continuing education for pharmacists

Volume XXXIV, No. 9

Treatment of Pulmonary Disease in Cystic Fibrosis

Kelly J. Wright, R.Ph., PharmD, BCACP, TTS

Dr. Kelly J. Wright has no relevant financial relationships to disclose.

Goal. The goal of this lesson is to provide a review of pulmonary disease and treatment in cystic fibrosis, including clinical manifestations, current treatment recommendations, and new drug therapies.

Objectives. At the completion of this activity, the participant will be able to:

1. demonstrate an understanding of the basic epidemiology, etiology, pathophysiology, and clinical manifestations of pulmonary disease in cystic fibrosis patients;
2. recognize how CF is diagnosed in newborns;
3. identify the pharmacologic treatments indicated for treatment of pulmonary disease in CF;
4. list infection control measures indicated for CF patients; and
5. recognize the CFTR modulators and their effects on pulmonary disease in CF.

Background

Epidemiology. There are approximately 30,000 people in the United States living with cystic fibrosis (CF), which is a genetic, autosomal recessive, multi-organ disease. The expected life span of CF patients has improved dramatically to around 40 years of age. Therefore, around 45 percent of the CF population is over the age of 18. The incidence varies by ethnic background. In the U.S., Caucasians have the highest incidence at approximately one in every 3,000 live births, followed by Hispanics (1:9,200), Native Americans (1:10,900), African Americans (1:15,000), and Asian Americans (1:30,000).

Complications of CF can include obstructive lung disease, chronic respiratory tract infections, pancreatic insufficiency, intestinal obstructions, hepatobiliary disease, CF related diabetes, nutritional deficiencies, infertility in males, decreased fertility in females, and psychosocial impairments. Although CF is a multi-organ disease, it is important to note that the majority of CF-associated morbidity and mortality is attributed to respiratory impairment. This lesson is limited to the discussion of pulmonary disease in CF.

Etiology. CF is caused by mutations in both alleles of a single large gene on chromosome 7 that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The most common mutation identified in CF patients is delta F508 (found in approximately 70 percent of Caucasian CF patients in the U.S.), but there are more than 1,900 known mutations in the CFTR gene that can cause disease. These mutations have been divided into five different classes. Generally, mutations in classes I to III cause more severe disease than those in classes IV and V. However, the genotype-phenotype correlations of a mutation or set of mutations are not completely predictable, because gene-modifiers also affect the scope and severity of disease in an individual. Identified gene-modifiers are not directly related to the CFTR gene, but can exacerbate the severity of clinical manifestations of CF. For example, CF patients with polymorphisms in the transforming growth factor-beta (TGF-beta) gene have been found to have more severe lung disease. Given all of these factors, there is much variance in the clinical manifestations and severity of CF among those diagnosed.

Pathophysiology and Clinical Manifestations of Pulmonary Disease in CF. CFTR is a regulated transmembrane transport chloride channel that belongs to the ATP-Binding Cassette (ABC) family of proteins and is found on the surface of exocrine endothelial cells in the pulmonary system, gastrointestinal system, sweat glands, and reproductive tract. CFTR performs numerous cellular functions, including regulation of chloride transport across the cell membrane. This in turn helps regulate the sodium homeostasis and fluidity of secretions in these systems. Normally, the chloride and sodium ions are reabsorbed from the lumen by the CFTR and apical sodium channels, respectively. However, in CF, CFTR does not work properly and chloride is not reabsorbed. This

failed process produces a highly negatively charged ductal lumen, which draws in more sodium. The result is highly viscous and difficult to clear secretions from the respiratory, pancreatic, and biliary epithelium and, thence, the clinical manifestations of CF.

In the respiratory system, the thick, viscous airway secretions build up in the lungs and facilitate chronic airway obstruction and colonization with pathogenic bacteria. Neutrophils, the primary inflammatory mediator, and other mediators infiltrate the lungs in response, compounding the problem and contributing to tissue degradation, irreversible bronchiectasis, and eventual respiratory failure. This process usually begins early in life, as do the associated clinical manifestations, which progressively worsen as the child ages. Clinical manifestations can include chronic sinus disease, chronic productive cough, wheezing and air trapping (i.e., bronchiolitis/asthma), allergic bronchopulmonary aspergillosis (ABPA), bronchiectasis, digital clubbing, and acute infections/exacerbations.

Diagnosis. Newborn screenings for CF with the immunoreactive trypsinogen test (IRT) are required in all 50 states as of 2010. If elevated blood levels of IRT are found, then CF is strongly suspected and either a second IRT test or a DNA analysis for mutations in CFTR is performed. The IRT/DNA screening protocol is more expensive, but results in fewer delayed or missed diagnoses. Sweat chloride testing using the quantitative pilocarpine iontophoresis sweat test (QPIT) is the primary diagnostic test for CF and should be performed on infants with screening results positive for CF. Pilocarpine is used to stimulate secretion of sweat, which is collected and analyzed for chloride content and quantified as: normal (≤29 mmol/L, CF very unlikely), intermediate (30 to 59 mmol/L, possible CF), or abnormal (≥60 mmol/L, diagnosis of CF).

Treatment of Pulmonary Disease in CF

There are multiple dimensions to the treatment of pulmonary disease in CF patients, including the need for both chronic and acute treatments. Acute treatments are aimed at eliminating infective pathogens and providing respiratory support, while chronic treatments aim to prevent exacerbations through improving airway clearance, decreasing inflammation, preventing or controlling bacterial colonization with antibiotics, and improving the function of the CFTR protein. This lesson will focus on the pharmacologic treatments recommended by the Cystic Fibrosis Pulmonary Guidelines which were published in 2013 and are supported by the Cystic Fibrosis Foundation. Pulmonary complications and treatments not covered by this lesson include spontaneous pneumothorax, hemoptysis, supplemental oxygen, mechanical ventilation, and lung transplants.

Airway Clearance Therapies (ACT). Impaired mucociliary clearance that results in thick sputum predisposes CF patients to chronic infections and inflammation. Therefore, clearance of this mucus from the airways is an important fundamental of pulmonary care in CF and it is recommended that ACT begin within the first few months of life. ACT is typically a regimen of chest physiotherapy, inhaled bronchodilators, and nebulized mucolytics performed twice daily; however, the particular routine (e.g., duration of treatment, number of treatments per day, combination of drugs) is based on the patient's needs.

Chest physiotherapy loosens mucus in the lungs so that it can be more easily expelled by coughing. It can be done by hand percussion on the chest, external percussion vests, and a variety of breathing and coughing techniques. Some of these techniques require assistance and others that can be done independently. Aerobic exercise is also an effective way to mobilize secretions.

Bronchodilator therapy in ACT is recommended for patients ≥6 years of age who demonstrate bronchiole hyperresponsiveness or a positive response to bronchodilators. It facilitates clearance of airway secretions, limits bronchoconstriction that can be induced by inhaled mucolytics and antibiotics, and potentially improves the penetration of these drugs in the airways. Albuterol, a short-acting ß2 agonist, is the most commonly used bronchodilator for this purpose, with a dose of two puffs prior to each ACT session. Salmeterol, a long-acting ß2 agonist, and ipratropium, an anticholinergic, have also been shown to be effective for this purpose, but are not commonly used.

The two mucolytics recommended by the guidelines are dornase alfa (Pulmozyme®) and inhaled hypertonic saline (HyperSal™). Dornase alfa (Pulmozyme®) is an enzyme (DNase I) that cleaves the extracellular DNA released when neutrophils in the lung die. Eliminating the DNA results in decreased viscosity and improved mucociliary clearance of mucus. Chronic treatment with dornase alfa is recommended to improve lung function and reduce exacerbations in CF patients ≥6 years of age regardless of symptoms or pulmonary function tests. The approved dose is 2.5 mg once daily, inhaled via an approved nebulizer. It is not FDA approved for use in infants or children <5 years old, however some small studies have shown that it has a similar safety and efficacy profile in this population as in older children. Inhaled hypertonic saline (HyperSal™) also improves mucus clearance by increasing the volume of airway surface liquid through osmosis. The guidelines conclude that it is a recommended chronic treatment for CF patients age six years and older to improve lung function and quality of life and to reduce exacerbations. The typical dose is 4 mL, inhaled via nebulizer, two to four times daily. It has not been found to be beneficial in children younger

than six years. Albuterol from a metered dose inhaler (MDI) should be administered immediately prior to hypertonic saline to limit bronchospasm with treatment.

The guidelines do not provide a preference of either dornase alfa or hypertonic saline, therefore patients should be on both treatments if possible. However, several factors may limit their ability or willingness to use one of the treatments. For example, dornase alfa has a higher cost, hypertonic saline is administered twice daily while dornase alfa is only once daily, and dornase alfa may be better tolerated than hypertonic saline. Inhaled medications should not be mixed and nebulized at the same time. For patients on both mucolytic treatments, the suggested order of administration is: 1) albuterol by metered dose inhaler, 2) hypertonic saline, 3) chest physiotherapy/exercise and dornase alfa, in either order, and 4) other inhaled treatments such as aerosolized antibiotics.

Anti-inflammatory Therapies. Pulmonary inflammation begins early in the CF patient's life as neutrophils and other inflammatory cells respond to bacterial colonization of the airways. Anti-inflammatory therapies include glucocorticoids, ibuprofen, and azithromycin. Azithromycin is the most widely used chronic treatment for this purpose, and will be discussed in the "Antibiotic Therapies" section.

Both oral and inhaled glucocorticoids have been investigated for the treatment of CF lung disease. While some benefits have been found with chronic oral glucocorticoids (e.g., prednisone), they cause an unacceptably high incidence of abnormal glucose metabolism, cataracts, and growth failure. The adverse effects profile of inhaled glucocorticoids is less severe, but there is insufficient evidence for their benefit in CF patients to warrant their widespread use. The conclusion of the guidelines and most experts is that the chronic use of both systemic and inhaled glucocorticoids should be avoided unless the patient has another indication for treatment, such as concomitant asthma, ABPA (a complex hypersensitivity reaction to *Aspergillus fumigatus* colonization of the airways that occurs almost exclusively in patients with asthma or CF), or end stage lung disease. Short bursts of oral glucocorticoids are routinely used during acute pulmonary exacerbations in CF patients with predominantly asthma-like symptoms (e.g., chest tightness, response to bronchodilator, wheezing). The dose of prednisone for these patients is 0.5 to 1.0 mg/kg/day (maximum of 40 to 60 mg/day) for five days.

Chronic use of high-dose ibuprofen (20 to 30 mg/kg/dose BID) is recommended for CF patients between six and 17 years of age with a forced expiratory volume in one second (FEV_1) >60 percent predicted. However, it is not widely used (less than 10 percent of CF patients in the US are on this regimen) due to long-term safety concerns (e.g., gastrointestinal bleeds and nephrotoxicity) and the need for pharmacokinetic monitoring. Peak plasma concentrations must be monitored periodically and not exceed 50 to 100 mcg/mL.

Table 1
Recommended treatments for chronic *P. aeruginosa* colonization

Drug	Dose	Notes
Inhaled tobramycin	Bethkis®, TOBI®: 300 mg every 12 hours in cycles of 28 days on drug, followed by 28 days off drug TOBI Podhaler®: 4 capsules (112 mg) every 12 hours in cycles of 28 days on drug, followed by 28 days off drug	Data for patients as young as 6 months Routine monitoring of drug levels is unnecessary when renal function is normal Use a preservative-free formulation to prevent bronchospasm
Oral azithromycin	<40 kg: 250 mg three times a week ≥40 kg: 500 mg three times a week	A lower dose may be used if gastrointestinal side effects occur (e.g., diarrhea, vomiting)
Inhaled aztreonam	75 mg three times daily (at least 4 hours apart) in cycles of 28 days on drug, followed by 28 days off drug	Must use Altera® nebulizer, which is beneficial because it delivers the medication quickly (three minutes)

Antibiotic Therapies. Antibiotics are effective for the treatment of chronic and acute respiratory infections in CF patients and lead to improved pulmonary function and the prevention of pulmonary failure. Although many different pathogens (e.g., *Alcaligenes*, Stenotrophomonas, Mycobacteria, *Aspergillus*, *Burkholderia*, *Haemophilus*) affect CF patients, this article is limited to addressing the treatment of the most common pathogens: *Staphylococcus aureus* and *Pseudomonas aeruginosa*. There is a high risk of antibiotic resistance in CF patients due to incomplete clearance of pathogens from the airways, so this should always be a consideration when choosing antibiotic therapy.

Chronic Infections

Early in life, patients are most frequently colonized with *S. aureus*. Prophylaxis for *S. aureus* has not been found to be beneficial and is

Table 2
Antibiotics to treat acute CF exacerbations

Bacteria	Antibiotic	Pediatric dose	Adult dose	Comments
S. aureus (methicillin sensitive)	Cefazolin	100 mg/kg/day in 3-4 divided doses	1.5 g every 6 hrs or 2 g every 8 hrs	Maximum 6 g/day
	OR			
	Nafcillin	100-200 mg/kg/day in 4-6 divided doses	2 g every 4-6 hrs	Maximum 12 g/day
S. aureus (methicillin resistant)	Vancomycin	60 mg/kg/day in 3-4 divided doses	45-60 mg/kg/day in 3 divided doses	Maximum 1.25 g per dose initially. Dose and frequency adjusted to maintain a serum trough level of 15-20 mcg/mL
	OR			
	Linezolid	<12 years: 30 mg/kg/day IV or PO in 3 divided doses ≥12 years: use adult dose	600 mg IV or PO every 12 hrs	Risk of myelosuppression (e.g., thrombocytopenia) with treatment >14 days, or when renal insufficiency present
P. aeruginosa	**One of the following:**			
	Piperacillin-tazobactam	350-450 mg/kg/day in 4 divided doses	4.5 g every 6 hrs	Maximum 6 g/day
	Ticarcillin-clavulanate	400 mg/kg/day in 4-6 divided doses	3.1 g every 4-6 hrs	Maximum 18 g/day
	Ceftazidime	150-200 mg/kg/day in 3-4 divided doses	2 g every 6-8 hrs	Maximum 8 g/day
	Cefepime	150 mg/kg/day in 3 divided doses	2 g every 8 hrs	Maximum 6 g/day
	Imipenem-cilastatin	60-100 mg/kg/day in 4 divided doses	0.5-1 g every 6 hrs	Maximum 4 g/day
	Meropenem	120 mg/kg/day in 3 divided doses	2 g every 8 hrs	Maximum 6 g/day
	PLUS ONE OF THE FOLLOWING:			
	Ciprofloxacin	PO: 40 mg/kg/day in 2 divided doses. IV: 30 mg/kg/day in 3 divided doses	PO: 750 mg every 12 hrs IV: 400 mg every 8-12 hrs	Maximum doses: PO: 2 g/day in children; 1.5 g/day in adults; IV: 1.2 g/day. Less toxicity than aminoglycosides and colistin
	Tobramycin	10 mg/kg every 24 hrs	10 mg/kg every 24 hrs	Serum concentration monitoring required. Dose and interval adjustments needed for renal insufficiency
	Amikacin	30-35 mg/kg every 24 hrs	30-35 mg/kg every 24 hrs	
	Colistin (colistimethate sodium)	2.5-5 mg/kg (colistin base activity) per day in 3 divided doses IMPORTANT: Dose units and recommended dosing regimens vary by product and country. Doses shown here are specific to U.S.-licensed information for Coly-Mycin M®, which labels its product as units of "colistin base activity."	2.5-5 mg/kg (colistin base activity) per day in 3 divided doses	Maximum dose: 300 mg/day (colistin base activity) Colistin is a second-line drug that may be useful when the *P. aeruginosa* demonstrates *in vitro* resistance to all aminoglycosides, or when the patient fails to improve on an aminoglycoside-containing regimen.
S. aureus (methicillin sensitive), and *P. aeruginosa*	Same as shown above for *P. aeruginosa*, EXCEPT ceftazidime should not be used due to poor activity and against *S. aureus*.			
S. aureus (methicillin resistant) and *P. aeruginosa*	Same as shown above for *P. aeruginosa*, PLUS one of the following (3 antibiotics total): Vancomycin OR linezolid (doses shown above)			

Adapted from: Simon R., Cystic fibrosis: Antibiotic therapy for lung disease. UpToDate®. Oct. 20, 2015.

not recommended. As patients age, *P. aeruginosa* becomes the most common colonization and is an important predictor of morbidity and mortality. There are chronic antibiotic treatments for those age six years and older who are colonized with *P. aeruginosa*. Those that are recommended by the guidelines are inhaled tobramycin, inhaled aztreonam, and oral azithromycin (see Table 1). The specific regimen of chronic *P. aeruginosa* treatments is variable based on patient factors and prescriber preference. Antibiotics have a lower risk of adverse effects when aerosolized because they work topically at the site of the infection; however, they may cause bronchospasms, so albuterol MDI should be used prior to treatment. Aztreonam should be avoided in patients with a beta-lactam allergy, and tobramycin should be avoided if the patient is allergic to tobramycin or another aminoglycoside and in pregnant patients. The risk of nephrotoxicity and neurotoxicity (i.e., ototoxicity) is very low with inhaled tobramycin, but is possible. The recommendation for chronic azithromycin is not limited to patients who have *P. aeruginosa* colonization because its benefit of reducing exacerbations does not appear to be directly due to its antimicrobial effects, but rather to its anti-inflammatory effects. The mechanism by which azithromycin suppresses the inflammatory response it not well understood, but has been demonstrated clinically. For this reason, the guidelines recommend chronic treatment with azithromycin in all patients age six and older whether or not they have *P. aeruginosa* colonization.

Acute Exacerbations

The clinical presentation in any given patient may vary, but acute exacerbations requiring antibiotic treatment are associated with the following characteristics: increased cough, sputum production, chest congestion, fatigue, respiratory rate, dyspnea at rest, and nasal congestion; decreased exercise tolerance and appetite; change in sputum appearance; fever; and missing work or school. CF patients should have routine (i.e., every three months) sputum cultures analyzed so that when an exacerbation occurs there is current information regarding what bacteria they are carrying to guide antibiotic choices. Table 2 contains recommended antibiotic choices for exacerbations, based on the bacteria present. Treatments should be modified based on sensitivity testing results, renal function, and other patient characteristics. The recommended dosing in Table 2 is typical for CF patients, who require higher and more frequent dosing than usual. This is due to their increased volume of distribution (i.e., increased lean tissue per kg bodyweight and lack of adipose tissue), increased renal clearance, hypermetabolic state in setting of acute exacerbation, and resistant organisms and difficulty penetrating the site of infection.

Infection Prevention and Control. Prevention of infectious disease is a very important part of the pulmonary care plan of people living with CF. Of particular concern is the risk of transmitting resistant bacteria between patients. To avoid this, CF care centers must follow strict guidelines regarding hand hygiene, personal protective equipment, and disinfection of the healthcare environment and equipment. Patients and their families should be educated on methods to avoid infections outside the health care setting, such as avoiding close contact with other CF patients and performing regular, proper hand hygiene.

Another extremely important way to prevent infectious disease is by ensuring that CF patients receive all routine childhood vaccinations on schedule, as well as the annual influenza vaccine, palivizumab (Synagis®), and pneumococcal vaccinations. The annual influenza vaccination is recommended for all individuals age six months and older. Palivizumab is a monoclonal antibody indicated for the prevention of respiratory syncytial virus (RSV) in at-risk infants during RSV season for their first two years of life. It is dosed at 15 mg/kg intramuscularly once every month for five months, beginning in November. In 2010, PCV13 replaced PCV7 as the pneumococcal vaccine in the childhood vaccination schedule. All individuals with CF who did not complete the childhood vaccination schedule with PCV13 should receive the vaccine. CF patients age two years and older should also receive the PPSV23 immunization, which provides additional protection against pneumococcal disease. The Advisory Committee on Immunization Practices (ACIP) guidelines should be referenced for recommendations on the timing and number of doses of pneumococcal immunizations needed based on the patient's age and immunization history.

New Drug Therapies. CFTR modulators are a revolutionary new class of drugs that improve the functionality of the CFTR protein in certain patients with CF. They are the first CF treatments to address the main defect that causes CF, rather than one of the consequences or complications of that defect. FDA-approved CFTR modulators available in the U.S. include ivacaftor (Kalydeco®) and a combination of lumacaftor/ivacaftor (Orkambi®).

Ivacaftor was designed to target the G551D (class III) mutation which impairs the regulated opening of the ion channel that is formed by the CFTR protein. It is recommended for patients two years of age and older with G551D (occurs in around four to five percent of the CF population) or several other class III gating mutations (e.g. G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D, R117H). Detailed dosing information is detailed in Table 3. Patients should be told to take ivacaftor with fat-containing foods to improve its absorption. The granules formulation should be mixed with about one teaspoon of soft food or liquid and ingested immediately. Ivacaftor undergoes extensive he-

Table 3
Dosing of CFTR modulators

Ivacaftor		
Age 2 to <6 years and <14 kg	Usual dose With CYP3A strong inhibitors With CYP3A moderate inhibitors	50 mg granule packet by mouth every 12 hrs 50 mg granule packet twice weekly 50 mg granule packet once daily
Age 2 to <6 years and ≥14 kg	Usual dose With CYP3A strong inhibitors With CYP3A moderate inhibitors	75 mg granule packet by mouth every 12 hours 75 mg granule packet twice weekly 75 mg granule packet once daily
Age 6 years and older	Usual dose With CYP3A strong inhibitors With CYP3A moderate inhibitors	150 mg tablet by mouth every 12 hours 150 mg twice weekly 150 mg once daily
With CYP3A strong inducers	Use is not recommended	
Lumacaftor/ivacaftor		
Age 12 years and older	Two tablets (lumacaftor 200 mg/ivacaftor 125 mg) by mouth every 12 hours	
Patients maintained on strong CYP3A inhibitors	Initiate at one tablet (lumacaftor 200 mg/ivacaftor 125 mg) by mouth once daily. After one week, increase to usual dose. No adjustment needed when adding CYP3A inhibitor to patient maintained on lumacaftor/ivacaftor.	
Renal impairment	CrCl ≤30 mL/min	Use with caution
Hepatic impairment	Moderate impairment (Child-Pugh class B)	Reduce dose to two tablets in the morning and one tablet in the evening.
	Severe impairment (Child-Pugh class C)	Weigh risks and benefits of treatment. If therapy appropriate, then max dose is one tablet every 12 hrs.
Adjustment for toxicity	ALT or AST >5 times ULN without concomitant elevated bilirubin **OR** ALT or AST >3 times ULN with concomitant bilirubin >2 times ULN	Temporarily discontinue lumacaftor/ivacaftor; may resume if elevated transaminases resolved and after assessing benefits vs. risks of continued treatment

patic metabolism by CYP3A, therefore dose reductions are needed for patients with liver impairment or who are taking CYP3A inhibitors (e.g., itraconazole, clarithromycin). Coadministration with CYP3A inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin, St. John's Wort) is not recommended due to the resulting decreased efficacy of ivacaftor. Grapefruit juice and Seville oranges inhibit the metabolism of ivacaftor and should be avoided. Ivacaftor's adverse effects include increased liver enzymes and possible cataract development. Liver function tests (LFTs) are recommended prior to treatment, every three months for the first year, and then annually thereafter. If liver toxicity develops, ivacaftor should be held until resolution (see Table 3).

Pediatric and adolescent patients may be at risk for developing cataracts while on ivacaftor and should receive baseline and follow-up ophthalmological exams. Benefits of ivacaftor found in clinical trials include significant improvements in mean percent predicted FEV_1, decreased sweat chloride values, reduced frequency of pulmonary exacerbations, improved pulmonary symptoms, significant weight gain, decreased hospitalizations, decreased *P. aeruginosa* positive cultures, improved mucociliary and cough clearance, and lower adverse events than placebo.

Lumacaftor/ivacaftor is recommended for CF patients 12 years of age and older who are homozygous for the F508del mutation which causes malfunctions in both the protein folding and channel gating of the CFTR protein. Lumacaftor addresses the protein folding impairments, and as explained above, ivacaftor addresses the channel gating activity impairments. All dosing precautions and monitoring recommendations for ivacaftor described above apply to this combination as well. A large randomized, controlled clinical trial found improvements in percent predicted FEV_1, BMI, quality of life, and pulmonary exacerbation rates with lumacaftor/ivacaftor. Adverse effects found included a subgroup of participants with lower baseline lung function who developed

chest discomfort and dyspnea, and menstrual irregularities in women taking hormonal contraceptives.

The major limiting factor to treatment with CFTR modulators is financial. At the time of writing this lesson, the price for one month of treatment is around $20,000 to $30,000 in the U.S. However, if possible, all patients should undergo CFTR genotyping to determine if they are a candidate for either therapy and begin treatment due to the significant benefits and low risks of treatment.

CF Care Centers. Although the focus of this article is on pulmonary disease and treatments, it is very important to remember that CF is a multi-organ disease and must be treated comprehensively in order to ensure the best outcomes. This is best done at CF Care Centers accredited by the Cystic Fibrosis Foundation. A listing of these centers can be obtained at their website (www.cff.org). These care centers provide comprehensive care for CF patients throughout the life span. Multidisciplinary teams consisting of physicians, nurses, dietitians, respiratory therapists, physical therapists, social workers, program coordinators, psychologists, research coordinators, and pharmacists see patients regularly and address all aspects of the disease. The pharmacist's role may include teaching and counseling the patient on their medications, monitoring for drug interactions, managing dosing of medications, and other duties.

Conclusion

New research and availability of effective treatments for the pulmonary complications of CF have led to dramatic improvements in life expectancy in recent decades. The new class of CFTR modulators are very effective for a subset of CF patients and further developments in this area could continue to improve life expectancy and quality of life. For best outcomes, CF must be treated comprehensively, as the multi-system disease that it is, by a multidisciplinary team.

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This lesson is a knowledge-based CPE activity and is targeted to pharmacists in all practice settings. Disclosure: The OPF trustees and other individuals responsible for planning OPF continuing pharmacy education activities have no relevant financial relationships to disclose.

Program 0129-0000-16-009-H01-P

Release date: 9-15-16
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Treatment of Pulmonary Disease in Cystic Fibrosis

1. Which ethnicity has the highest incidence of CF?
   a. African Americans c. Caucasians
   b. Native Americans d. Hispanics

2. CF is caused by a mutation in the gene that encodes which protein?
   a. CF transmembrane conductance regulator
   b. Transforming growth factor-beta
   c. Apical sodium channels
   d. DNase I

3. Which is the primary inflammatory mediator that infiltrates the lungs in response to bacterial colonization in CF patients?
   a. Histamine c. Prostaglandins
   b. Neutrophils d. Lymphocytes

4. Newborn screenings for CF are required in all 50 states using which of the following tests?
   a. Quantitative pilocarpine iontophoresis sweat test
   b. DNA analysis
   c. Immunoreactive trypsinogen test

5. Which medication is used to limit the bronchoconstriction that can be induced by other inhaled medications?
   a. Hypertonic saline c. High-dose ibuprofen
   b. Albuterol d. Aztreonam

6. Which inhaled medication is recommended to be used chronically to improve lung function and reduce exacerbation in CF patients ≥6 years old?
   a. Glucocorticoids c. Hypertonic saline
   b. Albuterol d. N-acetylcysteine

Completely fill in the lettered box corresponding to your answer.

1. [a] [b] [c] [d]	6. [a] [b] [c] [d]	11. [a] [b] [c] [d]
2. [a] [b] [c] [d]	7. [a] [b] [c]	12. [a] [b] [c] [d]
3. [a] [b] [c] [d]	8. [a] [b] [c] [d]	13. [a] [b] [c] [d]
4. [a] [b] [c]	9. [a] [b] [c] [d]	14. [a] [b] [c] [d]
5. [a] [b] [c] [d]	10. [a] [b] [c] [d]	15. [a] [b] [c] [d]

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7. When high-dose ibuprofen is used as an anti-inflammatory in CF, peak plasma concentrations must not exceed:
   a. 10 mcg/mL. c. 100 mcg/mL.
   b. 40 mcg/mL.

8. The dose of oral azithromycin for the chronic treatment of *P. aeruginosa* colonization in children <40 kg is:
   a. 250 mg 3 times/week. c. 500 mg 3 times/week.
   b. 250 mg daily. d. 500 mg daily.

9. Which inhaled antibiotic is recommended for chronic treatment of *P. aeruginosa* colonization?
   a. Tobramycin c. Ceftazidime
   b. Piperacillin-tazobactam d. Meropenem

10. Which immunization/preventative treatment is only indicated during the first two years of a CF patient's life?
   a. Influenza c. PCV13
   b. Palivizumab d. PPSV23

11. Which medication is recommended only for CF patients two years of age and older with G551D or several other class III gating mechanisms?
   a. Ivacaftor c. Lumacaftor/ivacaftor
   b. Tobramycin d. Dornase alfa

12. What type of toxicity may develop with ivacaftor treatment?
   a. Ototoxicity c. Neurotoxicity
   b. Nephrotoxicity d. Hepatotoxicity

13. The dose of ivacaftor in patients age two to six years, weighing ≥14 kg and taking a strong CYP3A inhibitor is:
   a. 50 mg twice weekly. c. 75 mg twice weekly.
   b. 50 mg once daily. d. 75 mg once daily.

14. Children and adolescents treated with which of the following medications require baseline and follow-up ophthalmological exams?
   a. High-dose ibuprofen c. Palivizumab
   b. Lumacaftor/ivacaftor d. Azithromycin

15. What is the major limiting factor for the use of CGTR modulators?
   a. Cost c. Low efficacy
   b. Adverse effects d. Monitoring

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