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Principles and Practice of Hospital Medicine

Second Edition

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CHAPTER 234

Cystic Fibrosis

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1. How do mutations in the cystic fibrosis (CF) gene relate to the clinical manifestations of the disease?
2. What criteria help determine when a CF patient should be admitted to the hospital for respiratory complications of the disease?
3. What treatment modalities are most effective in restoring lung function to baseline for CF respiratory exacerbations?
4. Why is CF-related diabetes (CFRD) important to control during acute pulmonary exacerbations as well as at baseline?
5. What are the most effective treatment modalities for the two most common pulmonary complications of CF: massive hemoptysis and pneumothorax?

INTRODUCTION

■ DEFINITION AND OVERVIEW

Cystic fibrosis (CF) is an autosomal recessive disease due to mutations in the CF transmembrane conductance regulator (CFTR) gene. The CFTR gene is expressed in epithelial cells in a variety of organs including the lung, sinuses, pancreas, sweat gland, intestine, liver, and vas deferens, and thus CF is a multiorgan disease. CF is the most common inherited life-shortening disease of Caucasians in the United States. More than 90% of the morbidity and the mortality are due to lung disease. CF lung disease is characterized by the triad of altered mucociliary clearance, chronic polymicrobial infection of the airways, and an exaggerated inflammatory response. The ultimate outcome of CF lung disease is destruction of the normal airway architecture and death due to respiratory failure.

With therapy, primarily aimed at slowing the progression of lung disease and improving nutrition, median survival is approaching 40 years of age. Unfortunately, there is no cure for CF. However, for CF patients with select CFTR mutations, there have been recent advancements and FDA approval of CFTR potentiator/corrector medications. The first FDA approved CFTR potentiator, ivacaftor, exerts its effects by improving the function of the defective CFTR protein. Unfortunately, ivacaftor benefits a small segment (about 5%) of the CF population with specific CFTR mutations (eg, G551D). More recently, a combination pill comprised of the potentiator ivacaftor and a CFTR corrector, lumacaftor, has been approved for CF patients homozygous for the ΔF508 mutation. This accounts for approximately 50% of the CF patients in North America. These medications are metabolized by the CYP3A system, and particular care must be taken by the hospitalist whenever additional medications that alter CYP3A function (such as many anti-fungal medications) are added into the therapeutic regimen for CF patients currently on one of these CFTR potentiator/corrector medications. Despite these therapeutic advancements, clinical improvements for patients with CF on these newer medications remain modest. As such, there remains ongoing aggressive research and development for other CFTR potentiators and correctors. The average CF adult can expect to spend 2 to 3 hours a day taking a variety of inhaled medications, ingest 30 to 50 pills per day, and be hospitalized about once per year for a period of a few days to weeks. Even with insurance, most CF patients have out-of-pocket health care costs approximately $10,000 per year.

In contrast, some CF patients with lung function within the normal range rarely require hospitalizations and need few medications to control their disease. Thus, tremendous variability exists in the severity of the pulmonary phenotype in this monogenic disease, ranging from death in childhood due to respiratory failure to living to retirement and the thought of enjoyment of family and friends through middle age and into old age.

■ GENETIC EPIDEMIOLOGY—INCIDENCE AND ETHNIC DISTRIBUTION

The incidence of CF varies tremendously according to ethnicity. In the United States CF occurs in about 1 in 3500 Caucasian births, 1 in 17,000 African Americans, and 1 in 90,000 Asians in Hawaii. Once considered a disease affecting only children, the life expectancy in CF has increased dramatically in the past 3 decades. Now 41% of CF patients are over 18 years of age, and the median predicted survival in 2013 is 40.7 years.

PATHOPHYSIOLOGY

The CFTR protein is a chloride channel in the apical aspect of epithelium in a variety of organs, including the lungs, sweat ducts, vas deferens, liver, pancreas, and intestines. Through unknown mechanisms, expression of mutant CFTR and the resultant failure to conduct chloride also causes marked increase in sodium import through the epithelial sodium channel, ENaC. In the lung epithelium, this results in marked reduction in the depth of the airway surface lining fluid and loss of effective mucociliary clearance. Expression of mutant CFTR also results in failure to export glutathione to the extracellular compartment, resulting in extremely low levels of antioxidant capacity in the epithelial lining fluid and more susceptibility to damage. CFTR may be additionally expressed in pancreatic beta cells, thus providing a potential molecular mechanism for the very high prevalence of diabetes in CF.

Expression of mutant CFTR, particularly in neutrophils and airway epithelial cells, results in an abnormal proinflammatory response characterized by an excessive and persistent neutrophil dominated inflammation. The CF airway shows a tremendous preponderance of neutrophils even shortly after birth. These neutrophils are a source of elastase and reactive oxygen species that destroy lung tissue. Furthermore, dying neutrophils in the CF lung do not undergo apoptosis but rather necrosis, resulting in release of massive amounts of sticky, uncoiled DNA that markedly increases the viscosity of airway secretions.

Persistent airway bacterial infection (particularly with Pseudomonas aeruginosa and Staphyloccocus aureus) is the hallmark of CF lung disease, and proposed mechanisms for this include defective phagocytosis, defective intracellular killing, increase in the number of receptors for bacteria on epithelial cells, and promotion of biofilm formation by the bacteria.

The CFTR gene (chromosome 7) has more than 1800 disease causing mutations within six classes (Table 234-1). The most common mutation, ΔF508, accounts for 66% of the CF mutations worldwide. About 15 mutations may account for 80% to 90% of the mutations seen in Caucasians.

Mutations where there is little or no full length CFTR at the outer plasma membrane are considered "severe" and those where there is a full length protein, but in some way the protein has defective function, are considered "mild." However, significant discordance between gene mutations and severity of lung disease suggests the importance of modifier genes and environmental interactions in disease expression, and explains why two cystic fibrosis patients with the same gene defect in the CFTR gene can present with very different disease severity and clinical course.

Cystic fibrosis may affect multiple organs, but the vast majority of morbidity and mortality occurs due to lung disease. The triad of impaired mucociliary clearance, persistent airway infection, and exaggerated inflammatory response leads to bronchiectasis and ultimately respiratory failure and death. Lung function declines progressively in most CF patients, with an annual rate of decline in function varying from 1% to 4% per year. The rate of decline may be punctuated by acute pulmonary exacerbations with precipitous drops in lung function and incomplete recovery from the exacerbation. Resetting of baseline lung function at a new lower level may occur following respiratory exacerbations. Frequent respiratory exacerbations are the hallmark of lung disease severity in CF, and significantly impact quality of life, health care costs and survival.

The cause of acute pulmonary exacerbations is currently unknown but likely related to increased bacterial load rather than infection by a different strain of bacteria. Other risk factors include increased exposure to particulate air pollutants and viral infections (eg, influenza virus, respiratory syncytial virus). However, nearly 20% of CF pulmonary exacerbations have no identified inciting cause.

TABLE 234-1 Class of Gene Defects

Class	Mutation Example	Cellular/Molecular Phenotype
I	W1282X	Absent CFTR production due to nonsense mutations, frameshift mutations, or abnormal mRNA splicing
II	ΔF508	Improper intracellular processing of CFTR with less than normal amounts of CFTR protein at the apical plasma membrane
III	G551D	Defective regulation of CFTR channels at the apical plasma membrane
IV	R117H	Defective permeation of anions through CFTR channels at the apical plasma membrane
V	3849 + 10KbC > T	Reduced synthesis of normal CFTR
VI	Q1412X	Altered apical membrane residence time of CFTR channels with truncated c-termini

CFTR, cystic fibrosis transmembrane receptor.
Reproduced, with permission, from Kreindler JL. Pharmacol Ther. 2010;125: 219-229.

DIFFERENTIAL DIAGNOSIS

The diagnosis of CF should be considered in patients with any of the following conditions:

- Symptoms of chronic obstructive pulmonary disease (COPD) or asthma who are not responding as expected to treatment
- Bronchiectasis of unknown etiology
- Isolation of mucoid Pseudomonas in a person with chronic respiratory symptoms
- Isolated pancreatitis or recurrent pancreatitis unexplained by alcohol, medications, or gallstones
- Pansinusitis
- Nasal polyps in healthy adolescents younger than 20 years old
- Male infertility (as males born with CF have nearly 100% congenital absence of the vas deferens)

DIAGNOSIS

CF may be suspected in a patient because of having one or more characteristic phenotypic symptoms (see differential diagnosis), a positive history of CF in a sibling, or a positive newborn screen (performed in all US states). The diagnosis of CF is made by two positive sweat chloride results done on separate days using quantitative pilocarpine iontophoresis in a clinical laboratory certified by the Cystic Fibrosis Foundation. However, a small, but not insignificant, portion of patients with clinical symptoms concerning for CF will have a sweat chloride in the indeterminate or normal range. In this situation, a CFTR genotype and sequencing can identify whether the person has two disease-causing mutations. Additionally, all CF patients should undergo gene sequencing to identify whether they carry a mutation responsive to a CFTR potentiator (ie, ivacaftor) as well as to provide information on prognosis.

In 2013, 65% of all CF cases were diagnosed by newborn screen. Prior to newborn screening, about 3% to 5% of CF patients were diagnosed as adults. This number will decrease with time, but it will take several years to decades before diagnosis of CF in adulthood is a rarity. In addition, many states screen only for the most common mutations and thus newborn screening may not identify all persons with CF.

■ PULMONARY EXACERBATION DIAGNOSTIC TESTING

Diagnostic testing in the setting of acute pulmonary CF exacerbation should include CF sputum cultures (using the Cystic Fibrosis Foundation approved methods for detecting polymicrobial isolates), complete blood count, comprehensive chemistry panel, and posterior-anterior and lateral chest x-ray. Pregnancy test should be obtained for the women of childbearing age. CF patients with change in symptoms should undergo the pulmonary function testing (PFTs) with spirometry to assess FEV_1 and any change from the patient's baseline level. A significant decrease in FEV_1 from baseline (even with unimpressive symptoms or physical examination) may prompt inpatient admission for IV antibiotics rather than outpatient management.

Additional testing for patients who have not responded to standard treatment of a CF pulmonary exacerbation as expected may include sputum for fungal stain and cultures, sputum for acid fast bacilli (AFB), and immunoglobulin (Ig) E level (to evaluate for allergic bronchopulmonary aspergillosis, [ABPA]).

Chest computed tomography (CT) is not necessary for treatment of routine acute pulmonary exacerbations. However, if suspicion for lung abscess, pulmonary embolus, or nontuberculous mycobacteria (NTM) is high, chest CT may be helpful.

Follow-up inpatient PFTs may be considered to document recovery of lung function after initiation of therapy, but acutely in the hospital setting the results may be discordant with the patient's clinical course. Therefore, inpatient surveillance PFTs (prior to completion of antimicrobial course for CF pulmonary exacerbation) are not indicated in most situations.

For patients with cystic fibrosis-related diabetes (CFRD) who are doing carbohydrate counting to dose their insulin, 2-hour postprandial blood sugars should be obtained in addition to preprandial and bedtime blood sugars in order to determine if failure to achieve glycemic control is responsible for failure to restore lung function to baseline.

Sinus CT is only indicated based on significant new sinus symptoms during the patient presentation. They should not be ordered routinely for pulmonary exacerbation in the absence of new sinus symptoms or signs.

TRIAGE/HOSPITAL ADMISSION

Although there is currently no standard definition of an acute pulmonary exacerbation in CF, a number of different criteria have been devised for clinical trials and clinical care. The majority of definitions capture respiratory symptoms such as increased cough, increased sputum production, shortness of breath and chest pain, as well as other measures such as loss of appetite, fatigue, and missing either work or school. However, CF clinicians put the most reliance on a decrease in lung function and will diagnose a pulmonary exacerbation in the absence of any reported change in symptoms if there is a significant decrease in FEV_1. This may be particularly true in those exacerbations that develop over a period of a few weeks and the patient is simply unaware of how much symptoms have increased until lung function and symptoms return to baseline following appropriate treatment.

Treatment of the exacerbation, if not severe, begins with outpatient oral antibiotics, increase in airway clearance, and emphasis on compliance with chronic pulmonary medications. More frequent clinic visits and greater use of antibiotics is associated with better PFT results. Close follow-up, usually within a week or two, is needed to make sure lung function has returned to the patient's baseline.

If lung function does not improve despite a trial of oral antibiotics, then the standard of care is hospital admission to start intravenous (IV) antibiotics and ensure aggressive airway clearance. Once inpatient therapy with IV antibiotics has been initiated and tolerated by the patient, and the patient is clinically improving, then it may be possible to complete the remainder of the treatment in the patient's home setting. It is very important that intravenous antibiotics in a nonhospital setting not be done unless resources and support equivalent to the hospital setting can be assured for the treatment entirety of an acute CF pulmonary exacerbation. Issues to consider when deciding whether completion of IV antibiotics therapy can be performed in the outpatient setting include the severity of the exacerbation, patient comfort and safety for maintaining long term central venous access, whether adequate delivery of other treatments such as airway clearance therapies can be maintained, and the presence of co-morbidities such as malnutrition and diabetes that may require inpatient care. It is not uncommon for a CF patient to receive two or three different IV antibiotics for therapy of their CF pulmonary exacerbation. The potential IV antibiotic therapy has to be of a reasonable regimen so as to allow the patient accurate dosing. For example, it is rarely feasible for a patient to solely administer an IV antibiotic every 4 to 6 hours for 14 to 21 consecutive days without having a missed antibiotic administration time or significant sleep deprivation. Also, as many IV antibiotics routinely used for treatment of a CF pulmonary exacerbation require frequent blood monitoring, it is very important that a specialized team closely follow the outpatient on IV antibiotic therapy to ensure that they are continuing to respond to antibiotics and appropriate blood test are being monitored at proper intervals. With careful patient selection, support, and close monitoring, completing IV antibiotic therapy in the home setting following hospitalization is a reasonable option.

Hemoptysis, often a sign of pulmonary exacerbation, is a common presenting complaint, occurring in about 9% of CF patients and can range from slight streaking to massive bleeding. Massive hemoptysis (which occurs in 4% of CF patients) is defined as more than 240 mL of blood in a 24-hour period. It is due to arterial bleeding from hypertrophied bronchial arteries. There are no evidence-based data to guide triage of hemoptysis in CF patients, but current consensus-based recommendations from the Cystic Fibrosis Foundation are that patients with at least mild hemoptysis (measured as > 5 mL) should contact their health care provider and scant hemoptysis (< 5 mL) should contact their health care provider if it is the first ever episode or if it persists.

Scant hemoptysis may not require hospital admission if there is no other evidence of a significant acute pulmonary exacerbation, but massive hemoptysis (> 240 mL) always requires hospital admission. Given the potential for significant morbidity, most, if not all, cases of massive hemoptysis should be admitted to an ICU setting.

About 3% of CF patients will have a pneumothorax during their lifetime with an annual incidence of about 1 in 167 patients, with attributable mortality as high as 16%. Disease severity predicts pneumothorax complication, with 75% of pneumothoraces occurring in patients with an FEV_1 < 40% predicted. CF patients with a pneumothorax should almost always be admitted to the hospital as the risk of progression and further respiratory compromise is high.

Pulmonary exacerbation

- Consider the diagnosis if there is a significant decrease in FEV_1 even in the absence of any reported change in symptoms.
- Glucocorticoid steroids are not routinely recommended for the treatment of a CF pulmonary exacerbation.

Hemoptysis

- Pulmonary exacerbation often manifest with mild hemoptysis; > 5 mL of blood should be treated with antibiotics.

- Bronchial artery embolization (BAE) is the initial treatment for massive hemoptysis. There is little evidence that bronchoscopy can localize bleeding in these patients, and it may delay a lifesaving procedure.

Pneumothorax

- All CF patients with a pneumothorax should be admitted to the hospital, regardless of size.
- Surgical pleurodesis with video assisted thorascopic surgery (VATS) is the preferred treatment for recurrent pneumothorax, and should be done soon to avoid respiratory infections related to splinting and immobility.

MANAGEMENT

■ ACUTE PULMONARY EXACERBATION MANAGEMENT

Many, if not most, of the large, multicenter, double-blind, placebo-controlled clinical trials evaluating ef cacy of pulmonary drugs in CF have been for outpatient management to prevent respiratory exacerbations, rather than for the management of an exacerbation once it is severe enough to require hospitalization. Therefore, recommendations for inpatient treatment rely on limited studies of small number of patients and on expert opinion. An inpatient admission protocol for CF patients with an acute respiratory exacerbation provides specific details of care in addition to being an educational tool for hospital staff.

The current mainstay of treatment for inpatient management of acute respiratory exacerbations consists of IV antibiotics and enhanced airway clearance. In addition, pulmonary and nonpulmonary complications of CF that may impair the ability to restore lung function to baseline require evaluation and management; and nutritional support must be addressed. P. aeruginosa is the most frequent organism found during an acute exacerbation. However, polymicrobial infections are also common, particularly with Staphylococcus aureus as well as multiple strains of Pseudomonas, each with a different pattern of antibiotic sensitivity. More recently, organisms previously thought to be commensals, such as Stenotrophomonas maltophilia, are now viewed as potentially pathogenic. Early isolates of pseudomonas are nonmucoid and have a broader range of antibiotic sensitivity. However, in the CF airway the organism can mutate to a mucoid form and also can form a biofilm. Such mutations, particularly toward a biofilm, may make antibiotics less effective.

Antimicrobials

The Cystic Fibrosis Foundation guidelines—for the treatment of a respiratory exacerbation in patients whose culture grows pseudomonas—recommend using two IV antibiotics of different classes (Table 234-2). Depending on the antibiotic sensitivities on the sputum culture, an aminoglycoside and a beta-lactam antibiotic is the preferred combination. Dual therapy may prevent the development of resistance and may have more benefit than monotherapy. There have been some clinical trials comparing monotherapy with combination therapy, but there is insuf cient evidence due to the small number of patients in each trial to recommend one over the other.

If possible, a new sputum culture should be obtained at the initial presentation of the CF pulmonary exacerbation. So, as not to delay antibiotic therapy, initial antibiotic selection should be based on the most recent sputum susceptibility results and later adjusted if there is inadequate response. Antibiotics can be further tailored based on culture results and sensitivities obtained during the onset of the current exacerbation. Finally, if current sputum results indicate broad resistance with no good antibiotic options, a previously successful regimen may be started as initial therapy.

TABLE 234-2 Antibiotic Recommendations and Dosing for Acute Respiratory Exacerbations*

Pseudomonas only (Recommend two-drug therapy, tobramycin plus beta lactam if pseudomonas is sensitive)
Tobramycin 10 mg/kg IV every 24 h†
Amikacin 10 mg/kg IV every 8 h†
Ceftazidime 50 mg/kg IV every 8 h (max. 10 g/d)
Piperacillin-tazobactam 4.5 mg IV every 6 h
Meropenem 2 g IV every 8 h
Colistimethate 2.5 mg IV every 12 h
Aztreonam 2 g IV every 8 h (major indication is severe PCN or cephalosporin allergy)
Methicillin-sensitive staphylococcus aureus and pseudomonas. Recommend two-drug therapy: one of the following plus tobramycin 10 mg/kg/24 h if pseudomonas is sensitive
Ticarcillin-clavulanate 3.1 g IV every 4 h
Cefepime 2 g IV every 8 h
Meropenem 2 g IV every 8 h
Piperacillin-tazobactam 4.5 mg IV every 6 h
Methicillin-resistant S aureus
Linezolid 600 mg IV every 12 h
Tigecycline 100 mg bolus then 50 mg IV every 12 h
Vancomycin 15-20 mg/kg every 8–12 h§

*Dosing for normal renal function. Adjustments may be necessary when renal dysfunction is present.
†Pharmacokinetics or infectious diseases consultation recommended.
§Trough levels of 15-20 mcg/mL recommended.

Despite poor-to-moderate lung penetration, aminoglycosides are frequently used in the treatment of acute pulmonary exacerbations. CF patients, particularly those under 40 years of age, require higher doses than non-CF patients to achieve therapeutic blood levels. Also, once daily tobramycin dosing has been shown to be as effective as multiple daily dosing and is associated with less renal toxicity. Clinical pharmacy consultation is critical for monitoring aminoglycoside levels. Some patients may deserve concomitant inhaled aminoglycoside to offer improved action against Pseudomonas species infections.

Although some cystic fibrosis centers are routinely using continuous infusions of beta-lactam antibiotics in the treatment of acute pulmonary exacerbations, there are not enough data to support this practice routinely.

Renal function and relevant monitoring of electrolytes and blood counts may be necessary, depending on the antibiotic choices and known side effects. Infectious disease consultants should assist with antimicrobial selection and clinical pharmacists, when available, should assist with antimicrobial dosing and monitoring.

The ultimate goal of therapy is to restore lung function back to baseline and this can take from 10 to 21 days, or in some cases even longer. The optimal duration of intravenous antibiotic treatment for a CF pulmonary exacerbation is not known. Most often, repeat pulmonary function test are performed following a 14 to 21 day course of antibiotic therapy with the results informing whether antibiotic therapy has been successful and can be discontinued (ie, the patient's pulmonary function test have returned to baseline) or whether therapy should be further continued.

Chronic CF pulmonary therapies

During therapy for acute pulmonary exacerbations, chronic pulmonary maintenance therapies may be continued (Table 234-3).

TABLE 234-3 Chronic Pulmonary Maintenance Therapy

Inhaled
Dornase alpha 2.5 mg nebulized daily or twice a day
Aztreonam 75 mg nebulized three times a day for 1 mo every other month—can rotate with another aerosolized antibiotic
Tobramycin 300 mg nebulized twice a day for 1 mo every other month—can rotate with another aerosolized antibiotic*
Colistimethate 150 mg nebulized twice a day for 1 mo every other month—can rotate with another aerosolized antibiotic
Sodium chloride 7% 4 mL nebulized twice a day to three times a day for FEV_1 > 40%. Most often hypertonic saline is preceded by inhaled beta-2 agent. Can be used in patients with lower lung function but may not be tolerated. In this situation, can use lower concentrations, like 5% or 3% but these have not been studied
Oral
Azithromycin 500 mg orally Monday, Wednesday, and Friday
Ivacaftor 150 mg orally every 12 h†
Lumacaftor/ivacaftor 400 mg/250 mg orally every 12 h§
Airway clearance therapies
Chest physiotherapy using manual, vest, Acapella valve twice a day
Active cycle breathing technique
Exercise¥

*An alternate dry powder formulation exists (TOBI podhaler).
The recommended dosing is inhalation of four-28 mg capsules twice per day for 1 mo every other month.
†Only for patients with the following CFTR mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, and R117H/5T.
§Only for patients whose genetic mutation is homozygous ΔF508
¥While exercise is important to overall physical health and encouraged, it should not be used as a replacement to other dedicated airway clearance therapies such as chest physiotherapy or active cycle breathing techniques.

CFTR modulators

In 2012, the first drug that targets the defective CFTR protein was approved by the US Food and Drug Administration for therapy in CF patients 6 years and older with specific CFTR mutations. Ivacaftor is a potentiator that binds to dysfunctional CFTR and increases the transport of chloride through the CFTR channel. However, ivacaftor exerts its effects on CFTR proteins that have been correctly traf cked to the cell surface, but otherwise do not conduct chloride effectively. As such, ivacaftor only works in specific CF mutations and has only been approved for CF patients with the following CFTR gene mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, and R117H/5T.

In 2015, a combination pill that included a CFTR potentiator (ivacaftor) and a CFTR corrector (lumacaftor) was approved in the United States for CF patients 12 years old and older who are homozygous for the ΔF508 mutation (Orkambi™). This accounts for approximately 50% of the CF population in North America. However, the combination drug has not been extensively studied in patients under the age of 12 or with severe lung dysfunction (FEV_1 < 40% predicted).

Ivacaftor is a sensitive CYP3A substrate, and any new medications added to a CF patient's regimen that includes ivacaftor should be closely checked for drug interactions, particularly with drugs that are CYP3A inhibitors and inducers. For example, co-administration of ivacaftor with rifampin, a strong CYP3A inducer, greatly reduces the therapeutic effectiveness of ivacaftor. Therefore, it is recommended ivacaftor not be co-administered with strong CYP3A inducers such as rifampin, phenobarbital, carbamazepine or St. John's Wort. Inhibitors of CYP3A increase ivacaftor exposure and often require potentiator dosing adjustments. Common inhibitors of CYP3A include ketoconazole, voriconazole, and certain antibiotics such as clarithromycin and erythromycin. Additionally, grapefruits and Seville oranges inhibit CYP3A and should generally be avoided while a patient is on ivacaftor.

Macrolides

Azithromycin (500 mg 3 times per week) has immunomodulatory and anti-inflammatory properties, in addition to antimicrobial properties, and has been shown in large, multicenter, placebo-controlled studies to reduce the rate of hospitalizations for acute pulmonary exacerbations and improve FEV_1 in those patients infected with P. aeruginosa. Recent data indicate that the chronic use of azithromycin may be helpful in the CF patients with methicillin-resistant S. aureus.

Airway clearance

Airway clearance through increased chest physiotherapy (compared to home regimen, and up to 4 times per day) can improve exacerbation outcomes and improve symptoms more rapidly. Manual chest physiotherapy may be performed by respiratory care, nursing staff, physical therapists, other clinicians or family members. Mechanical chest physiotherapy using vibrating vests and Acapella devices may also be employed. In addition, aerosols aimed at improving clearance, such as inhaled 7% hypertonic saline and the endonuclease dornasealfa (Pulmozyme™), can be prescribed at increased frequencies.

Inhaled antibiotics

When chronically infected with pseudomonas, most CF patients are administered inhaled antibiotics that are usually delivered in 28 day on-off cycles (ie, 28 days on the therapy followed by 28 days off of the therapy). There are insuf cient data to guide whether inhaled antibiotics should be continued or discontinued if similar IV antibiotics are given during an acute pulmonary exacerbation. Utilizing both routes of delivery could enhance antimicrobial activity in the lungs but could also increase the risk of toxicity. Therefore, the decision to continue dual route therapy should be made on an individual basis.

Glucocorticoid steroids

Systemic glucocorticoid steroids have been used in the past as adjunct therapy for a CF respiratory exacerbation. However, two placebo-controlled studies in a small number of children showed that the addition of glucocorticoid steroids to the regimen of IV antibiotics and enhanced airway clearance was no better than placebo in improving the recovery rate from the exacerbation. Glucocorticoid steroids also worsen hyperglycemia, which is known to contribute to oxidative stress and inflammation in the CF lung. Thus, glucocorticoid steroids are not routinely recommended for the treatment of a CF pulmonary exacerbation and some would suggest they are contraindicated because of side effects.

In the past, inhaled steroids have been prescribed with the goal of achieving the anti-inflammatory effects of glucocorticoids while limiting the harmful systemic side effects. However, the most recent Cochrane review of inhaled steroids in CF found no evidence that inhaled glucocorticoid steroids reduced inflammation in CF lungs. Additionally, there was some evidence that inhaled steroids may be harmful, particularly in increasing the risk of infection. As such, with the exception of concurrent asthma, use of inhaled corticosteroids in CF is not recommended.

Respiratory failure

Hypoxemic and hypercapneic respiratory failure may occur during hospitalization. In select patients who are alert and can maintain their airway, noninvasive positive pressure ventilation (NIPPV) may be employed to try to avoid endotracheal intubation and mechanical

ventilation. NIPPV may unload respiratory muscles and work of breathing, increase minute ventilation and thereby improve gas exchange and alveolar ventilation. Patients with poor baseline status due to chronic progression often have difficulty liberating from mechanical ventilation. Discussions regarding end-of-life care should be done before acute intervention is required.

■ INFECTIOUS PULMONARY COMPLICATIONS

Burkholderia cepacia complex

Burkholderia cepacia complex is a group of Gram-negative rod bacteria comprised of at least 17 different species that are phenotypically indistinguishable (ie, genomovars). *B. cepacia* complex is found in the natural environment, and certain species are commonly multidrug resistant and in CF patients can produce a pronounced inflammatory response associated with rapid loss of lung function. The most common *B. cepacia* complex species found in CF patients include *B. cepacia*, *B. cenocepacia*, *B. multivorans*, *B. vietnamiensis*, and *B. dolosa*.

Patients with *B. cepacia* complex were noted to have a very high mortality following lung transplantation as the high dose immunosuppression needed to prevent acute rejection frequently resulted in wide spread dissemination of the *B. cepacia* and death from multiorgan failure. Upon closer evaluation, the significant mortality seen in CF patients post lung transplant was in patients with the specific genomovar *B. cenocepacia*. Consequently, many transplant centers view the presence of *B. cenocepacia* as an absolute contraindication to lung transplantation. However, as *B. cepacia* complex has a number of other species, some of which are not associated with significant lung function decline, some specialized transplant centers will consider possible lung transplantation in patients colonized with *B. cepacia* complex genomovars other than *B. cenocepacia*. As such, if a CF patient cultures *B. cepacia* complex, it is very important that further speciation be performed at a lab familiar with typing of this bacteria so that the specific genomovar can be identified.

Nontuberculous mycobacteria

Nontuberculous mycobacteria (NTM) should be considered in CF patients with unexplained fatigue, night sweats, hemoptysis or progressive decline in lung function that is not responding to usual CF pulmonary treatment. NTM infections are found in approximately 13% of CF adults in the United States. The most frequently isolated NTM species in CF are *Mycobacterium abscessus* and *Mycobacterium avium* complex (MAC). Infection is diagnosed by at least two NTM positive sputum cultures collected on different days or a positive bronchoalveolar lavage culture along with clinical and radiographic findings consistent with NTM disease. NTM pulmonary disease should be treated for at least 12 to 18 months usually with a multidrug regimen to prevent development of resistance. MAC can have some sensitivity to oral antibiotics commonly prescribed in CF, such as macrolides and fluoroquinolones. These medications should be avoided in patients who have had a single sputum culture positive for NTM, or clinical symptoms suspicion for NTM pulmonary disease, until the disease can be confirmed and appropriate multidrug therapy can be initiated. MAC pulmonary disease is treated with long-term multidrug therapy (usually daily rifampin, ethambutol and a macrolide) for 12 to 18 months. *M. abscessus* can be very difficult to treat and eradicate as this species is usually resistant to typical antituberculosis drugs. Therapy often consists of parenteral treatment with amikacin and cefoxitin or imipenem for 2 to 4 months followed by prolonged enteral and aerosol therapy with susceptible drugs. As NTM infections can be very difficult to treat, it is recommended that therapy be guided by close consultation with an infectious disease specialist.

Fungal infections

Aspergillus fumigatus can be isolated in 40% to 60% and *Candida albicans* in 20% to 30% of patients. ABPA occurs in up to 10% of CF patients. Invasive aspergillosis and aspergillomas are very uncommon. ABPA may be clinically indistinguishable from a CF exacerbation as both may present with airway obstruction, fleeting pulmonary infiltrates, bronchiectasis, and hemoptysis.

ABPA should be considered in a CF patient with deteriorating lung function that is not responding to standard CF treatment. The minimal diagnostic criterion to diagnose ABPA in CF is finding an acute or subacute clinical deterioration, total serum IgE level greater than 500 IU/mL, immediate cutaneous reactivity to *Aspergillus* or presence of anti-*Aspergillus* IgE antibodies and either IgG antibody to *A. fumigatus* or new chest imaging abnormalities.

Treatment for ABPA requires high dose glucocorticoid steroid therapy (oral prednisone at 0.5-2 mg/kg, max 60 mg/d) plus itraconazole (5 mg/kg/d, max 200 mg orally twice per day). Itraconazole has the most data for therapeutic use in ABPA, though many physicians are using voriconazole more regularly as the anti-fungal agent of choice due to good bioavailability and patient tolerance. If the patient has CFRD, insulin dose usually needs to be increased. High-dose glucocorticoid steroids are given usually for 2 weeks before tapering. If total IgE is greater than 1000 IU/mL, glucocorticoid steroids often are not tapered until the IgE level is below 1000 IU/mL. If there is no improvement with high-dose steroids, the diagnosis should be questioned and corticosteroids tapered quickly followed by stopping the intraconazole.

■ HEMOPTYSIS MANAGEMENT

Because pulmonary exacerbation often manifest with mild hemoptysis, > 5 mL of blood should be treated with antibiotics. Lack of consensus about continuing versus stopping chest physiotherapy with mild-to-moderate hemoptysis leads some to stop the therapy until 24 to 48 hours after the bleeding has ceased, while others continue this intervention. Patients with scant and mild hemoptysis most often have aerosol treatments continued, while chest physiotherapy should be individualized for those with mild-to-moderate hemoptysis.

Bronchial artery embolization (BAE) is the initial treatment for massive hemoptysis. Bronchoscopy is not appropriate before BAE as there is little evidence that bronchoscopy can localize bleeding, and it can delay a lifesaving procedure. Lung resection may be considered only after other measures such as BAE have failed to control the bleeding. Chest physiotherapy should be stopped in massive hemoptysis. Aerosol treatments are often discontinued in patients with massive hemoptysis. There is significant risk of suffocation with massive hemoptysis well before exsanguination. As such, early intubation may need to be considered to secure a patient's airway, particularly in the setting of poor gas exchange and/or decreased mental status.

■ PNEUMOTHORAX MANAGEMENT

Most CF patients with a pneumothorax, regardless of size, should be admitted to hospital. However, the size does help determine the appropriate treatment. A small pneumothorax, defined as the distance between the apex and the cupola of ≤ 3 cm, may be treated with oxygen to help resorb the pneumothorax and serial examinations and chest x-rays are done to assess whether the pneumothorax is enlarging. A large pneumothorax (> 3 cm between the apex and the cupola) requires chest tube placement even in clinically stable patients. Good pain control is important in patients with a chest tube in place to avoid splinting and inadequate airway clearance.

Because 50% to 90% of CF patients with a pneumothorax will have a recurrence, pleurodesis should be considered for recurrent

large ipsilateral pneumothoraces. Pleurodesis does not reduce lung transplantation candidacy, and can be performed safely. Surgical pleurodesis with video assisted thorascopic surgery (VATS) is the preferred method, and should be done timely to avoid respiratory infections related to splinting and immobility.

There are no consensus guidelines as to whether all patients with pneumothoraces should receive antibiotics. However, antibiotics should be strongly considered if it is believed the pneumothorax was a manifestation of a pulmonary exacerbation or if the pneumothorax persists for more than a few days.

Airway clearance therapies that increase positive expiratory pressure and intrapulmonary percussive ventilation should not be used in patients with large pneumothoraces, and it may be appropriate to withhold such therapies in patients with small pneumothoraces. Aerosol treatments should not be stopped routinely in either large or small pneumothoraces, but may be held if they increase coughing in a patient.

■ EXTRAPULMONARY MANIFESTATIONS

CF is a multiorgan disease, and there are frequently extrapulmonary manifestations of the disease (Table 234-4). Often, hospital providers need to address these issues when patients are hospitalized for an acute pulmonary exacerbation. In addition, exacerbation of disease in other organs at times requires hospital admission. Clinicians

TABLE 234-4 Extrapulmonary Manifestations of Cystic Fibrosis

Organ System	Useful Diagnostic Test	Therapeutic Approach
Pancreas (exocrine)		
Pancreatitis	Elevated amylase and lipase, exclusion of other causes	Bowel rest, pain management
Pancreatic insufficiency	Steatorrhea, elevated fecal fat or decrease fecal elastase	Enteric-coated microencapsulated enzymes containing proteases and lipases
Nutritional deficiencies	Albumin, prealbumin; levels for vitamins A, E, and D, Protime (vitamin K)	Aggressive caloric intake, including a high fat diet, replacement of vitamin A, E, D, and K
Pancreas (endocrine)		
CF-related diabetes (CFRD)	Random glucose > 200 mg/dL on two or more occasions or Fasting blood glucose (FBG) > 126 mg/dL on two or more occasions or Oral glucose tolerance test (OGTT) with FBG > 126 mg/dL and 2-h value > 200 mg/dL or hemoglobin A_{1c} > 6.5%	Insulin with continued high calorie diet
Hepatobiliary		
Multilobular biliary cirrhosis	Workup includes liver function tests, ultrasound, ERCP, and exclusion of other causes of liver disease; liver biopsy often not needed	Ursodeoxycholic acid (UDCA)
Gallstones		
Microgallbladder		
Hepatic steatosis		
Hepatic congestion from cor pulmonale		
Gastrointestinal		
Neonatal meconium ileus	History, examination and abdominal radiographs	Systemic hydration, polyethylene glycol electrolyte (PEG) solutions by mouth or enemas, laparotomy and bowel resection (very rarely)
Distal intestinal obstruction syndrome (DIOS)		
Clostridium difficile associated colitis	Stool cultures and toxin, colonoscopy or abdominal CT scan	Antibiotic treatment
Fibrosing colonopathy	Contrast enema	Reduced enzyme dose, occasionally colonic resection
Appendicitis	Examination, ultrasound, abdominal CF scan	Appendectomy
Bone and joint disease		
Osteoporosis	Dual energy x-ray absorptiometry (DEXA)	Calcium and vitamin D supplements, consider bisphosphonates
Arthritis	Serological analysis to exclude other causes of arthritis	Short courses of nonsteroidal and steroidal anti-inflammatory medications
Hypertrophic pulmonary osteoarthropathy	Radiographs of long bones	Short courses of nonsteroidalantiinflammatory medications
Reproductive disease		
CBAVD* resulting in azoospermia	Semen analysis	Reproduction possible through sperm retrieval and assisted reproductive techniques
Cervical mucus abnormalities	Fertility may be normal	Counseling on contraception options, reproductive issues, and family planning

*CBAVD, congenital bilateral absence of the vas deferens.

Reproduced, with permission, from Hanley ME, Welsh CH. Current Diagnosis & Treatment in Pulmonary Medicine. New York: McGraw-Hill, 2003. Table 8-1.

should be able to diagnose and treat common extrapulmonary manifestations of CF and maintain a low threshold to evaluate for them.

Sinusitis

Close to 100% of patients with classic CF (elevated sweat chloride, typical pulmonary and gastrointestinal manifestations) have radiologic evidence of pansinusitis. Approximately 43% of CF patients have nasal polyps with 25% having symptoms due to polyps sometime during their lifetime.

CFTR ion transport abnormalities lead to abnormalities in mucociliary clearance in the sinuses, impairing drainage into the nasal cavity. It is not known whether infection is a major contributor to the pansinusitis seen on radiologic examination. However, once nasal polyps develop, the drainage problem is worsened by blocking the openings to the sinuses, leading to increased infection and inflammation. One quarter of adult CF patients have chronic symptoms of sinusitis, which may cause headaches, facial pain, fever, purulent nasal discharge, halitosis, double vision, blurred vision, proptosis, and postnasal drip.

Nasal polyposis may result in epistaxis, rhinorrhea, mouth breathing, obstruction of nasal air flow, distortion of facial features, halitosis, and decreased sense of smell. Nasal polyp resection provides immediate relief from nasal obstruction, but polyps will recur in 58% to 89% of CF patients.

Antibiotics should not be prescribed for asymptomatic CF patients with radiologic findings of sinusitis but are appropriate when patients become symptomatic. The possibility of coexisting allergies contributing to the development of nasal polyps should be considered. No consistent results have been demonstrated but nasal glucocorticoid steroids may be tried. Daily nasal irrigation and other supportive measures are often used. For particularly severe cases, intravenous antibiotics (selected based on results of sinus culture by otolaryngology) for 4 to 6 weeks may benefit patients, but well-designed studies have not been performed.

Sinus surgery benefits are often transient in CF; sinus surgery may be considered for symptomatic sinusitis that has failed routine medical therapy including a course of outpatient intravenous antibiotics. Limited evidence suggests that surgical treatment of sinusitis in CF may improve some health outcomes (eg, reduced average number of annual hospital days), but improvement in lung function should not be expected. Endoscopic sinus surgery is not recommended for CF patients before lung transplant as there are no strong studies to suggest prophylactic pretransplant sinus surgery changes survival rates.

Gastrointestinal tract

The most common GI tract complications of CF are esophagitis and ileal obstruction. Gastroesophageal reflux is exacerbated by coughing as well as the generation of larger negative intrapleural pressures leading to increased esophagitis incidence with more severe CF disease. Proton pump inhibitor therapy is usually effective.

CF can also lead to ileal obstruction (distal ileal obstruction syndrome [DIOS]) from retention of mucofeculent tenacious material in older children and adults. DIOS presents with crampy abdominal pain and relative constipation but can present acutely with abdominal obstruction. A tender right lower quadrant mass may be found on physical examination, and plain abdominal x-ray shows a speckled fecal gas pattern in the right lower quadrant. Often, the entire colon is full of impacted fecal material. The differential diagnosis includes appendicitis, constipation, and intussusception.

Incidence of DIOS has decreased (now only about 4% of CF patients) with the use of enteric coated microspheric pancreatic enzyme replacement therapy. In CF patients who undergo surgery and require narcotics for postoperative pain, DIOS incidence may increase and complete bowel obstruction may occur with just a few narcotic doses. Some institutions initiate stool softeners and cathartic medications (eg, lactulose) empirically in CF patients following lung transplantation as soon as patients begin taking liquids by mouth.

Extrapulmonary complications

- Distal ileal obstruction syndrome: increased incidence in CF patients who undergo surgery and require narcotics for pain. Complete bowel obstruction may occur with just a few narcotic doses. Consider stool softeners with cathartic medications (eg, lactulose) in the postoperative period as soon as patients begin oral liquids.
- CF-related diabetes: major diabetic complication is acceleration in the rate of decline in lung function. Diabetic diet restriction is not appropriate. Patients with CFRD should maintain a diet high in fat and protein intake with no restrictions on carbohydrates except to minimize simple sugars. Consult the endocrine service for assistance with management which includes insulin therapy.

Liver

Bile duct epithelial cells express CFTR leading to impairment in bile and mucus secretion. Localized stasis and obstruction generates an inflammatory response and reactive oxygen species leading to bile duct damage that is seen in nearly all CF patients. Some develop gall bladder disease, but few progress to biliary cirrhosis and liver failure.

Gall bladder disease is characterized by a small, shrunken gall bladder. Gallstones develop in 20% of CF adults but are symptomatic in only 5% of CF adults.

Cirrhosis and liver failure occur in about 2% of CF adults. CF patients with a history of DIOS have significantly higher risk of developing severe liver disease than those who have never had DIOS.

Abdominal imaging with ultrasound or magnetic resonance imaging may be indicated in CF patients with suspected liver disease.

Ursodeoxycholic acid for patients with CF-associated liver disease can often normalize serum alkaline phosphatase levels. However, the natural progression of CF liver disease may not change with such treatment. For end stage cirrhotic liver disease, liver transplantation may be the only option.

Pancreas

Mutant CFTR gene expression in the pancreatic ductal system results in failure of the normal postnatal development of the exocrine pancreatic gland, leading to pancreatic exocrine insuf ciency and malabsorption in 85% of CF patients. Abnormally low fluid secretion but normal protein secretion into the pancreatic duct causes protein precipitation, duct obstruction, and eventual pancreatic injury severe enough to cause malabsorption.

Symptoms of malabsorption may include diarrhea, bulky foul smelling stools, voracious appetite, abdominal pain after eating, and excess gas. Diagnosis of pancreatic insuf ciency occurs with finding levels of pancreatic elastase in the stool that are less than 200 mcg/g stool. Other causes of malabsorption in CF patients—lactose intolerance, celiac disease, Crohn disease, for example—can occur and should be considered in the differential if the patient does not respond to pancreatic enzyme replacement.

Pancreatic enzyme replacement therapy (PERT) dosage is individualized and should be adjusted based on symptoms. The most effective preparations are enteric-coated, acid-resistant microspheres,

now with greater formulation consistency, with recently required FDA approval. The initial dose is 500 lipase units per kg per meal and half that amount for snacks. The dose can be increased to a maximum of 2500 lipase units per kg per meal. If symptoms do not improve at maximum PERT doses, intestinal contents may never reach a suf ciently high pH (~5.0) to release the enzymes from the microspheres. Histamine (H2) blockers or proton pump inhibitors may then be given in addition to the pancreatic enzymes. Other malabsorptive syndromes should be considered if patient does not respond to acid inhibition with their PERT.

Enzyme replacement capsules should be taken at the very beginning of the meal or snack. However, if the meal lasts more than 30 minutes, a split dose can be given at the beginning and halfway through the meal. Care must be taken with enteric coated pancreatic enzyme microspheres used with continuous feeding as they can obstruct the feeding tubes. If the patient is able, it is recommended that they take three-fourth of the total enzyme dose at the beginning of the enteral feeding and the remaining one-fourth dose near the end. If they are to be mixed in with the formula, the microspheres must be added to a sodium bicarbonate solution and allowed to dissolve for 15 minutes. They may then be added to the enteral formula for distribution. The CF community is currently awaiting FDA approval of a powdered or liquid PERT formulation.

CF-related diabetes

CFRD has some features of type 1 and type 2 diabetes mellitus, with decreased insulin production and a component of insulin resistance (especially during stress). CFRD prevalence increases with age, with 50% of CF adults over age 30 years developing CFRD.

Early in the clinical course of CFRD, postprandial blood glucose levels are elevated, but most patients have normal fasting glucose levels and hemoglobin A_{1c} (HbA_{1c}) level. Yearly oral glucose tolerance testing (OGTT) is recommended to screen for CFRD in all CF patients 10 years and older. Standard ADA criteria for diagnosis of diabetes are used in CFRD and require two positive tests confirmed on two separate days when the patient is in stable baseline health. One of the tests should be an OGTT which consists of measuring a fasting plasma glucose (FPG) followed by oral administration of a 75 gm glucose solution and a subsequent repeat measurement of plasma glucose 2 hours later. An OGTT is positive if the FPG is > 126 mg/dL and/or the 2-hour plasma glucose is > 200 mg/dL. Other tests used for diagnosing CFRD include $HgA_{1c} \geq 6.5\%$ and a random plasma glucose level > 200 mg/dL in the presence of classic diabetic symptoms.

Often, the first manifestations of CFRD are seen during acute respiratory exacerbations, only to subside when the exacerbation has completely resolved but to reappear again with the next exacerbation. Therefore, for CF patients admitted to hospital for a respiratory exacerbation, fasting and 2 to 3 hour postprandial finger stick glucose levels should be measured in the first 48 hours of hospitalization. If fasting levels are >126 mg/dL and/or 2-hour postprandial > 200 mg/dL after the initial 48 hours of admission, finger stick monitoring should be continued, and plasma glucose levels measured. If two or more plasma glucose levels show an FPG > 126 mg/dL and/or 2-hour postprandial are > 200 mg/dL, then endocrinology should be consulted for further evaluation and management.

Complications of CFRD are quite different from those of type 1 or type 2 diabetes mellitus. Diabetic ketoacidosis occurs exceedingly rarely in CFRD and should prompt measuring islet cell antibodies to evaluate for type 1 diabetes. CF patients with diabetes have significantly worse lung function, more frequent acute respiratory exacerbations, and reduced survival rates compared to CF patients without diabetes. CFRD patients die of progressive pulmonary disease and respiratory failure, rather than macrovascular complications of diabetes. Microvascular complications occur in 10% to 23% of patients with CFRD, including retinopathy (16% of patients after 5 years and 23% after 10 years of CFRD), neuropathy, and nephropathy; but the severity of these microvascular complications is less severe than found in type 1 or type 2 diabetes.

The primary nutritional goal in CFRD is to maintain a high energy diet that is 120% to 150% of that recommended for age because higher BMI is associated with improved outcomes. For this reason, the standard dietary restriction of type 1 and type 2 diabetes do not apply to patients with CFRD. They are encouraged to maintain a diet high in fat and protein intake with no restrictions on carbohydrates except to minimize simple sugars.

Insulin is the preferred drug to treat CFRD. No trial has yet shown that an oral agent is superior to insulin in improving nutritional status or glucose control. Since CF adults are often advised to consume three 1000 calorie meals and two 500 calories snacks per day, the insulin regimen is tailored to their caloric intake. In addition, CF patients should exercise frequently, which also requires tailoring of the insulin regimen. Finally, during a respiratory exacerbation when insulin resistance can be substantial, rapid changes in insulin dosing may be required to maintain glucose levels at target.

Long-acting insulin for patients with fasting hyperglycemia and short acting insulin for meals using a specific dose of insulin per number of carbohydrates being consumed at that meal (ie, carbohydrate counting) helps maintain proper diabetic control. In addition, fingerstick glucose readings before meals can direct additional sliding scale short acting insulin needs for blood glucose levels above 180 mg/dL. All patients with CFRD may consider an insulin pump to reduce drug injections and improve quality of life. Target fasting glucose levels in adults with CFRD recommended by the American Diabetes Association (ADA), are between 70 and 130 mg/dL and 2 to 3 hours after meals less than 180 mg/dL. Further investigation will better delineate if more strict control than this will promote better outcomes. Little evidence exists for strict inpatient glucose control in patients with CF exacerbations, and ADA recommendations for other diabetic patients (maintain blood glucose 140-180 mg/dL) should guide practice.

■ NUTRITION IN THE HOSPITALIZED CF PATIENT

Malnutrition and malabsorption of fat soluble vitamins are common in CF patients. Malnutrition is multifactorial and due to a combination of decreased appetite, malabsorption, and increased energy requirement, especially during acute exacerbations.

Malnutrition, as indicated by a low body mass index (BMI), continues to be a major problem in CF. In 2009, almost 60% of CF adults in the United States were underweight (BMI < 22 for women and <23 for men). For those that are underweight, the following are important considerations: attention to appropriate doses of pancreatic enzymes; maintaining adequate calories for their needs; addressing underlying diseases that may decrease their oral intake (esophagitis, chronic abdominal pain, delayed gastric emptying, and depression); diabetes screening; and if diabetic, that target glucose levels are being met. About 10% of CF patients receive enteral tube feeds for nutritional failure. They are typically supplemented at night and encouraged to eat during the day.

Levels of fat soluble vitamins (A, D, E, K) should be assessed yearly in the outpatient setting. Up to 80% of CF adults are vitamin D deficient (related to malabsorption and other factors) leading to poor bone health and lower innate immunity of the lung. The Cystic Fibrosis Foundation recommends all CF patients maintain a serum 25-hydroxyvitamin D level of ≥30 ng/mL. High dose vitamin D3 (50,000 units once a week for 12 weeks) restores vitamin D levels in most CF patients to suf cient levels, but daily maintenance dosing of vitamin D3 is then required to maintain adequate levels and doses as high as 5000 to 7000 units per day may be necessary, especially during winter months.

■ CONSULTATION

For CF patients admitted to the hospital, hospitalists should facilitate subspecialty consultation with a pulmonologist who has expertise in CF as well as an infectious disease specialist familiar with CF management. Endocrinology consultation can assist with management of CFRD, especially since insulin requirements change rapidly with acute pulmonary CF exacerbations.

Respiratory care consultation can assist patients with inhaled therapies as well as chest physical therapy (device assisted [eg, Acapella and vest] and manual). Floor nursing staff and physical therapy consultation should also assist with chest physical therapy to assist patient in clearing the inflamed bronchioles.

In addition, the pharmacy team may provide invaluable assistance in dosing and monitoring of high risk antibiotics. Furthermore, nutrition service consultation should assist with caloric requirements during a respiratory exacerbation.

Finally, for those patients whose baseline FEV_1 is 30% predicted or less, introduction to a member of the lung transplant team (for patients seen in transplant centers) may help during the hospital admission to stage the timing for a lung transplant evaluation.

PROGNOSIS

The decline in lung function in CF follows a chronic disease trajectory of gradual decline punctuated by acute exacerbations causing sudden drops in lung function (usually assessed as FEV_1). Often, only partial recovery of lung function to a new, lower baseline follows a respiratory exacerbation. The number of exacerbations per year correlates with the rate of decline in FEV_1 and thus progression of disease. In addition, those with CFRD have significantly more respiratory exacerbations and more rapid disease progression than those CF patients without diabetes. Failure to return to baseline FEV_1 after an exacerbation is associated with female sex, CFRD, malnutrition, ABPA, a larger drop in FEV_1 during the exacerbation, and infection with Pseudomonas, B. cepacia complex, and/or methicillin-resistant S. aureus.

DISCHARGE PLANNING

If the patient is discharged before completion of the course of treatment, the patient must have close follow-up to determine duration of antibiotic treatment. Some centers with shorter hospital lengths of stay for admitted adult CF patients have demonstrated better outcomes compared to other centers where patients complete their antimicrobial course in the hospital. Inpatient versus outpatient management of acute pulmonary exacerbations of CF should be individualized based on the patient's social situation, local inpatient and outpatient resources for CF, and the patient's clinical condition.

Guidelines recommend that CF patients receive outpatient follow-up at least every 3 months at a center accredited by the Cystic Fibrosis Foundation and staffed by an interdisciplinary team consisting of pulmonologists, nurses, social workers, respiratory therapists, and nutritionists, all with expertise in CF clinical care. By far, the most frequent reason for additional clinic visits is an acute pulmonary exacerbation. Review of practices in CF Centers with the best pulmonary outcomes (as measured by median FEV_1 for the patients served by that center) indicate that these centers treat each exacerbation quickly and aggressively with the expectation of returning lung function to baseline.

QUALITY IMPROVEMENT

■ PREVENTION

Infection control

Even if pathogenic organisms are not found on sputum culture, all CF patients should be assumed to have transmissible organisms and contact isolation instituted. The Cystic Fibrosis Foundation strongly recommends that CF patients avoid physical contact with each other, and therefore CF summer camps and other gatherings of CF patients are no longer recommended and in fact actively discouraged.

Cohorting CF patients when hospitalized to prevent nurses from taking care of multiple CF patients (when possible) will help reduce transmission of resistant organisms to other CF patients. When nurses or clinicians must care for multiple CF patients, those with less resistant organisms should be seen first each day. Providers should always see the patients with B. cepacia last during the day to decrease the chances of spreading this deadly organism to other CF patients.

CONCLUSION

Cystic fibrosis is the most common inherited life-shortening disease of Caucasians in the United States caused by mutation in the CFTR gene. Cystic fibrosis can affect a variety of organs, but 90% of mortality is due to lung disease. However, it may present as asthma, pancreatitis, pansinusitis, or nasal polyps and not be initially recognized as cystic fibrosis. Increased respiratory symptoms are indicative of an acute pulmonary exacerbation but an isolated drop in FEV_1 without any reported change in symptoms is also concerning for exacerbation. The mainstay of treatment for acute pulmonary exacerbations is antibiotic therapy and enhanced airway clearance. Hemoptysis and pneumothoraces are major pulmonary complications that may require hospitalization. Nonpulmonary complications of CF such as pancreatic insuf ciency, sinusitis, malnutrition, and CF-related diabetes are important contributors to morbidity and mortality. Appropriate subspecialists who have expertise in CF management should be consulted. Respiratory therapists, nutritionists, and pharmacists also play vital roles in the care of the CF patient. Finally, referral for lung transplant evaluation should be considered when the baseline FEV_1 drop to 30% predicted or less. The Cystic Fibrosis Foundation is very active in quality improvement through the national Cystic Fibrosis Patient Registry as well as specific initiatives to improve the care of people with cystic fibrosis.

SUGGESTED READINGS

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