

Smith Seminars
Continuing Education Credits
AARC-Approved for 2 CRCE
Cystic Fibrosis

Objectives

1. Define and identify Cystic Fibrosis
2. Lists pathogenesis and pathophysiology of Cystic Fibrosis
3. List symptoms, signs and complications of Cystic Fibrosis
4. Diagnosis and testing process for Cystic Fibrosis
5. Clinical Monitoring of Cystic Fibrosis
6. Current treatment for Cystic Fibrosis
7. Current research programs for Cystic Fibrosis

Cystic Fibrosis or CF is a disease caused by an inherited genetic defect of the exocrine glands, primarily affecting the GI and respiratory systems, but symptoms can vary between patients. It is a monogenetic disorder that presents as a multi-system disease. The first signs and symptoms typically occur in childhood.

Each year approximately 3,200 white babies are born in the U.S. with CF. The disease is much less common among blacks and Asian-American children. Two-thirds of the infants born with CF will be diagnosed in the first year of life. CF affects approximately 30,000 persons each year, 30% are adults. The life expectancy for CF patients is markedly shortened with many patients dying in their 20's and 30's. The median survival age of CF patients has risen significantly in the past 35 years. In the 1940's, CF patients rarely lived past the age of ten. In 1969, the median age rose to 14. Now, the age is much higher due to the development of improved medication and aggressive therapy.

Pathogenesis

CF is an autosomal recessive disease resulting from mutations in a gene located on chromosome 7. The most common mutation in the CF gene is a 3-bp deletion that results in an absence of phenylalanine at amino acid position 508 (delta F508) of the CF gene protein product, known as the CF transmembrane regulator (CFTR). The CFTR protein is a single polypeptide chain containing 1480 amino acids that appears to function both as a cyclic AMP-regulated CF channel and a regulator of other ion channels. In normal cell, CFTR is synthesized in rough endoplasmic reticulum (RER), is in the golgi apparatus, and functions as a chloride channel and regulator of other ion channels when located in the plasma membranes.

If a mutation, such as Delta F508 is present, CFTR is degraded intracellularly so no protein is transported to the plasma membrane. With other mutations, the abnormal protein is processed to the plasma membrane but functions abnormally at that site.

Epithelial Dysfunction

The epithelia affected by CF exhibit different functions in their native state. Some are volume-absorbing (airways and distal intestinal epithelia), some are salt-absorbing but not volume absorbing (sweat duct), and others are volume-secretory (proximal intestine and pancreas). CF produces very different effects on patterns of electrolyte and water transport.

Organ-specific Pathophysiology

Lung

The diagnostic biophysical hallmark of CF is the raised transepithelial electric potential difference (PD) detected in airway epithelia. The transepithelial PD reflects components of both rate of active ion transport and the resistance to ion flow of the superficial epithelium. CF airway epithelia exhibit both raised transport rates (sodium) and decreased chloride permeability. Raised sodium absorption is a routine feature of CF airway epithelia. It appears that CFTR inhibits sodium channel activity as a part of its general function to act as a “switch” that coordinates the balance between sodium absorption and chloride secretions. An abnormally high rate of sodium absorption and low rate of chloride secretions reduce the salt and water content of mucus and deplete the volume of the periciliary liquid (PCL). Both the thickening of the mucins and the depletion of the PCL lead to a failure to clear mucus normally from the airways by either ciliary or airflow-dependent (cough) mechanisms. Evidence suggests that the lungs are histologically normal at birth.

Pulmonary damage is probably initiated by diffuse obstruction in the small airways by abnormally thick mucus secretions. Bronchiolitis and mucopurulent plugging of the airways occurs secondary to obstruction and infection. Bronchial changes are more common than parenchymal changes. Emphysema is not prominent.

As pulmonary process progresses bronchial walls thicken, the airways fill with purulent, viscid secretions, and areas of atelectasis develop. The hilar lymph nodes enlarge. Chronic hypoxemia results in muscular hypertrophy of the pulmonary arteries, pulmonary hypertension, and right ventricular hypertrophy.

Gastrointestinal Tract

In the exocrine pancreas, the absence of the CFTR chloride channel in the apical membrane of pancreatic ductal epithelia, limits the function of an apical membrane chloride bicarbonate exchanger to secrete bicarbonate and sodium (by passive process) into the duct. The failure to secrete sodium bicarbonate and water leads to retention of enzymes in the pancreas and ultimately destruction of virtually all pancreatic tissue. The CF intestinal epithelium, because of the lack of chloride and water secretion, fails to flush the secreted mucins and other macromolecules from intestinal crypts. The diminished CFTR-mediated regulation of sodium absorption (both mediated by sodium channels and possibly other sodium transporters, e.g., sodium hydrogen exchangers). Both dysfunctions lead to desiccated (loss of moisture) intraluminal contents and obstruction of both the small and large intestines.

In the hepatobiliary system, defective hepatic ductal chloride and water secretion causes retention of biliary secretions and focal biliary cirrhosis and bile duct proliferation in approximately 25-30% of patients with CF. The inability of the CF gallbladder epithelium to secrete salt and water can lead to both chronic cholecystitis and cholelithiasis (formation of gallstones).

Sweat Gland

Patients with CF secrete nearly normal volumes of sweat in the sweat acinus, but they are not able to absorb sodium chloride from sweat as it moves through the sweat duct due to the inability to absorb chloride across the ductal epithelial cells.

Reproductive Organs

Men with CF produce sperm, but the method of sperm transport to the semen is defective due to an absent or blocked vas deferens. 98% of males with CF are infertile. Females with CF are normal structurally, but thick and viscous cervical mucus may act as a barrier to sperm. The process of carrying a child and delivery can compromise the health of CF woman and the risks must be weighed when pregnancy is being considered.

Symptoms, Signs and Complications

Symptoms usually appear during the first year of life, but may not be evident until adolescence or later. CF patients may experience a variety of symptoms and may not follow the same pattern in all patients. Meconium ileus due to obstruction of the ileum by viscid meconium is the earliest sign and is present in 15 to 20% of affected newborns. It may be associated with delayed neonatal passage of meconium and with the meconium plug syndrome. Disease onset is frequently heralded by a delay in regaining birth weight and inadequate weight gain at 4 to 6 weeks of age. Infants with CF who have been on soy protein formula or breast milk may develop hypoproteinemia with edema and anemia secondary to protein malabsorption. 50% of patients with pulmonary manifestation, usually chronic cough and wheezing associated with recurrent or chronic pulmonary infections. Cough is the most troublesome complaint, often accompanied by sputum, gagging, vomiting, and disturbed sleep.

Disease progression includes intercostal retractions, use of accessory muscles, barrel-chest, digital clubbing, cyanosis, nasal polyps, chronic or recurrent sinusitis. Adolescents may have retarded growth, delayed onset of puberty, and a declining tolerance for exercise. Pulmonary complications in adolescents and adults include pneumothorax, hemoptysis, and/or right heart failure secondary to pulmonary hypertension. Pancreatic insufficiency is clinically apparent in 85-90% of patients, usually presents early in life, and may be progressive. Manifestations include frequent passage of bulky, foul-smelling, oily stools, abdominal protuberance, poor growth pattern with decreased subcutaneous tissue and muscle mass and rectal prolapse. Excessive sweating in hot weather or with fever may lead to episodes of hypotonic dehydration and circulatory failure. In arid climates, infants may present with chronic metabolic alkalosis. Salt crystal formation and a salty taste on the skin are highly suggestive of CF. Insulin-dependent diabetes develops in 10% of adult patients. Multilobular biliary cirrhosis with varices and portal hypertension develops in 4 to 5% of adolescents and adults. Inflammatory complications may include vasculitis and arthritis. Chronic and/or recurrent abdominal pain may be related to intussusception, peptic ulcer disease, periappendiceal abscess, pancreatitis, gastroesophageal reflux, esophagitis, gallbladder disease, episodes of partial intestinal obstruction, and/or vitamin deficiency.

Diagnosis

The standard diagnostic test for CF is a sweat test, which measures the amount of sodium and chloride in a person's sweat. The test is performed twice and a consistently high level of salt indicates CF. Newborns do not produce enough sweat for testing, so a genetic analysis of a blood sample may be performed to confirm a diagnosis of CF. The quantitative pilocarpine iontophoresis sweat test is standard for diagnosing CF. The test

must be interpreted in the clinical context. Sweat tests are well tolerated and can be performed on patients as young as 4 weeks of age. Consider genotyping for use in diagnosis or reproductive counseling. There are commercially available kits for genotyping patients with suspected CF or screening heterozygote carriers. A test that identifies two allelic mutations is highly specific for the diagnosis of CF, but the absence of identification of one or two mutations does not rule out CF. This test is accomplished by a simple blood draw. Patient who have positive sweat chloride tests may also undergo genotyping, because it is useful for reproductive counseling. There is current investigation into therapies that are specific for functional differences associated with different allelic genotypes, and thus identification of the genotype may benefit the patient when these therapies become available.

Nasal Transepithelial Potential Differences (NPD)

About 1%-2% of patients with clinical CF have normal sweat chloride levels, and about 50% of these patients have a single mutation of the CFTR gene. NPD are often diagnostic in these and other patients with indeterminate sweat chloride tests and unidentifiable gene mutations. The NPD testing involves placing an electrode behind the medial nasal turbinate and locally infusing solutions that alters sodium or chloride conductance such as amiloride. The potential difference of the nasal mucosa in persons without CF is less negative at baseline and has different patterns of response to various infused solutions. This test, still primarily a research tool, is only available in a few CF centers. Patient must sit upright and be fully cooperative for almost 30 minutes, difficult to do on small children.

Clinical Monitoring

Respiratory disease is the major cause of death in the CF patients. Nutritional health is closely related to respiratory health. CF patients should maintain normal body growth and weight to assure normal lung development, allow for normal exercise, and reduce frequency of respiratory infections. CF patients are at risk for zinc and vitamin deficiencies due to malabsorption of fats, particularly during the first year of life. Vitamin E and beta carotene are essential for protecting the airways from oxidant injury and lung damage. All CF patients should be monitored for clinical signs and symptoms of respiratory compromise. Chronic throat clearing, increased mucus production, persistent cough, and crackles in a previously clear chest are one of the best indicators of a respiratory exacerbation.

Symptoms of the respiratory system which are important to assess include exercise tolerance, wheezing, sputum production, sputum appearance, hemoptysis, and sleep quality.

Clinical signs suggesting chronic lung disease include digital clubbing, chest hyperinflation, increased second heart sound, and kyphosis.

Pulmonary Function Monitoring

Spirometry is the most specific and sensitive monitoring tool for following the clinical status of the CF patients. Initially the lung function of the CF patient is normal. Then, airway obstruction develops and usually involves the smaller, more peripheral airways first. Spirometry, either a volume-time or flow-volume curve, will initially show changes in flow at lower lung volume (forced expiratory flow during the middle half of the forced

vital capacity), followed by decreased flow at higher lung volumes, FEV1, eventually by decreased volume, FVC. With actively growing children, pulmonary function values are plotted as percent-of-predicted values, whereas with adult patients the absolute values may be plotted. A 10% FEV1 decrease is considered a sign of worsening lung disease, and if acute, is a sign of a respiratory exacerbation. Post-bronchodilator spirometry should be performed with patients who have detectable airway obstruction to see if bronchodilator therapy would be helpful and to look for complicating conditions such as asthma.

Respiratory rate and pulse oximetry can help provide early signs of worsening lung function, particularly in young children in whom abnormalities of smaller airways are more likely to decrease oxygenation. For older patients tachypnea and poor oxygenation are signs of more severe disease or an acute respiratory exacerbation. Oxygenation during sleep is an important measurement that should be done in all patients with acute respiratory deterioration or who show signs of pulmonary hypertension. Night time desaturation can be quite severe in patients who have a normal daytime saturation. Patients with FEV1 < 30% of predicted as a particular risk of nocturnal hypoxia and hypercarbia. If pulmonary function indicates restrictive changes, it may indicate substantial air trapping. Exercise tolerance studies can be used to monitor worsening or improving lung functions. Pulse oximetry should be monitored during exercise tolerance studies because desaturation is a common complication. Carbon dioxide monitoring during exercise may be indicated in patients with severe obstructive disease (FEV1 <40% predicted).

X-Rays

Chest X-rays are indicated yearly for all CF patients to detect structural changes. CAT scan may be valuable for early detection of airway disease and bronchiectasis in the middle age child with normal pulmonary function.

Current Therapy

The new Cystic Fibrosis guidelines were based on a two-year review of published research on patients aged six and older. The guidelines are published in the second issue for November 2007 of the American Journal of Respiratory and Critical Care Medicine. "Physicians treating patients with CF are faced with a growing number of treatment options. We are hopeful that clinicians will find these recommendations to be useful in their care of patients with CF," the guidelines' lead author, Dr. Patrick A. Flume, said in a prepared statement.

CF is a genetic disease that affects the lungs and other organs. It's characterized by thick, sticky mucus that makes it almost impossible for CF patients to fight off germs and infections. The disease is always fatal, and lung disease accounts for 85 percent of deaths among CF patients. However, advances in treatment in the last 60 years have increased life expectancy from just a few years to about 36 years.

Flume and his colleagues looked at a number of treatments and rated their effectiveness. Those with the strongest, most consistent results were given an "A" grade recommendation. They are:

Inhaled tobramycin -- an antibiotic -- to suppress chronic *Pseudomonas aeruginosa* infections in CF patients with moderate to severe disease, to improve lung function and reduce exacerbations.

Dornase alfa, which degrades the free DNA that accumulates in CF mucus thereby loosening the mucus, promoting airway clearance, improving lung function and reducing exacerbations.

"B" grade recommendations were given for:

Inhaled tobramycin, to suppress *Pseudomonas aeruginosa* infections in CF patients with mild disease or who are asymptomatic, to reduce exacerbations.

Dornase alfa for CF patients with mild disease who are asymptomatic to improve lung function and reduce exacerbations.

Hypertonic saline which hydrates surface liquid in patients with CF thereby improving lung function and decreasing exacerbations.

Beta 2-adrenergic receptor agonists, which relax smooth muscles and dilate bronchial passages, which improve lung function in CF patients, and are well-tolerated.

The guidelines recommend against:

Systemic corticosteroids in children because of "an excess number of adverse events," including abnormalities in glucose metabolism, cataracts, and percentage of patients "colonized" with *Pseudomonas*. This recommendation excludes patients with concomitant asthma.

Inhaled corticosteroids, because there's no clinical benefit. This recommendation excludes patients who also have asthma, however.

Prophylactic anti-Staphylococcal antibiotics because of the lack of clinical efficacy and an apparent increase in *P. aeruginosa* infections with their use.

Delivery Devices

Effective therapy, with nebulized medications, is dependent on the education of the patient or parents to use proper administration technique. Use a mouthpiece (children over 3 years old), breathe through the mouth (may require nose clip), use the appropriate nebulizer, and complete the entire dose. For the younger children, a face mask should be used and always placed snugly onto the face. Simply moving the mask away from the face by 2 cm reduces drug delivery by 85%. A metered-dose inhaler should always be used with a spacer which improves delivery and decreases adverse effects. In bronchodilators, more than 2 puffs are frequently required because the total dose is often much less than in a nebulizer. Dry powder inhalers are increasingly popular, but needs good patient education to assure the patient can generate adequate inspiratory flow. Dry powder inhalers should not be used by children under 4-6 years old.

Delivery devices are a potential cause of nosocomial infection, and infections control standards need to be rigidly followed.

Disinfection Options for Reusable Items Contacting the Patient

Boil in water for 5 minutes, or use a standard cycle dishwasher if water >160F is maintained for > 30 minutes, or microwave for 5 minutes, or immerse in one of the following:

1:50 dilution of 5.25-6.15% sodium hypochlorite (bleach) for 3 minutes

70% isopropyl alcohol for 5 minutes

3% hydrogen peroxide for 30 minutes

Following disinfection by immersion, the device should be rinsed with sterile water (not tap or distilled water) and allowed to air dry. An alternative is to rinse with tap water, followed by rinsing with 70-90% alcohol.

Airway Clearance Techniques

All CF patients should routinely have airway clearance therapy. There can be benefits from airway clearance in the asymptomatic patient before daily coughing and mucus production is present, which may contribute to the deterioration of the lung function. Airway clearance therapy should be done prior to eating to avoid stomach upset. Bronchodilators or mucolytic medications are given prior to or during airway clearance therapy. The decision on which technique to use should be based on the patient's age and preference after trying different approaches.

Chest Physiotherapy

CPT is also known as Percussion-and-drainage or chest clapping. CPT is typically performed with a cupped hand or a plastic cup and rapid "clapping" onto the chest. Mechanical devices are available, although they do not clear the airways better than manual techniques. During CPT the patient is placed in several positions to enhance mucus clearance. Percussion is usually performed for 1 to 2 minutes in each position, followed by encouraging the patient to cough. The goal is to move peripheral mucus into more central airways, this will happen even in the absence of a cough. Oxygen saturations may decrease during CPT and patients with severe lung disease should be monitored. To reduce desaturation, inspiratory pressure-support ventilation can be added during CPT. Gastroesophageal reflux can be exacerbated during CPT, so the head-down position should be avoided in all patients.

Active Cycle of Breathing

This technique is a combination of breathing control, thoracic expansion, and forced expiratory technique. It improves lung function without decreasing oxygenation. Breathing control is normal tidal breathing with the lower chest, allowing the upper chest and shoulders to relax (also referred to as diaphragmatic breathing). During active cycle of breathing technique, breathing control is used between periods of thoracic expansion and forced expiratory technique. Thoracic expansion exercises involve deep breathing, focusing on active inspiration. Deep inspiration is often followed by a several-second hold, which is particularly valuable for the postoperative patient, in whom it aids in avoiding atelectasis. Thoracic expansion is repeated 3-4 times followed by a period of breathing control. The forced expiratory technique combines 1 to 2 huffs (forced exhalations) with periods of breathing control. Huffs can be more effective than coughing and patients often use a modified forced expiratory technique when they need to move mucus, such as while in the shower or other moist environment. Huffing can be performed at various lung volumes. At low lung volumes, the huff moves mucus primarily from the more peripheral airways, whereas at high lung volumes, the huff clears the secretions from the larger, more proximal airways. The forced exhalation produces a dynamic compression of the airway, leading to airway collapse downstream (toward the mouth) from the point where pressure outside the airway is similar to inside the airway (referred to as equal pressure point or flow-limiting segment). Any mucus

within this distance of compressed airway will be exhaled from the lung by increased air turbulence. As the lung volume decreases, the area of airway compressions moves upstream (toward the alveolus), resulting in movement of more peripheral mucus. A prolonged huff, or a series of coughs without intervening breaths, moves the compressing segment deep into the segmental bronchi. Huff results in lower transpulmonary pressure than a sequence of coughs, resulting in less complete airway collapse. The huff is a forced but not violent maneuver and can be varied by length and force to optimize mucus clearance. Young children can be taught to huff by playing games. It is important to remember the goal is not to do a maximal flow maneuver such as that performed for pulmonary function testing.

Autogenic Drainage

The goal is to breathe at different lung volumes and create the highest possible air flow in different airway subdivisions. The mucus is “unstuck” at low lung volume, “collected” at middle lung volume, and “evacuated” at high lung volumes. The patient breathes tidally below his normal FRC for a few minutes. This causes mucus to be cleared from the more peripheral airways. Exhalation is mildly forced, to shear mucus from the airway walls. Then the patient inspires a small amount, raising the volume for tidal breathing. This cycle is repeated several times, eventually raising lung volumes well above FRC. Often mucus is expectorated without the need for forced coughing. Oxygenation is unaffected during autogenic drainage. Frequently, autogenic drainage is combined with several aspects of active cycle of breathing technique, including doing the forced expiratory technique between different levels of lung inflation. The patient should be encouraged to experiment with the different techniques to find the optimal way to clear secretions.

Positive Expiratory Pressure and Flutter

Positive expiratory pressure (PEP) is an airway clearance technique developed to reduce the airway collapse caused by bronchiectasis. There are 3 modifications of PEP technique: low-pressure PEP, high-pressure PEP, and oscillating PEP.

Low-Pressure PEP

Consist of a mouthpiece or face mask attached to a low-pressure, expiratory resistor. Usually there is some form of manometer to measure the expiratory pressure. The degree of expiratory resistance can be varied so the patient can exhale, without exertion, and maintain pressures of 10-20 cm H₂O. Inspiration is passive and exhalation slightly active against the resistance. Techniques differ, but usually involve 1-2 minutes of tidal breathing or 15-20 expiratory breaths of 3 seconds each. The PEP is removed and the patient does several forced exhalations and coughs. This cycle is repeated 3-4 times, with the entire treatment lasting 15-20 minutes. Low-pressure PEP is similar to CPT for airway clearance, although there may be less oxygen desaturation.

High-pressure PEP

This technique uses forced expiratory maneuvers against the resistor, creating high pressure. The patient inhales to total lung capacity and performs a FVC maneuver, creating pressures between 40 and 100 cm H₂O. The expiratory resistor is adjusted to provide for optimal airway distention and should prevent airway closure.

Oscillating PEP

Most commonly performed with the Flutter device or the Acapella device. The patient exhales into the Flutter device. During exhalation, the steel ball inside the device bounces, causing vibratory obstruction to airflow, this oscillates both the pressure and the air flow. The angle at which the device is held determines the oscillation frequency (usually between 6 and 26 Hz), and the patient's expiratory effort determines the pressure. The Acapella combines the principle of high-frequency oscillation and PEP by employing a counterweighted lever and magnet. Patient exhales through a cone, which is intermittently occluded by a plug attached to the lever, producing air flow oscillations. A knob located at the distal end of the device adjusts the frequency, amplitude, and mean pressure. The Acapella is available in 2 models, one for patients who can sustain at least 3 seconds of expiratory flow >15 lpm, and one for patients with expiratory flow <15 lpm. As with other PEP techniques, the patient repeats the maneuver for 10-15 breaths and then does several huffs or coughs without the device. This cycle is repeated 3-4 times, resulting in a 15-20 minute airway clearance session.

Intrapulmonary Percussive Ventilation

With IPV there are continuous oscillating pressures during both inhalation and exhalation. The pressure and frequency of these oscillations can be varied, but typically the frequency is 6-12 Hz and the pressures are 10-20 cm H₂O. Following IPV therapy, sputum production and pulmonary function improvement is similar to that following standard CPT. Fluid can be delivered during IPV, similar to IPPB except there is not an attempt to breathe for the patient. The oscillating pressure is layered on top of the patient's normal tidal breathing. Studies of drug deposition via IPV is needed to assure clinical effectiveness, since some medications, such as dornase alfa (Pulmozyme), may be broken down when delivered via non-approved nebulizers.

High-Frequency Chest Compression

HFCC (The Vest) was developed to provide oscillation to the external chest. Oscillation has potential benefit both by shearing mucus from the airway wall and by modifying the viscoelastic properties of the mucus. Shearing occurs at the mucus-airway surface interface and results from the kinetic energy released by high-velocity air flow. Peak flows during HFCC are similar to those produced with coughing, although for briefer duration. The result is to enhance release and downstream flow of mucus. Mucus viscoelasticity can be altered mechanically as well as chemically. HFCC is clinically safe and effective in CF patients and the patient can independently perform. Patient acceptance and adherence with prescribed routine may be better with HFCC. In-patient HFCC therapy is also effective, and although the initial equipment cost is high, subsequent savings in therapist time can be expected.

Exercise

Closely supervised exercise programs, encourage the patient to adhere to exercise routines, and provides monitoring. Although, many CF patients are unable to maintain prolonged, high-intensity programs, studies indicate that patients in regular exercise programs have better lung function than less active patients and improved quality of life.

Aerobic fitness may be an indicator of disease status and prognosis. There is a lower mortality among CF patients who exercise regularly, even when controlled for pulmonary function. Oxygenation during exercise should be monitored. CF patients with mild lung disease (FEV1 > 80% of predicted) will not have exercise-related desaturation. Patients with severe pulmonary disease (FEV1 < 40% of predicted) are likely to experience both hypoxia and hypercarbia with exercise. These patients are at risk for adverse events during exercise and should have close cardiopulmonary monitoring if they plan to exercise. Continuous positive airway pressure or supplemental oxygen during exercise may help these patients by reducing the work of breathing. Once the patient is cleared for exercise he should be encouraged to exercise for at least 30 minutes, 3 times a week. The reduced deterioration of lung function related to exercise is seen only when combined with routine airway clearance.

Noninvasive Ventilation

BiPAP has increasing value for “bridging the gap” between respiratory failure and lung transplant in CF patients. Nocturnal BiPAP reduces hypoxia, hypercarbia, and work of breathing and may enhance airway clearance and reduce pulmonary hypertension.

Lung Transplantation

Lung transplantation has become an accepted treatment for respiratory failure due to CF. Effective means of patient selection surgical technique, immunosuppression, and post-transplant management permit survival as good as that of transplant patients with other diseases. The new lungs do not acquire the CF ion transport abnormalities but are subject to the usual post-transplant complications. CF problems in other organ systems can persist and may be worsened by some of the immunosuppressive regimens required to prevent rejection of the transplanted lung. Living donor lobar transplantation is a procedure that involves the removal of a lower lobe from each of two donors and subsequent transplantation into a child or small adult. Survival rate post transplant is as high as 80-90% for one year and 60-70% for five years.

Research

The Cystic Fibrosis research programs support investigator-initiated research grants encompassing both fundamental and clinical studies of the etiology, molecular pathogenesis, pathophysiology, diagnosis, and treatment of cystic fibrosis and its complications.

Particular areas of emphasis of the program include the characterization of the cystic fibrosis gene, its mutations, and the molecular mechanisms by which mutations cause dysfunction. Studies of the cystic fibrosis transmembrane regulator (CFTR) protein encoded by the cystic fibrosis gene, including its processing, trafficking, and folding, and the mechanisms by which mutations alter CFTR trafficking and structure/function. Also elucidation of the pathways of electrolyte transport in affected epithelia and the relationship between CFTR and other epithelial ion channels. and elucidation of the potential roles of CFTR in transport of molecules other than chloride, post-translational processing of mucins and other proteins, exocytosis and recycling of cell membranes, subcellular organelle function, and other cellular processes.

Studies of the relationship between genotype and phenotype in cystic fibrosis and identification of genetic or environmental factors which explain the variable clinical presentations and severity of disease. Delineation of the mechanisms underlying the inflammation and infection characteristic of cystic fibrosis and how mutations in the cystic fibrosis gene and alterations in CFTR function result in inflammation and infection. Research on other clinical manifestations of cystic fibrosis, including the pathophysiologic mechanisms underlying malnutrition and growth failure, impaired fertility, liver disease, and overall physical and psychosocial development, and approaches to ameliorate the complications of cystic fibrosis.

Development of potential therapeutic approaches to modulating the transport defect in cystic fibrosis and to stabilize mutant CFTR and enhance its targeting and integration into the cell membrane is being studied. Also development of safe and effective methods for gene therapy. Development of animal or cell models useful for study of cystic fibrosis and its therapy. Evaluation of therapeutic interventions in cystic fibrosis in clinical studies or animal models.

Clinical Trials

Gene Therapy

The goal of gene therapy is to deliver a normal copy of the CFTR gene to the cells that need it. The DNA inserted into target cells should direct synthesis of the normal CFTR protein and reverse the primary biochemical abnormality of CF. Introduction of the gene should replace all functions of the CFTR protein, including any that have not yet been recognized. Choice of vector, mode of delivery to airways, translocation of genetic information, and sufficient expression level of the normalized CFTR gene are issues that currently are being studied. Clinical trials are underway to evaluate the effectiveness of tgAAVCF (Target Genetics adenoassociated virus cystic fibrosis). tgAAVCF uses an AAV vector to deliver functional copies of the CFTR gene directly into the lungs. Because a faulty gene causes cystic fibrosis, adding normal copies of the gene to cells should correct these cells and ultimately cure the disease.

Use of compacted DNA (non-viral) to introduce normal copies of the gene into CF airways. A Phase 1a trial demonstrated chloride current changes in the noses of CF patients, but no evidence of gene expression. The gene therapy product is being reformulated prior to additional clinical trials in an attempt to improve the amount and duration of gene expression.

Protein Assist/Repair

This therapy is designed to correct the function of the defective CFTR protein made by the CF gene to allow chloride and sodium (salt) to move properly in cells lining the lungs and other organs.

PTC 124 is a novel, small molecule compound, that promotes the read-through of premature truncation codons in the CFTR mRNA. It has been demonstrated to be safe, orally available and well tolerated in Phase 1 single dose trial in healthy volunteers. A Phase 2 trial in CF patients conducted in the U.S. and Israel demonstrated safety and encouraging biological results.

VX-770 is a new compound called a "potentiator" that may act upon the CFTR protein and help to open the chloride channel in CF cells. Phase 1 dosing has been completed in patients. Researchers are evaluating results and Phase 2 has begun.

Correct abnormal processing of CFTR in the cell. Curcumin appears to work in some strains of CF mice but not all. A previous Phase 1 trial in CF patients did not show correction of CFTR. A follow-on study at a higher dose is ongoing to confirm these findings.

S-Nitrosoglutathione (GSNO) levels are low in the lungs of CF patients. GSNO has been shown to promote trafficking of deltaF508 CFTR in some, but not all, tests on cultured cells. Nitrox LLC is developing inhaled GSNO for CF and is presently carrying out required preclinical safety studies as well as formulation studies.

CFTR Modulators including Correctors and Potentiators: These screening programs are in the research phase to identify correctors of the CFTR trafficking defect and additional potentiators of CFTR-mediated ion transport.

Restore Salt Transport

The goal of this approach is to hydrate thick CF mucus in the lungs by correcting the amount of salt (sodium & chloride) along the cell surface.

Denufosal was a recently completed Phase 2 trial to determine the effect of drug on pulmonary function in CF patients demonstrated efficacy. A Phase 3 trial has begun. SPI-8811 an oral agent believed to bypass transport defect of chloride ions. Initial Phase 2a trial evaluating safety and efficacy.

Parion 552-02 is thought to correct the CF ion transport defects by acting primarily on abnormal sodium reabsorption. Phase 1 trials in normal volunteers and a single dose Phase I trial and a Phase II trial in CF patients are complete.

Inhaled Moli1901 is designed to correct the chloride channel transport problem in CF cells. A Phase 1 trial demonstrated safety. Placebo-controlled, multi-dose, dose-ranging Phase II trial in Europe demonstrated positive changes in pulmonary function with highest dose.

Mucus Treatment

The following studies are being evaluated for their effectiveness in thinning and clearing the thick mucus from the airways.

Pulmozyme was the first drug developed specifically for CF in 30 years and was approved by the FDA in 1993; it became available in 1994. It is currently being used by more than 18,000 U.S. patients. Clinical trials were conducted in the CFF's care center network.

Hypertonic Saline – A CF Foundation-supported study in Australia showed hypertonic saline to be safe and effective in adults with CF, helping clear mucus and leading to better lung function. The drug is now being evaluated for safety and effectiveness in younger people with CF.

Anti-Inflammatory

Anti-inflammatory drugs are being studied for their ability to reduce inflammation in CF lungs.

Oral N-acetylcysteine, an antioxidant, replenishes glutathione levels in neutrophils. Placebo-controlled 12-week study at Stanford Univ. demonstrated decreases in inflammatory cells in lung and positive indications of changes in pulmonary function. People with CF appear to have lower than normal levels of DHA, a fatty acid that may be important to protecting the body against inflammation. A lack of DHA in people with CF may contribute to increased inflammation in the lungs. Pilot study to examine effect of infant formula fortified with DHA on pathogenesis of CF in 120 newly diagnosed patients at 16 centers began in 2003.

Low-dose Methotrexate; Pioglitazone; Hydroxychloroquine are approved therapies (approved for non-CF indications) are being evaluated in exploratory Phase 1 trials in CF to determine if they are tolerated and if anti-inflammatory effects are seen.

Simvastatin is a HMG-CoA reductase inhibitor that increases nitric oxide (NO) production in cultured CF epithelial cells. Investigators are evaluating whether simvastatin increases exhaled NO production in CF patients, synthesis of pro-inflammatory cytokines and whether measures of inflammation in the upper respiratory tract correlate with those from the lower respiratory tract.

Inhaled Glutathione A Phase 1 trial of inhaled glutathione began in Germany in mid-2007. HE-2000 is a hormone that may help to regulate the immune system, which is in “overdrive” in CF lungs. An oral immune-regulating hormone is in preclinical testing.

Anti-Infective

The following drugs are being studied for their effectiveness in fighting lung infections for people with CF.

TOBI aerosol antibiotic received FDA approval in 1998. Currently is being used by more than 15,000 patients worldwide. Benefit at first sign of Pseudomonas infection is being evaluated.

Azithromycin in patients with chronic PA, this oral antibiotic improved lung function and weight gain, and decreased hospitalization rate. Two follow up studies are in progress.

Aztreonam, a Phase 3 trial is complete with several other Phase 3 studies of the aerosolized form of aztreonam, a widely used IV antibiotic in CF, ongoing; drug may be ready for market.

TIP (TOBI Inhaled Powder).developing TOBI as a powder to enable a faster, more convenient dosing regimen. Dosing of TIP will take a fraction of the time of liquid TOBI. An inhaled version of the antibiotic ciprofloxacin is being developed for treatment of airway infections.

SLIT-amikacin is a liposomal formulation of the antibiotic amikacin. Animal model studies have shown it to decrease the PA burden in the lung.

MP-610.205 is a bacterial efflux pump inhibitor that may increase the effectiveness of antibiotics in the treatment of chronic and acute bacterial respiratory infections in CF. A single-center Phase 1b clinical trial did not reveal safety concerns with the aerosolized product in CF patients.

Kalobios KB001 in a Phase I clinical trial has been initiated to test the safety of this antibody approach for the treatment of Pseudomonas aeruginosa lung infections. Several companies are in preclinical development of pseudomonas vaccines.

Lung Transplant Drugs

A lung transplant drug is currently being evaluated to help improve the chances of successful transplants.

Inhaled formulation of cyclosporine was tested in a randomized placebo controlled trial. The group treated with inhaled cyclosporine showed a significant decrease in number of deaths and the development of chronic rejection. An additional clinical trial has been requested by the FDA before this drug is approved for clinical use.

Despite the advancements in our understanding of the pathogenesis of CF, it remains a potentially devastating disease. Antibiotic therapy remains to be the hallmark of management in CF patients that have chronic lung disease in an attempt minimize or eliminate lower respiratory tract infections; drug resistance is a growing problem. New antibiotics, new ways of using old antibiotics and new therapeutic modalities under development such as gene therapy, will offer improved outcomes in patients with CF.