



Review of Cystic Fibrosis

Introduction

Cystic Fibrosis is a rare, autosomal recessive disease caused by a genetic mutation (defect) on chromosome 7. The defective gene results in abnormalities in the production and function of a protein called the cystic fibrosis transmembrane conductance regulator (CFTR) found on epithelial cells.^{1,2} Approximately 30,000 children and adults in the United States have cystic fibrosis. An additional ten million more - or about one in every 31 Americans - are carriers of the defective CF gene, but do not have the disease.³

In simplified terms, CFTR acts as a chloride and bicarbonate channel involved in salt and fluid transport. In CF, a defective CFTR results in an imbalance of sodium and chloride exchange, with resulting dehydration of the airway surface, which is believed to contribute to the deleterious cascade of mucus accumulation, infection, inflammation, and destruction that characterizes CF lung disease.^{4,5} There are over 1500 mutations of the CFTR gene, which are cataloged into one of the six classes of known defects^{1,2} (Table 1). The widespread presence of epithelial cells, and thus CFTR, throughout the body (lungs, pancreas, liver, kidneys, sweat ducts and reproductive tract) helps to explain why CF is a multisystem condition affecting many organs and is also a progressive disease over time.¹ Yet, lung disease accounts for 85% of the mortality.

Table 1. Description of the Six Classes of Defects Resulting from CFTR Mutations^{1,2}

- Complete absence of CFTR protein synthesis
- Defective protein maturation and early degradation (caused by the most common mutation, $\Delta F508$)
- Disordered regulation (diminished ATP binding and hydrolysis)
- Defective chloride conductance or channel gating (caused by the G551D mutation)
- Diminished transcription due to promoter or splicing abnormality
- Accelerated channel turnover from the cell surface

Symptoms of Cystic Fibrosis

The severity of CF symptoms and extent of system involvement is different from person to person. The most common symptoms are⁶:

- Very salty-tasting skin
- Persistent coughing, at times producing phlegm
- Frequent lung infections, such as pneumonia or bronchitis
- Wheezing or shortness of breath
- Poor growth/weight gain in spite of a good appetite
- Frequent greasy, bulky stools or difficulty in bowel movements
- Small, fleshy growths in the nose called nasal polyps.

History and Current Management

CF has been transformed from a diagnosis fatal in infancy or childhood to a chronic disease of children and young adults. With aggressive treatment, the average life span has increased to about 38 years nationally¹ and close to 50 years at the University of Minnesota CF center. As a result, adult CF centers are being created to care for the increasingly older population. Although life expectancy has increased dramatically, management of the disease still requires a complicated daily regimen of preventive and therapeutic interventions. On a daily basis, a cystic fibrosis patient may take up to 15 pills and invest at least one hour for secretion clearance; patients with severe CF may ingest up to 60 pills and undergo two and a half hours of secretion clearance treatment.⁷ Patients are often prescribed oral and IV antibiotics or antifungals to continually combat invading organisms, as aggressive treatment of pulmonary

exacerbations improves the lifespan of patients with CF.^{5,8} Table 2 provides a summary of the organ systems affected by CF, the symptoms and consequences and the therapeutic classification of the drug types used when possible to target the symptoms.

Disease Process

It is important to understand the disease process to have insight into the complexity of care that CF patients require. The basic defect, a poorly functioning or absent chloride channel, results in diminished cellular water flow and the buildup of thick mucus. In the pulmonary system, this environment invites bacterial, viral and fungal infections, which give rise to inflammation and tissue destruction.⁵ Neutrophils go to the site of tissue damage and neutrophil elastase is released, which destroys bacteria and also destroys epithelial cells causing permanent damage to lung tissue surface. Degenerating neutrophils release DNA, adding further thickening of the mucus, and contributing to the continuous cycle of infection.

Another major organ that is affected by CF is the pancreas, and thus the endocrine and GI systems. In CF, thick mucus obstructs the pancreatic duct, scar tissue accumulates, and over time, digestive enzyme secretion is interrupted. Because digestive enzymes do not reach the intestines, patients experience malabsorption and malnutrition.⁵ CF is one of the most common causes of irreversible pancreatic insufficiency.⁹ Up to 80-90% of patients require exogenous

pancreatic enzymes and nutritional supplementation; their caloric needs can be 120-150% RDA or up to 5000 calories per day. Some patients find this very challenging and require feeding tubes (e.g. G Tube or J Tube) to allow extra calories and nutrition via supplemental foods. Longitudinal studies demonstrate that under nutrition is closely related to the decline of lung function and early infection with *Pseudomonas aeruginosa*.⁵ Furthermore, there is a positive relationship between improved weight and nutritional status and lung function,^{1,5} thus maintaining or improving body weight is an important patient goal.

Literature indicates that about 30% of people who have CF develop CF related diabetes (CFRD) by their third decade of life due to pancreatic complications.¹⁰ However, with aggressive screening up to 50% of CF patients will be identified as having CFRD. CFRD has an insidious onset, and thus it is important to screen for it every year. CFRD is different from both type 1 and type 2 diabetes. Similar to type 1 diabetes, the only treatment is insulin, but patients with CFRD have no dietary restrictions.¹⁰ Instead, the CF team will titrate insulin needs to the individual patient.

Lung Transplant

Lung transplantation is a final therapeutic option for patients with endstage lung disease.¹ When transplanted, the new lungs do not have the cystic fibrosis gene and will function normally. However, the patient is subject to a new problem set of immune suppression. Patients must demonstrate a certain level of compliance with current CF therapies before they are allowed on the transplant waiting list.¹

Clinical Care Guidelines

Because CF is a complex disease that affects so many organ systems, proper care requires specialized knowledge. The best place to receive that care is at one of the more than 110 accredited CF centers nationwide. These centers of excellence meet national standards of care and are reviewed yearly for accreditation. Care center staff includes a multi-disciplinary group of specialists, including doctors, nurses, respiratory and physical therapists, dietitians and social workers. This specialized team works with each patient to create an individualized plan to meet that person's specific needs and to keep them as healthy as possible.⁶ The accredited centers strive to meet nationally recognized clinical care guidelines (Table 3) which have been identified to provide optimal care for these complicated patients.

Recently Approved Oral Therapy: Kalydeco

There has been a research shift from evaluating drugs aimed at treating the secondary manifestations of CF to evaluating drugs targeted toward the primary prevention of chronic lung disease. Extensive research has led to the discovery of compounds that increase the function of a poorly-functioning CFTR protein (eg, potentiators) and compounds which allow a defective CFTR protein to reach the cell membrane before being degraded by the internal cellular components (correctors).²

Ivacaftor (Kalydeco[™]) [Vertex] represents the first approved drug for cystic fibrosis that targets the underlying defect of CF, whereas all other available therapies target symptoms. Ivacaftor is classified as a CFTR potentiator as it helps the CFTR protein function more normally as a chloride channel once it reaches the cell surface.¹² It is approved for patients age 6 years and older, who have a G551D mutation on the CFTR gene.¹³ Approximately 4% of those with CF, or about 1,200 people in the United States, are believed to have the G551D mutation.¹²

A more common mutation (about 88%), the $\Delta F508$, codes for a CFTR protein that does not reach the cell surface in normal amounts.¹¹ We know that ivacaftor alone is not effective in CF patients who have two copies of the $\Delta F508$ mutation on the CFTR gene.¹³

Table 2. Summary of the Affected Organ System, Consequences and Treatments*^{1,5,8,9,10}

Organ System	Abnormalities	Some Possible Consequences	Some of the Therapies to Target CF Consequences
Lungs	Viscous secretions Infections	<ul style="list-style-type: none"> Chronic obstructive endobronchial infection Chronic bacterial infections (Staphylococcus, Pseudomonas) Sinusitis Chronic pulmonary infection Airway obstruction Bronchiectasis Hemoptysis Pneumothorax Respiratory failure 	<ul style="list-style-type: none"> Inhaled bronchodilators (e.g., albuterol, levalbuterol) Inhaled antibiotics (e.g., Tobi®, Cayston®, Colistimethate) Inhaled mucolytics (e.g., Pulmozyme®, hypertonic saline, acetylcysteine) Oral anti-fungals Oral antibiotics Infused antibiotics Anti-inflammatory agents (e.g., daily azithromycin, ibuprofen, prednisone)
Pancreas	Digestive Enzyme (amylase, lipase, protease) deficiency	<ul style="list-style-type: none"> Maldigestion Malnutrition Chronic pancreatitis Diabetes mellitus 	<ul style="list-style-type: none"> Pancreatic enzymes (to replace digestive enzymes) Proton pump inhibitors (to enhance pancreatic enzyme dissolution) Nutritional supplements, vitamins, minerals (to combat poor absorption) Insulin (to treat poor or absent insulin secretion)
Intestines	Viscous secretions, biliary cirrhosis, fatty infiltrates	<ul style="list-style-type: none"> Meconium ileus Distal intestinal obstruction syndrome (DIOS) Chronic obstructive portal hypertension Esophageal varices Malabsorption Gastroesophageal reflux Rectal prolapsed 	<ul style="list-style-type: none"> Miralax® (polyethylene glycol)
Sweat Glands	Failure to reabsorb sodium	<ul style="list-style-type: none"> Hyponatremia Salty skin 	None
Reproductive	Males: obstruction of epidymis, vas deferens, seminal vesicles Females: viscous cervical mucous	<ul style="list-style-type: none"> Aspermia Decreased fertility 	None
Renal		<ul style="list-style-type: none"> Nephrolithiasis 	None
Hematologic	Chronic Disease	<ul style="list-style-type: none"> Anemia 	Little evidence available to direct treatment
Bones and Joints	Unknown	<ul style="list-style-type: none"> Arthritis, osteoporosis 	<ul style="list-style-type: none"> Calcium supplementation
Hepatobiliary		<ul style="list-style-type: none"> Focal biliary cirrhosis Steatosis Cholelithiasis 	<ul style="list-style-type: none"> Ursodiol

*This table provides limited information about the drug therapies used for cystic fibrosis, and does not provide complete information about the benefits and risks associated with the drugs listed.

Table 3. Annual Care, Screening and Prevention Guidelines for People with CF¹¹

<ul style="list-style-type: none"> 4 or more clinic visits 4 or more respiratory cultures 2 or more pulmonary function tests (PFTs) if 6 years of age or older and physically able An influenza (flu) vaccine if 6 months of age or older Fat-soluble vitamin levels measured An oral glucose tolerance test (OGTT) if 10 years of age or older Test to measure liver enzymes in the blood

In clinical trials, ivacaftor was shown to produce sustained improvement in lung function (FEV₁), reduce exacerbations, and while not a primary outcome measure, increase body weight.¹² The sweat chloride test, which is a definitive test used to diagnosis CF, was also used as a secondary outcome measure in this trial. Study results showed that ivacaftor clearly has an effect on the sweat test. Patients in the ivacaftor group had reductions in sweat chloride from a mean value of 100.4 mmol/L to a mean value of 48 mmol/L, which is well below 60 mmol/L, the diagnostic cutoff point. This change was consistent over 48 weeks.¹²

The results from these clinical trials, which studied a small subset of patients with CF, indicate promise for all CF patients, as there are more oral therapies on the horizon designed to target the underlying defect of mis-made proteins. We are pleased to report that Fairview Specialty Pharmacy has access to ivacaftor, which requires special ordering and proactive screening for significant drug-drug interactions. Patients receiving ivacaftor are closely monitored by Fairview Specialty pharmacists.

Fairview Specialty Pharmacy Approach

Fairview Specialty Pharmacy offers CF patients integrated, comprehensive, and coordinated care that addresses the complex needs of this patient population. We provide extensive, personalized, initial and ongoing counseling for CF medications. CF specialty patients require multiple prescriptions including high cost specialty drugs, generic drugs, frequent infused therapies, and OTC vitamins. Patients or their parents often need help to decipher drug coverage and preferred drug lists, and navigate billing to multiple entities. We facilitate communication that improves patients' understanding of benefits and identify resources to break down barriers to receiving optimal care. In addition, we coordinate and provide all medications, from specialty inhaled drugs to over-the-counter vitamins.

A recent example illustrates the importance of coordinated care. An 8 year old child was hospitalized for weight loss and CF exacerbation. The parent insisted that all therapies had been taken as directed. At the request of the treating pulmonologist, a Fairview pharmacist contacted two payer groups to obtain pharmacy claims (the patient was not using Fairview Specialty Pharmacy) and discovered that no claims for pancreatic enzyme therapy had been billed for the past five months. The doctor re-established enzyme therapy at the previously prescribed dose. Had the pharmacist not uncovered the facts, the physician might have started a feeding tube or increased the dose of pancreatic enzymes, with potential risks to the child and higher costs for the payer. Upon discharge, the child's mother received extensive pharmacist counseling and education about the importance of maintaining nutritional status and optimal use of pancreatic enzymes.

Conclusion

CF is a complicated, specialty disease that requires the combined efforts of a multi-disciplinary team of health care professionals for optimal management. Remarkable progress has been made in the understanding of CF, which has lead to therapeutic advancements for the treatment of this disease, with more on the horizon. With aggressive treatment, the outlook for people diagnosed with CF has improved substantially in the past 10-20 years.

Fairview Specialty Pharmacy, in conjunction with the University of Minnesota Cystic Fibrosis Center, has developed clinical programs to meet the specialized needs of these very complex patients. Fairview Specialty Pharmacy partners with patients, providers, and payers to ensure that the complicated and costly CF drug regimens are used most efficiently and effectively. In providing knowledgeable outreach to patients, we help patients safely stay on track with CF drug regimens to achieve optimal clinical outcomes.

References

1. O'Sullivan BP, Freedman SD. Cystic fibrosis. *Lancet*. 2009; 373:1891-904
2. Sloane PA, Rowe SM. Cystic fibrosis transmembrane conductance regulator protein repair as a therapeutic strategy in cystic fibrosis. *Curr Opin Pulm Med*. 2010;16:591-597.
3. What is Cystic Fibrosis. Online article. Available at <http://www.cff.org/AboutCF/>.
4. Gibson R, Burns J, Ramsey B. Pathophysiology and Management of Pulmonary Infections in Cystic Fibrosis. *Am J Respir Crit Care Med*. 2003; 168:918-951.
5. Cohen-Cymbarkoh M, Shoseyov D, Kerem E. Managing Cystic Fibrosis, Strategies That Increase Life Expectancy and Improve Quality of Life. *Am J Respir Crit Care Med*. 2011; 183:1463-1471.
6. Where can people with CF get the best care. Online article. Available at http://www.cff.org/AboutCF/Faqs/#Where_can_people_with_CF_get_the_best_care?
7. Online article. New Hope for Cystic Fibrosis. Available at <http://www.childrenscolorado.org/research/patient-stories/research-cystic-fibrosis.aspx>.
8. Flume P. Pulmonary Complications of Cystic Fibrosis. *Respir Care*. 2009; 54(5):618-627.
9. Fieker A, Philpott J, Armand M. Enzyme replacement therapy for pancreatic insufficiency: present and future. *Clin Experim Gastroenterol*. 2011;4:55-73.
10. Costa M, Potvin S, Berthiaume Y, et al. Diabetes: a Major Comorbidity of cystic fibrosis. *Diabetes Metab*. 2005; 31:221-232.
11. Cystic Fibrosis Foundation Patient Registry: Annual Data Report 2010. Cystic Fibrosis Foundation. Available at <http://www.cff.org/UploadedFiles/LivingWithCF/CareCenterNetwork/PatientRegistry/2010-Patient-Registry-Report.pdf>.
12. Ramsey BW, Davies J, McElvaney G, et al for the VX08-770-102 Study Group. A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation. *N Engl J Med*. 2011;365:1663-72.
13. Kalydeco prescribing information. Vertex Pharmaceuticals. January 2012. Available at http://pi.vrtx.com/files/uspi_ivacaftor.pdf.

Fairview Specialty Pharmacy provides comprehensive specialty pharmacy services. As part of Fairview Health Services, a nonprofit healthcare system including the University of Minnesota Medical Center, we have expertise across the full spectrum of specialty diseases and provide a personalized approach that builds trust with our patients. We leverage our relationships with clinical experts and key opinion leaders at the University of Minnesota Medical Center and other specialist providers to provide comprehensive and cohesive care for patients who require specialty medications.



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