order to be efficacious. The mutation first studied with ivacaftor was the missense mutation, G551D. Approximately 4% to 5% of patients with cystic fibrosis have the G551D mutation on one allele of the CFTR protein. Ivacaftor is indicated in patients who have one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data. The FDA approved 97 additional mutations for use with ivacaftor based on in vitro demonstration of modulator-induced increase chloride transport and clinical benefit. The in vitro-responsive mutations did show clinical benefits in a small randomized trial. Ivacaftor is approved for patients as young as four months old and is available as granule packets for children 4 months to 5 years and tablets for patients 6 years of age or older. As with the other agents, dose reductions are needed in patients with hepatic impairment. See dosing Table 47-4.

TABLE 47-4

Ivacaftor Dosing

Dosage Form	Age	Recommended Dose	Counseling Points
Granules	4 months to 6 months	One 25 mg packet every 12 hours	Shake the packet, and pour into 1 teaspoon (5 mL) with soft food or liquid that is at or below room temperature. (Ex: breast milk, formula, applesauce, milk, yogurt, juice)
	6 months to 6 years old	• 11 pounds (5 kg) to less than 15 pounds (6.8 kg): one 25 mg packet every 12 hours • 15 pounds (6.8 kg) to less than 31 pounds (14 kg): one 50 mg packet every 12 hours • 31 pounds (14 kg) or more: one 75 mg packet every 12 hours	
Tablet	6 years and older	One tablet 150 mg twice daily	With fat-containing food

In patients with a G551D mutation, ivacaftor increased the FEV1, decreased sweat chloride, reduced pulmonary exacerbations, improved pulmonary symptoms, and increased body weight.[46] The long-term effects demonstrated lower risks of death, hospitalizations, and transplantations.[47] Lower prevalence of *P. aeruginosa* along with lower acquisition rates and higher clearance rates have also been noted in patients on ivacaftor monotherapy.[48-50]

As with the correctors, elevations in hepatic enzyme concentrations and noncongenital lens opacities have also been reported with ivacaftor. Therefore, ivacaftor monitoring includes cataracts at baseline and then annually, as well as liver function tests at baseline and every 3 months during the first year of treatment and then annually thereafter.

CFTR Amplifiers

Amplifiers work by increasing the amount of CFTR protein in the cell and stabilizing CFTR mRNA through translational elongation.[51] In phase II trials, nesolicaftor appears well-tolerated and did increase the production of CFTR; however, it did not impact lung function in patients taking

tezacaftor/ivacaftor with two copies of the F508del mutation.

Airway Clearance Therapy

Airway clearance therapies are recommended for all patients with CF for clearance of sputum, maintenance of lung function, and improved quality of life.[52] Cystic fibrosis is characterized by dehydration of the airway surface liquid and impaired mucociliary clearance. Dehydration occurs as a direct result of the inherited abnormality in the cystic fibrosis transmembrane regulator protein which leads to a reduced chloride section and increased absorption of sodium and water from the airway surface liquid.[53] The dehydrated mucus layer eventually becomes adherent to the airway surface.[54] This tenacious adhesive mucus, leading to airway obstruction, creates an environment conducive to the growth of bacteria followed by a neutrophilic host response in the airway lumen. Subsequently, the DNA from dead neutrophils left in the airways further increases the viscosity of already abnormal secretions. Dehydration of the airway surface liquid layer is the primary initiating event in CF-related lung disease; therefore, therapeutic interventions to improve mucus clearance and reduce the obstruction, infection, and inflammation remains a cornerstone of treatment in CF.[29]

In addition to non-pharmacological measures to facilitate mucus clearance, pharmacologic therapies including mucolytics such as dornase-alfa and hyperosmolar agents such as aerosolized hypertonic saline are also used to improve mucus clearance. In addition, bronchodilators are utilized to support ACT by opening the airway to facilitate the removal of secretions along with deeper deposition of other inhaled medications into the smaller airways. Bronchodilators should be administered prior to CPT or other ACT techniques.

Mucoactive Agents

Dornase alfa (Recombinant human DNase)

Dornase alfa (recombinant human DNase, rhDNase), an enzyme that selectively hydrolyzes the extracellular DNA in the sputum of CF patients and reduces sputum viscoelasticity, is FDA-indicated in conjunction with standard therapies for the management of CF patients to improve pulmonary function.[55] The recommended dosage is one 2.5 mg single-use ampule inhaled once daily using a recommended nebulizer; however, some patients may benefit from twice-daily administration. The most common adverse reactions (occurring in ≥3% of patients treated with dornase alfa over placebo) seen in clinical trials in CF patients were: voice alteration, pharyngitis, rash, laryngitis, chest pain, conjunctivitis, rhinitis, decrease in FVC of ≥10%, fever, and dyspnea.

Both short-term and long-term clinical trials have demonstrated improvement in lung function as measured by FEV_1 as well as reductions in exacerbations requiring the use of parenteral antibiotics compared to placebo.[56-60] Increases in FEV1 have been noted in both short-term studies lasting from 1 to 2 weeks in duration and in long-term studies lasting from 24 weeks to 3 years.

The CF guidelines recommend the chronic use of dornase alfa to improve lung function and reduce exacerbations in all cystic fibrosis patients >6 years of age and older with asymptomatic/mild disease as well as moderate to severe disease.[61]

Hypertonic Saline (Nebusal™ 4 mL 7%)

Hypertonic saline acts as an osmotic agent which draws water into luminal secretions resulting in the restoration of airway hydration.[54] It is a solution possessing an osmotic pressure greater than that of a physiologic isotonic salt solution (0.9%NaCl).[62] By drawing water from CFTR defective airway epithelial cells, the periciliary layer becomes rehydrated and mucociliary clearance reestablished.[63,64]

In CF patients, 7% hypertonic saline has been shown to be safe, well-tolerated, and effective in restoring mucus clearance, reducing disease exacerbations, and slowing progressive airway obstruction. Short-term administration is associated with improved lung function, increased mucociliary clearance for at least 8 hours in a dose-dependent manner, and increased sputum expectoration.[65] Among infants and children with cystic fibrosis less than 6 years old, the use of inhaled hypertonic saline compared with isotonic saline did not reduce the rate of pulmonary exacerbations over 48 weeks of treatment.[66] In the majority of trials hypertonic saline was used after pre-treatment with bronchodilators and as an adjunct to chest physiotherapy; in both cases, this may be important to ensure its efficacy.[67]

As intolerability due to oropharyngeal irritation and bronchospasm generally relates to the concentration of hypertonic saline and its rate of delivery,

the selection of a dose for an individual patient is typically made by determining the maximally tolerated concentration.[54] For individuals with CF, 6 years of age and older, the Cystic Fibrosis Foundation recommends twice-daily use of inhaled hypertonic saline to improve lung function and quality of life and reduce exacerbations.[61]

Mannitol

Inhaled mannitol, an osmotic agent with a high molecular weight, has been proposed as an additional strategy to improve the airway surface hydration by the slow influx of water through a pericellular pathway and mucociliary clearance in patients with CF.[62]

A two-week course of inhaled mannitol in patients with CF resulted in an increase in mean FEV1 from baseline as well as mean FEF_{25-75} compared with placebo.[68] While an international trial assessing the effect of inhaled dry powder mannitol on lung function in CF showed a sustained clinical benefit, there have been no large randomized trials comparing the effect of hypertonic saline versus mannitol.[69]

Inhaled mannitol is considered a second line as a replacement for hypertonic saline in adult patients who fail the combination of hypertonic saline and dornase alpha. Inhaled mannitol was only recently approved by the FDA for use in cystic fibrosis adult patients.

Antibiotics

Infection is one of the main influences on the morbidity and mortality of CF and CF lung disease. Treating infections in CF involves not only antibiotics but chest physiotherapy and inhaled mucolytics play an important adjunction role. Most patients with CF develop chronic bacterial infections; however, the goal of antibiotic treatment is to delay the colonization by pathogens as long as possible. The prevalence of bacterial type varies with age; the most common pathogens include *P. aeruginosa, Staphylococcus aureus,* methicillin-resistant *Staphylococcus* (MRSA)*, Burkholderia cepacia complex,* and *nontuberculous mycobacteria.*

CF patients have an increased susceptibility to *P. aeruginosa* which is an independent risk factor for a decline in pulmonary function and decreased survival.[70,71] With chronic infection, *P. aeruginosa* converts from “dry” to a “mucoid” phenotype with the production of an alginate biofilm and becomes much more difficult to treat leading to a worse prognosis. *S. aureus* is another pathogen commonly found in the respiratory secretions of CF patients. Co-infection with *S. aureus* and *P. aeruginosa* has an independent and additive effect on airway inflammation.[72] As with *P. aeruginosa*, chronic infection with *B. cepacia* complex is associated with an accelerated decline in pulmonary function and shortened survival.

Strategies should be employed to prevent *P. aeruginosa* acquisition including measures to prevent transmission between CF patients and early eradication of both *P. aeruginosa* and *S. aureus* with appropriate treatment regimens. The CF Foundation recommends a 28-day cycle of inhaled tobramycin for the treatment of patients with newly acquired *P. aeruginosa*. Other regimens have been evaluated but were not as effective as inhaled tobramycin or had similar outcomes as inhaled tobramycin. Eradication protocols for MRSA are more difficult but can be offered to highly selected patients who are capable of following the protocol. The regimen typically includes oral rifampin, oral trimethoprim-sulfamethoxazole, nasal mupirocin, chlorhexidine oral rinses, body wipes, and environmental decontamination.[73]

Inhaled Antibiotics

Chronic colonization with *P. aeruginosa* necessitates chronic treatment with inhaled antibiotics. Currently available regimens include tobramycin, aztreonam lysine, and colistin with all of these agents administered initially in a cyclic phase (28 days on followed by 28 days off) or alternatively as continuous treatment by alternating in 28-day cycles between two different inhaled antibiotics.

Inhaled tobramycin is recommended as a first-line treatment. Inhaled aztreonam may be used in patients who do not tolerate tobramycin, whose pulmonary status is declining while on inhaled tobramycin, or who is or attempting to become pregnant. Adherence may be better with inhaled tobramycin because it is administered twice daily versus three times a day with aztreonam. Conversely, the aztreonam dose is delivered in less than 3 minutes, whereas tobramycin requires a 15 to 20-minute nebulization. If patients do not tolerate either tobramycin or aztreonam or pulmonary function continues to decline on either agent or both agents, inhaled colistin is an alternative. Inhaled colistin does not have the renal toxicity or neurotoxicity typically seen when administered intravenously and is administered twice daily for 28 days, alternating with 28 days off treatment.

Oral Azithromycin

Azithromycin has demonstrated clinical benefits in CF patients with chronic infection with *P. aeruginosa*. These benefits do not appear to be exclusively related to its antimicrobial effects but also an anti-inflammatory effect.[74-77] The antimicrobial effects center around the ability of macrolides to reduce the ability of *Pseudomonas* to produce biofilms, whereas the anti-inflammatory effect relates to azithromycin's ability to suppress the excessive inflammatory response noted in CF patients. In CF patients 6 years of age and older who are chronically infected with *P. aeruginosa,* azithromycin is typically prescribed as a 10 mg/kg dose administered three times a week. Smaller daily dosing rather than three times a week dosing could also be used with similar efficacy. Azithromycin may also be initiated at the time of a first positive culture for *P. aeruginosa* in children as young as 6 months and continued for 18 months rather than waiting until becoming chronically infected in order to initiate therapy.[78] Azithromycin therapy can be discontinued after multiple negative cultures over the previous year. Macrolide therapy should not be initiated in patients with a positive sputum sample for nontuberculous mycobacteria. The use of oral azithromycin may reduce the efficacy of inhaled and intravenous tobramycin. In retrospective studies, the concurrent use of tobramycin (either acute or chronic therapy) and azithromycin were associated with less improvement in lung function based on FEV1 when compared to tobramycin use alone.[79-82]

Anti-inflammatory Agents

Oral ibuprofen has also been used in cystic fibrosis for its anti-inflammatory properties and limited data has demonstrated a slower decline in lung function when used at a high dose in children who have good lung function (FEV1 > 60% [0.6] predicted).[61,83,84] However, the need for pharmacokinetic monitoring and the risk of side effects have restricted its use. A serum concentration between 50 and 100 mcg/mL (mg/L: 242-485 µmol/L) is needed.[85]

Inhaled glucocorticoids are only recommended in cystic fibrosis patients with a co-diagnosis of asthma.[61,86] These agents should not be routinely used in patients with cystic fibrosis without definite signs of asthma. Other agents that are not recommended in cystic fibrosis include chronic use of systemic glucocorticoids and cromolyn due to a lack of efficacy, potential for adverse effects, and increased expense.

Pancreatic Disease

Pancreatic exocrine insufficiency (PI) occurs in cystic fibrosis patients as a result of pancreatic duct obstruction due to a viscous exocrine fluid that congeals in the proximal pancreatic ducts.[87] Pancreatic function correlates strongly with genotype with 60% of infants being affected at birth. Patients with two "severe" CFTR mutations usually are associated with PI.[88-90] If left untreated, PI can lead to growth failure, weight loss, abdominal bloating, foul-smelling stools, or diarrhea.

The most common way to screen and diagnose pancreatic insufficiency in patients with cystic fibrosis is the use of the fecal pancreatic elastase-1 test. When values of the fecal pancreatic elastic-1 test result in a value of less than 100 micrograms/gram, it is likely, given the specificity and sensitivity of the elastase test, that the patient is pancreatic insufficient. Patients are often tested for PI at diagnosis and annually if deemed to be pancreatic sufficient.

Pancreatic Enzymes

Pancreatic enzyme replacement therapy (PERT) is the treatment of choice. PERTs are a combination of lipase, protease, and amylase. The PERT dose is generally expressed in lipase units. Typically, PERTs are known to increase fat absorption and provide more consistency in stool frequency and consistency when compared to placebo. There are multiple formulations of PERTs; however, the formulations are not interchangeable as recommended by the Cystic Fibrosis Foundation Guidelines.[91] High doses of PERT could lead to colonic stricture; therefore doses of PERT should not exceed 25,000 lipase units per kilogram per meal. Recommended doses are provided with three meals a day and with two to three snacks a day. The snack doses are traditionally half the dose at meal times. It is important to ensure the doses are taken prior to eating and not during or after eating. Enzymes can always be opened, and the contents may be mixed with small amounts of applesauce or alkaline food but should not be crushed or allowed to sit in food. Doses may be titrated based on symptoms of malabsorption such as foul-smelling stools, weight loss, abdominal bloating, or diarrhea. Prior to increasing the dose always take into consideration adherence, dietary factors, liver disease, intestinal hyperacidity, and abnormal intestinal motility. Dosing is also provided similarly when patients are on continuous overnight gastrostomy tube feedings.

There are six different FDA-approved pancreatic enzymes each consisting of various amounts of the combination of lipase, protease, and amylase. Most products are proprietary and there is only one generic pancreatic enzyme formulation available. Each formulation of pancreatic enzymes has

different characteristics. Some are delayed-release capsules. One product contains bicarbonate-buffered enteric-coated microspheres; this raises the pH of the duodenal environment to help delay the enzymes' inactivation by the stomach acid. Another product has a non-enteric coat and thus must be taken with a proton pump inhibitor to reduce the enzymes from being broken down in the stomach too quickly.

Common adverse events from pancreatic enzymes include headache, abdominal pain, flatulence, and cough. Some of these events may be related to malabsorption and may require dose increases. A dose-limiting side effect is fibrosing colonopathy as previously described.

Vitamins

Patients with CF, especially those that are pancreatic insufficient are at increased risk for fat-soluble vitamin deficiency. The fat-soluble vitamins include A, D, E, and K. Supplementation of these vitamins should begin as soon as CF is diagnosed and at typically higher doses than recommended for the general population. Monitoring of serum retinol, 25-hydroxyvitamin D, alpha-tocopherol, prothrombin time, and PIVKA II for assessment of vitamin K deficiency should occur at least annually.

Vitamin D deficiency is probably the most commonly studied vitamin deficiency in CF patients and appears to have an impact on inflammation and maintenance of bone health. The cystic fibrosis foundation has guidelines specifically for vitamin D to ensure that the serum 25-hydroxyvitamin D levels remain at least at 30 ng/mL (75 nmol/L) or higher in all patients with cystic fibrosis.[92] Vitamin D3 or cholecalciferol is the currently recommended oral supplement by the CF Foundation as opposed to vitamin D2, ergocalciferol.

Specific CF-formulated vitamins come in all formulations from drops, chewables, soft gels, and tablets. In addition, individual supplements may also be needed for continued vitamin-specific deficiency.

Pulmonary Exacerbations

Pulmonary infection is a major contributor to CF lung disease. A typical clinical course in most CF patients includes acute episodes of worsening pulmonary status with a decrease in FEV1 along with worsening symptoms such as increased cough and sputum production. Although viruses such as coxsackie/echovirus, rhinovirus, respiratory syncytial virus, parainfluenza, adenovirus, and influenza are often detected during acute exacerbations in children, most patients with CF also have a bacterial infection of the airways that are the same pathogens associated with chronic infections. These bacterial pathogens include *P. aeruginosa, S. aureus, B. cepacia* complex, non-typeable *Haemophilus influenzae, Stenotrophomonas maltophilia, Achromobacter* species, and nontuberculous mycobacteria. Treatment of pulmonary exacerbations requires a multimodal approach including antibiotics, chest physiotherapy, inhaled medications, anti-inflammatory agents, optimization of nutrition, and exercise as tolerated.

Systemic antibiotics are the mainstay of therapy for an acute exacerbation. The severity of the infection dictates the route of administration. Mild exacerbations can be treated with oral antibiotics, whereas severe exacerbations require the use of intravenous antibiotics. In general, the CF guidelines recommend using one antibiotic to cover each pathogenic bacteria and two antibiotics to cover *P. aeruginosa*.[93] Treatment with antipseudomonal antibiotics has demonstrated an improvement in pulmonary function tests, reduction in sputum bacterial density, and inflammatory markers.

The specific antibiotic selection should be patient-specific based on historic sputum culture and sensitivities and then narrowed or altered based on sputum cultures and sensitivities obtained at the onset of the exacerbation. Oral therapy with antipseudomonal coverage includes ciprofloxacin or levofloxacin. For moderate to severe exacerbations, an antibiotic combination of a beta-lactam along with either a fluoroquinolone or tobramycin should be used. If clinical response is inadequate after approximately 5 days of treatment, consideration should be given to switching the beta-lactam. Other alternatives may include switching the fluoroquinolone to tobramycin or exchanging tobramycin with amikacin. Colistimethate may also be an option when there is treatment failure.

The selection of antibiotic coverage for *S. aureus* will be dependent on if it is methicillin-sensitive or methicillin-resistant. Mild exacerbations with methicillin-sensitive *S. aureus* may be treated with trimethoprim-sulfamethoxazole, doxycycline, or amoxicillin-clavulanate. Trimethoprim-sulfamethoxazole and doxycycline may still be used for methicillin-resistant *S. aureus* in mild infections; however, severe exacerbations require the use of oral linezolid, intravenous vancomycin, or intravenous ceftaroline. When culture results reveal both *Pseudomonas* and *Staphylococcus*, a combination of the above agents is required. Due to the lack of sensitivity of ceftaroline against *P. aeruginosa* and the use of another beta-lactam for *Pseudomonas* coverage, ceftaroline is generally not encouraged in these situations in order to avoid using two beta-lactams simultaneously. In addition, the combination of piperacillin-tazobactam with vancomycin and tobramycin should be avoided due to the increased risk of renal toxicity.

Dosing of antibiotics in CF patients can be a challenge to ensure adequate lung penetration and maximum bactericidal activity. For instance, beta-lactam's effect is based upon time above the minimum inhibitory concentration, whereas aminoglycosides and fluoroquinolones killing effect is dependent upon the peak antimicrobial tissue concentration along with the post-antibiotic effect. In addition, the pharmacokinetics of antibiotics in CF patients differ compared to most other individuals. The volume of distribution and total body clearance is increased in CF patients for hydrophilic drugs such as aminoglycosides, penicillins, and cephalosporins. Specifically, the aminoglycoside's initial dose is higher than the general population and adjusted based on patient-specific pharmacokinetic parameters. The CF guidelines also support the use of extended-interval dosing or once-daily dosing of aminoglycosides in patients with normal renal function. The recommended target peak concentration differs between once-daily dosing and conventional dosing. The target peak concentration for once-daily dosing is 20 to 30 mcg/mL (mg/L) versus the 8 to 12 mcg/mL (mg/L) for conventional dosing. The calculated concentration at 18 hours should be <0.5 mcg/mL (mg/L) to minimize toxicity and to ensure at least a 6-hour period with low serum concentrations prior to the next dose.

Vancomycin, on the other hand, can be dosed and monitored in CF patients similar to the general population. The pharmacokinetics of vancomycin appears to be unaltered in CF patients. Patient-specific pharmacokinetic calculations should be used to maintain a trough concentration of 15 to 20 mcg/mL (mg/L; 10.4-13.8 µmol/L) in adults and 7 to 10 mcg/mL (mg/L; 4.8-6.9 µmol/L) in children. AUC-guided dosing may also be used instead of trough-driven dosing.[94] A target AUC between 400 and 600 × h/L is suggested for adults and pediatric patients.

The duration of treatment for an acute exacerbation is not standardized. Some centers continue antibiotic regimens until the resolution of symptoms and others continue therapy until there are improvements in the FEV1. Typically, antibiotics are continued for 10 days to 3 weeks depending upon the clinical course.

Bone Disease

Bone disease is a common complication of CF and is characterized by low bone mineral density (BMD). Factors that may contribute to bone disease over time may include malabsorption of vitamin D, poor nutritional status, physical inactivity, glucocorticoid therapy, and delayed pubertal maturation. It is thought that loss of bone mass occurs in childhood and worsens around puberty. Puberty plays a role in bone development and peak bone accruals usually occur during the growth velocity. Delay can be seen in patients with poor nutrition and poor control of CF. Dual-energy x-ray absorptiometry (DXA) scans should be performed routinely on adults and children older than 8 years if they are less than 90% of their ideal body weight, their FEV1 is less than 50% (0.5) of predicted, they received systemic glucocorticoids for more than 90 days in the previous year, have delayed puberty, or a history of fracture.[95] Osteoporosis is defined as having a BMD T score > –2.5, and osteopenia with a score between –1 and –2.5. Low BMD is common among adults with CF. A T-score less than –1 has been observed in 85% of adult patients with CF. As much as 34% of adult CF patients have a Z score less than –2 and 10% have T-scores less than –2.5. In pediatric patients, osteopenia is found in up to 47% of patients and osteoporosis in up to 34% of patients. Z scores are typically used for children less than 18. T scores are not meaningful in children. Both T and Z scores are useful in patients 18 to 30 years of age and T scores should be used in those 30 years and older.

Strategies for preventing the loss of bone minerals in patients with CF include maintaining good lung function, treatment of pulmonary exacerbations in a timely manner, optimizing nutritional care, and promoting the maintenance of lean body mass. Oral and inhaled steroids should be avoided as much as possible. Weight-bearing activities and exercise are recommended. Vitamin D and calcium supplementation should be continued as directed by the Cystic Fibrosis Foundation guidelines. Specifically, vitamin D3 (cholecalciferol) should be supplemented to achieve and maintain serum 25-hydroxyvitamin D concentration of 30 to 60 ng/mL (75-150 nmol/L) along with 1,300 to 1,500 mg of calcium per day.

An area of active research includes the use of growth hormone (GH) in patients with CF. With the use of GH, improvement in height and bone mineral content has been demonstrated. Long-term studies are still in progress to determine the optimal management of GH in patients with CF.

If DXA T score is greater than –1 or Z score is greater than –2.0, fragility fractures have occurred, or a patient is awaiting transplant, or BMD loss is greater than 3% to 5% a year, bisphosphonates are indicated in these patients. If the T/Z score is less than or equal to 2.0 then bisphosphonates are indicated. Bisphosphonates have been studied in trials in adults with CF and trials have yet to be heavily studied in children with CF. Pamidronate resulted in gains in the lumbar spine and total hip after 6 months; however, there were significant adverse effects from bone pain, fever, and phlebitis in 75% of the patients, some of which required hospitalization. The IV bisphosphonate, zoledronic acid, showed benefit; however, the patient dropout rate was 20% due to bone pain.[96]

In patients aged 5 to 30 years old with CF and low BMD, oral alendronate, 5 mg/day and 10 mg/day based on weight, increased BMD by 16.5% and was well-tolerated.[97] Additionally, alendronate is the only bisphosphonate available in liquid formulation. Risedronate 35 mg once weekly in patients older than 18 with CF was found to improve lumbar spine BMD.[98] There were reports of bone pain in the first 56 days of risedronate use, with some leading to discontinuation of risedronate.

Denosumab is a monoclonal antibody that works to inhibit osteoclasts differentiation and activation and functions as an anti-resorptive therapy to reduce bone breakdown. It is approved for the treatment of osteoporosis in men and post-menopausal women and glucocorticoid-induced osteoporosis. There are no studies published evaluating the use of denosumab in patients with CF. Until more studies can be conducted denosumab is considered second-line for patients who cannot tolerate, have a contraindication, or fail bisphosphonate therapy.

There are other adverse effects to monitor when initiating an oral bisphosphonate such as esophageal ulcers, osteonecrosis, and hypocalcemia. IV bisphosphonates appear to have that acute-phase reaction after the initial infusion leading to flu-like symptoms but have been seen to be more severe in patients with CF for an unknown reason. A short course of NSAIDs or acetaminophen was found to mitigate the effect.

Long-term data is lacking for the safety of bisphosphonates in children and young adults, the general approach is to minimize bisphosphonate treatment to typically less than 5 years with periods of off treatment or bisphosphonate holidays.[99] Following this off-treatment period, patients may be monitored via DXA scans every 1 to 2 years to assess for interval bone loss. If no treatment is needed following a DXA scan, DXA scores may be repeated every 5 years unless there is a change in risk factors if T or Z scores are –1 or better. Individuals between –1 and –2 should have a repeat DXA every 2 to 4 years and annually for scores greater than –2.

Cystic Fibrosis–Related Diabetes

CFRD is the most common comorbidity in patients with CF, occurring in 20% of adolescents and 50% of adults. The course is progressive in nature, and patients may move back and forth between an impaired state and CFRD. Uncontrolled CFRD may correlate with pulmonary function decline, weight loss, and *P. aeruginosa*. This comorbidity is difficult to manage as patients are directed to have high caloric intake due to having CF. Diabetes ketoacidosis (DKA) is rare.[22] CFRD may present like in the honeymoon period when compared to type 1 diabetes patients because they may still have endogenous insulin secretion.

Following the diagnosis of CFRD, patients should be treated with insulin therapy instead of oral anti-hyperglycemic medications. Data suggests that therapies such as sulfonylureas, metformin, meglitinides, and thiazolidinediones are not as effective as insulin. After an acute illness or systemic glucocorticoid treatment, insulin requirements may increase and take about 4 to 6 weeks to return to baseline. Close monitoring is required to ensure that hypoglycemia does not occur in these patients following acute illness. Dosing for insulin is usually between 0.5 and 0.8 units/kg/day in both adolescents and adults. If a patient has fasting hyperglycemia a basal/bolus regimen is recommended. The starting dose for basal insulin is 0.125/units/kg and may be titrated up to 0.25/units/kg. For meal coverage doses start at 0.5 to 1 unit for every 15 grams of carbohydrates consumed. The doses may be titrated by 0.5 units per 15 grams of carbohydrates to achieve 2 hours post-prandial blood glucose. Carbohydrate counting is recommended to best determine a pre-meal insulin dose. Correction doses are typically 0.5 to 1 unit of rapid-acting insulin based on a insulin sensitivity factor of 1 unit for every 50 mg/dL (2.8 mmol/L) above 150 mg/dL (8.3 mmol/L). Some lifestyle recommendations differ in patients with CFRD when compared to patients with diabetes mellitus. Carbohydrate intake is individualized, there is no restriction on fat intake, protein intake is doubled, sodium intake is liberalized, and regular supplementation with ADEK vitamins is needed. Weight loss is not recommended.

Blood glucose (BG) should be self-monitored at least three times daily and goals should be individualized. Monitoring can also occur using a continuous glucose monitoring (CGM). Plasma glucose goals for CFRD are similar to patients with diabetes as recommended by ADA but some patients may benefit from higher or lower goals. Glucose monitoring may be useful to detect early glucose abnormalities that the OGTT and A1c cannot detect. While CGM's are not approved to diagnosis diabetes, they can be useful in detecting glucose excursions when titrating insulin therapy. The patient's A1c may falsely indicate good glycemic control despite the fact that the patient may have frequent hyperglycemia or hypoglycemia.[23] Like other patients with diabetes mellitus, the A1c treatment goal should be ≤7% (53 mmol/mol) to reduce the risk of microvascular complications; however, goals must be individualized. An A1c should be ordered quarterly. Monitoring of microvascular complications such as nephropathy, retinopathy, and neuropathy is important. Screening for these complications should be initiated 5 years after diagnosis of CFRD.[22] The use of ACEI or ARBs are appropriate, and cough associated with ACEI use is seen in ~10% of patients. Nephropathy should be monitored using urine protein testing, with an albumin to creatinine ratio of 300 µg/mg (33.9 mg/mmol) or greater indicating macroalbuminuria and progression toward renal failure. Retinopathy is

seen in 10% to 20% of patients with CFRD and should be monitored through regular dilated retinal exams. Neuropathy may be less severe in patients with CFRD but annual foot evaluations are still recommended. An annual lipid profile is recommended for patients with CFRD.

Cystic Fibrosis Liver Disease

Cystic fibrosis liver disease (CFLD) is the third leading cause of death among patients with CF.[21] There is a wide variety of presentations of liver disease from steatosis, cholelithiasis, and multilobular cirrhosis.

The aim of the treatment of CFLD is to prevent further liver damage and complications related to portal hypertension and cirrhosis. There is currently no long-term treatment that has proven efficacy; however, there are treatments for the complications of CFLD. Ursodiol displaces toxic bile from enterohepatic circulation, has a cytoprotective effect on cells that are exposed to toxic bile acids, stimulates Ca-activated chloride channels, and has immunoregulatory properties. It may delay the progression of cirrhotic changes in patients with CFLD. It is dosed 20 to 30 mg/kg/day. Table 47-5 for medical management of complications of CFLD. In patients with advanced CFLD with decompensated liver failure, transplantation is the treatment of choice.

TABLE 47-5

Medical Management of Complications Related to Cystic Fibrosis Liver Disease

Indication	Treatment of choice
Hepatic steatosis	Optimize nutritional status and evaluate for deficiencies of essential fatty acids, carnitine, and choline
Hepatic congestion	Optimize cardiopulmonary function
Cholestasis	Treatment of fat-soluble vitamin deficiency
Portal hypertension	Beta-blocker use with caution, variceal band ligation
Ascites	Salt restriction, or transjugular intrahepatic portosystemic shunt

Cystic Fibrosis GI Disease

Gastrointestinal complications have become a common cause of morbidity in the cystic fibrosis population and include conditions such as gastroesophageal reflux (GERD), constipation, distal intestinal obstruction syndrome, and fibrosing colonopathy along with others.

GERD in the CF patient is similar to that of the general population. Even though there has been some association between GERD and pulmonary disease, there is not overwhelming evidence to support a causal association, nor that treatment has a beneficial effect on pulmonary function. There are pros and cons to the management of GERD with proton pump inhibitors (PPIs) including improving fat absorption in patients with pancreatic insufficiency, whereas potential harm would be the negative effects on bone health in a population already at increased risk for osteoporosis. A clear goal should be determined when initiating PPIs in cystic fibrosis patients with GERD and therapy discontinued if no improvement in symptoms is noted. Patients should be monitored for increased pulmonary exacerbations, vitamin B12 deficiency, hypomagnesemia, and bone health while receiving PPI treatment.

Constipation affects 25% to 50% of cystic fibrosis patients and is a common cause of flatulence and abdominal pain. Constipation in the CF patient results from abnormal intestinal fluid composition, dysmotility, and pancreatic insufficiency even though pancreatic sufficient patients have a relatively dehydrated bowel. Treatment generally consists of osmotic laxatives with or without electrolytes along with an assessment of the PERT dosing to ensure an adequate dose. Lubiprostone may be considered a second-line option in adult cystic fibrosis patients with severe refractory constipation.

Distal intestinal obstruction syndrome (DIOS) results from either a complete or incomplete obstruction of the ileocecum by thickened intestinal

contents and is manifested by cramping abdominal pain, abdominal distention, flatulence, weight loss, and poor appetite. Unlike constipation which is a gradual onset of fecal impaction, DIOS occurs acutely to intermittently with symptoms becoming progressively more severe over time. DIOS is more common in those with pancreatic insufficiency and having the F 508 del genotype. Others at risk of DIOS include patients with poorly controlled malabsorption, dehydration, and opioid use. Treatment should target fluid and electrolyte abnormalities along with a regimen of either oral/nasogastric rehydration and osmotic laxatives or hyperosmolar enemas with or without laxatives. Prevention should be the goal once the impaction is removed by optimizing the pancreatic enzymes and sufficient hydration.

Fibrosing colonopathy, a dose-limiting side effect of pancreatic enzymes, is a severe intestinal process involving fibrosis and strictures. First detected in patients receiving large doses of pancreatic enzymes, pancreatic enzyme dosing recommendations now limit the maximum dose to 2,500 lipase units/kg/meal or 10,000 lipase units/kg/day. Adjunctive therapy with H2 blockers or proton pump inhibitors helps maintain the recommended dosing range while boosting the stability of the pancreatic enzymes in the acidic environment of the GI tract and increasing the efficiency of the prescribed pancreatic dose in managing the fat malabsorption.

Mental Health

Managing CF is complex and takes about 2 to 4 hours of the day, especially, if other complications arise which may increase this time. The burden of this disease may lead to patient and parent depression and anxiety. Depression prevalence ranges from 8% to 29% in children and adolescents and 13% to 33% in adults.[100,101] Similarly, 22% of the adolescent population and 32% of the adult population reported anxiety.[102] Reports of depression and anxiety have been associated with decreased lung function, lower body mass index, worse adherence, and worse health-related quality of life.[103] It is recommended by the Cystic Fibrosis Foundation that all children with CF who are 7 to 11 years old be assessed for depression and anxiety or when there is a concern for the child exhibiting symptoms of depression or anxiety by his/her team or caregivers. Annual screening for depression and anxiety is recommended for all individuals with CF beginning at 12 years of age utilizing the PHQ-9 and GAD-7. Screening is also recommended for caregivers.

When caring for patients with CF it is important to provide behavioral interventions to help alleviate distress when it relates to medical procedures. Additionally, to provide supportive intervention when PHQ/GAD scores are elevated. Patients who are aged 7 to 11 who present with clinically significant or elevated PHQ and GAD scores may undergo evidence-based psychological interventions such as cognitive-behavioral therapy (CBT) with continued monitoring. For those that are 12 years of age and older with mild symptoms of depression or anxiety, education can be provided, as well as preventative and supportive interventions and to continue to follow up at the next scheduled visit. For those 12 years of age and older with moderate symptoms it is appropriate to engage in CBT, if this treatment is not alleviating symptoms, psychotropic medication may be considered next. For those 12 and older, selective serotonin reuptake inhibitors (SSRIs) are recommended for the treatment of depression and anxiety. Doses of SSRIs may need to be increased when used in combination with lumacaftor. Additionally, linezolid is not recommended for use with SSRIs when alternatives are available. QTc prolongation may be more significant with the use of citalopram and may require EKG monitoring when used with other medications that may cause QT prolongation.

EVALUATION OF THERAPEUTIC OUTCOMES

CF patients are typically monitored every month for the first year after diagnosis and then every 1 to 3 months, depending on the stability of their illness. Clinicians should evaluate the patient's pulmonary function and lung volumes using pulmonary function tests (PFTs) quarterly and assess for unusual or increased respiratory symptoms at each clinic visit to determine if the current pharmacotherapy regimen is effective. Quarterly sputum cultures are typically collected to determine which organisms are growing in the patient's lungs. Airway clearance, inflammation, and bacterial colonization must be under control for optimal pulmonary function. Weight and height should be measured at every visit to assure adequate growth (pediatrics) and nutrition (pediatrics and adults). A BMI greater than the 50th percentile in children and greater than 22 in female adults and 23 in male adults is associated with optimal lung function. The pharmacist is integral to the multidisciplinary CF team to ensure optimization of pharmacotherapy and to evaluate and encourage patient/family adherence to recommended treatments, both nonpharmacologic and pharmacologic.

CONCLUSION

Cystic fibrosis is a multi-system disease requiring a multi-modal treatment approach administered through a multidisciplinary team to provide optimal care and the best patient outcomes. This multidisciplinary team consists of nurses, physicians, respiratory therapists, dietitians, social workers, and an

overall program coordinator as required team members. The CF Foundation recommends that pharmacists, physical therapists, psychologists, and a research coordinator also be a part of these teams.

With the advancements in science and treatment options, not only is the quality of life for cystic fibrosis patients increasing but their overall lifespan is also expanding. Thus, it is crucial that the healthcare team optimizes treatment to reduce pulmonary exacerbations, delay colonization by pathogens and maintain lung health; maximizes adequate nutrition with appropriate dosing of pancreatic enzymes and vitamin supplementation; and initiates CFTR modulators to target the underlying pathology and advance the management of cystic fibrosis.

ABBREVIATIONS

ACT	Airway Clearance Technique
ADA	American Diabetes Association
ADEs	adverse drug events
ALT	alanine transaminase
AST	aspartate aminotransferase
BMD	bone mineral density
BMI	body mass index
CBAVD	congenital bilateral absence of the vas deferens
CBT	cognitive behavioral therapy
CF	cystic fibrosis
CGM	continuous glucose monitoring
CFLD	cystic fibrosis liver disease
CFMS	cystic fibrosis metabolic syndrome
CFRD	cystic fibrosis–related diabetes
CFTR	cystic fibrosis transmembrane conductance regulator
CMP	comprehensive metabolic panel
CPT	chest physical therapy
DIOS	distal intestinal obstruction syndrome
DXA	dual-energy x-ray absorptiometry
EKG	electrocardiogram
FDA	Food and Drug Administration

FEF_{25-75}	forced expiratory flow at 25% and 75%
FVC	forced vital capacity
FEV1	orced expiratory volume in 1 second
GAD-7	generalized anxiety disorder assessment
GERD	gastroesophageal reflux disease
GGTP	gamma-glutamyl transpeptidase
GGT	gamma-glutamyl transferase
GH	growth hormone
G-tube	gastrostomy tube
H2 Blockers	histamine 2 receptor antagonist
HTS	hypertonic saline
IRT	immunoreactive trypsinogen
MRSA	methicillin-resistant *Staphylococcus aureus*
OGTT	oral glucose tolerance test
PEP	positive expiratory pressure
PERT	pancreatic enzyme replacement therapy
PHQ-9	Patient Health Questionnaire
PI	pancreatic insufficiency
PIVKA II	protein induced by vitamin K absence-II
PPI	proton pump inhibitor
QTc	corrected QT interval
SMBG	self-monitoring blood glucose
SOCAP	subjective, objective, calculations, assessment plan note

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SELF-ASSESSMENT QUESTIONS

1. Which of the following organisms is typically found earliest in respiratory cultures of patients with cystic fibrosis?
   A. *Staphylococcus aureus*
   B. *Pseudomonas aeruginosa*
   C. *Burkholderia cepacia*
   D. *Haemophilus Influenza*
2. What class of Mutation is Delta F508 (the most common mutation found in cystic fibrosis)?
   A. Class 2
   B. Class 3

C. Class 5

D. Class 6

3. Which tests is used to diagnose cystic fibrosis?

A. Sweat Test

B. Nasal potential difference

C. Genetic testing

D. All of the above

4. Which of the following BEST describes the genetic acquisition of cystic fibrosis?

A. Only one parent is a carrier of the CF gene

B. Only one grandparent is a carrier of the CF gene

C. Both parents are carriers of the CF gene

D. Cystic fibrosis is not acquired genetically

5. A 6-year-old patient is admitted for a pulmonary exacerbation. The patient typically grows methicillin-resistant *S. aureus* (MRSA) and Pseudomonas. Which of the following antibiotic regimens would be the best initial treatment?

A. Nafcillin and tobramycin

B. Vancomycin and ciprofloxacin

C. Vancomycin Tobramycin and Ceftazidime

D. Linezolid and Ceftazadime

6. You are seeing a 16-year-old CF patient for their yearly visit. While taking a history, the patient mentioned that she almost had an accident 3 nights ago as they were unable to see the oncoming car that merged into the lane. Which of the following should be the next step in evaluating this patient?

A. refer to ophthalmology

B. check vitamin levels

C. perform vision screen in clinic

D. check fecal elastase

7. Which of the following CFTR modulators is indicated in seven-year-old patients with only one delta F 508 mutation?

A. Ivacaftor

B. Elexacaftor/tezacaftor/ivacaftor

C. Lumacaftor/ivacaftor

D. Tezacaftor/ivacaftor

8. AA's family is thinking about initiating lumacaftor/ivacaftor. AA is four years old. What monitoring parameter is most appropriate to obtain prior to

initiating lumacaftor/ivacaftor?

A. Complete blood count

B. DEXA scan

C. Hearing exam

D. Liver function panel

9. BA is found to be indicated for pancreatic enzyme replacement therapy (PERT). BA weights 20 kg. Accounting for all of BA's meals and snacks, what is the max dose that should be prescribed for BA and their PERT therapy.

A. 50,000 lipase units per meal and 25,000 lipase units per snack

B. 20 lipase units per meal and 10 lipase units per snack

C. 40,000 lipase units per meal and 10,000 lipase units per snack

D. 40 lipase units per meal and 20 lipase units per snack

10. Which is the *most* appropriate treatment for a patient with CFRD with impaired glucose tolerance?

A. Metformin

B. Pioglitazone

C. Insulin Glargine

D. Insulin Aspart

11. When assessing a 13-year-old patient with CF who may have a high disease burden. This patient has anxiety involving their treatment as well the team has seen a decrease in lung function over the last year, lower BMI over the last year, and the patient has been skipping their treatments in the evening. This patient refuses a referral to a mental health professional. What is the most appropriate next treatment step for this patient?

A. Initiate citalopram 40 mg daily

B. Initiate CBT

C. Initiate mirtazapine 15 mg nightly

D. Initiate melatonin 5 mg nightly

12. The purpose of using hypertonic saline in a cystic fibrosis patient is to

A. Decrease bacterial growth

B. Decrease sweat chloride content

C. Hydrate pulmonary secretions

D. Increase serum sodium content

13. A cystic fibrosis patient is using the following inhaled medications:

Cayston

Hypertonic saline

Albuterol

Pulmozyme

In what order should these medications be administered (listed first to last)?

A. Cayston, Hypertonic saline, Albuterol, Pulmozyme

B. Pulmozyme, Albuterol, Hypertonic Saline, Cayston

C. Albuterol, Pulmozyme, Cayston, Hypertonic Saline

D. Albuterol, Hypertonic Saline, Pulmozyme, Cayston

E. Hypertonic Saline, Albuterol, Cayston, Pulmozyme

14. Chronic management of airway inflammation in cystic fibrosis should (typically) includes which of the following?

A. Hypertonic Saline

B. Aerosolized aztreonam

C. Azithromycin

D. Cholecalciferol

15. The Cystic Fibrosis Foundation recommends all individuals with cystic fibrosis maintain a serum 25-hydroxyvitamin D goal of at least _____ ng/mL.

A. 15 (37 nmol/L)

B. 30 (75 nmol/L)

C. 60 (150 nmol/L)

D. 90 (225 nmol/L)

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** Haemophilus influenza. The patient is typically colonized with *Staphylococcus aureus* second and non-mucoid pseudomonas after that. *Burkholderia cepacia* is typically found in older patients with more advanced lung disease.

2. **A.** class 2 mutations occur when the mutant protein is made in its entirety but fails to fold properly inside the cell, This results in the absence of mature CFTR in the cellular membrane to perform its specific chloride ion conductance function.

3. **D.** Sweat test is still the gold standard all can be used in the diagnosis of CF. Genetic testing is used to determine the patient's specific mutations and is helpful in determining which modulators the patient will qualify for. Nasal potential difference provides evidence of the abnormal function of the cystic fibrosis transmembrane conductance regulator as values less than −40 mV is abnormal.

4. **C.** Cystic Fibrosis occurs in a classic single-gene (Mendelian) autosomal recessive pattern. Autosomal recessive patterns of inheritance require both parents to be carriers of the gene.

5. **C.** Nafcillin does not typically cover methicillin-Resistant staph aureus. Vancomycin is one preferred IVC treatment for MRSA. Ciprofloxacin is typically reserved for outpatient therapy, as it is one of the few oral antibiotics that can treat pseudomonas. Pseudomonas is typically treated with 2 antibiotics to decrease the development of antibiotic resistance.

6. **B.** pancreatic insufficiency causes decreased absorption of fats and which then leads to malabsorption of fat-soluble vitamins. In a 16-year-old patient, symptoms would be likely related to suboptimal adherence to vitamin therapy as opposed to malabsorption. An early symptom of vitamin A deficiency is night blindness. Vitamin E can cause neurologic deficits, Vitamin K clotting disorders and easy bleeding, and Vitamin D rickets

7. **B.** Is the only CFTR modulator agent that is indicated for patients six and older with at least one delta F 508 mutation.

8. **D.** When initiating a CFTR modulator it is important to assess baseline transaminases such as ALT and AST as well as obtaining an eye exam in pediatric patients.

9. **A.** The maximum dose per meal is 2,500 lipase units per kilogram per meal with snacks being half the dose at mealtimes.

10. **D.** Due to patients with CFRD having multimodal reasons for impaired glucose tolerance. CFRD may be related to a loss of insulin-producing islet cells due to autolysis and fatty infiltration of the pancreas. As this is not a process due to entirely glucose resistance processes large doses of aspart may not be needed with impaired postprandial glucose. Insulin is usually the most appropriate treatment for CFRD, however, a patient's fasting glucose becomes impaired later in disease progression whereas prandial glucose is affected earlier on therefore not requiring insulin glargine initially.

11. **C.** May help with weight gain as well as anxiety and depression symptoms. Initiating citalopram may put the patient at QT prolongation. The patient is refusing counseling at this time and melatonin may not help with anxiety.

12. **C.** Hypertonic saline acts as an osmotic agent which draws water into luminal secretions resulting in the restoration of airway hydration. It is a solution possessing an osmotic pressure greater than that of a physiologic isotonic salt solution (0.9%NaCl). By drawing water from CFTR defective airway epithelial cells, the periciliary layer becomes rehydrated and mucociliary clearance reestablished.

13. **D.** Bronchodilators will open the airways and make it easier to expel mucus and allow medications to penetrate deeper into the lung. Hypertonic saline will mobilize the mucus and improve airway clearance by hydrating the airways. Pulmozyme will thin the mucus. All of these agents work to open and clear the airways of mucus allowing the inhaled antibiotics to work on the remaining bacteria.

14. **C.** Azithromycin has demonstrated benefits in CF patients with chronic infection with *P. aeruginosa*. These benefits do not appear to be exclusively related to its antimicrobial effects but also an anti-inflammatory effect. The antimicrobial effects center around the ability of macrolides to reduce the ability of *Pseudomonas* to produce biofilms whereas the anti-inflammatory effect relates to azithromycin's ability to suppress the excessive inflammatory response noted in CF patients.

15. **B.** Vitamin D deficiency is probably the most commonly studied vitamin deficiency in CF patients and appears to have an impact on inflammation and maintenance of bone health. The cystic fibrosis foundation has guidelines specifically for vitamin D to ensure that the serum 25-hydroxyvitamin D levels remain at least at 30ng/mL (75 nmol/L) or higher in all patients with cystic fibrosis.