

## Advances in Cystic Fibrosis

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### Abstract

The purpose of this review was to identify the history of and advances in cystic fibrosis (CF). New treatment plans, medication developments, and a historical perspective of airway clearance therapy (ACT) will be presented. The importance of treatment compliance and time management in the care of cystic fibrosis patients will also be discussed. Furthermore, the development of cystic fibrosis clinics and the pivotal role they play in the treatment of the disease will be addressed. Lastly, a brief discussion concerning the need for and process of lung transplantation will be reported.

**Keywords:** *Cystic Fibrosis; Airway Clearance Therapy; Treatment Compliance; Lung Transplant*

### Abbreviations

CF: Cystic Fibrosis; ACT: Airway Clearance Therapy; CFTR: Cystic Fibrosis Transmembrane Conductance Regulator; MRSA: Methicillin-Resistant Staphylococcus Aureus; FDA: Food and Drug Administration; CPT: Chest Physical Therapy

### Introduction

Cystic Fibrosis (CF) was first discovered as a disease in 1938 by Dr. Dorothy Andersen. She found something bizarre about an autopsy on a child she was examining. The child was known to have died of celiac disease, the inability of the intestines to digest gluten, but Dr. Andersen did not only notice digestive issues with the intestines. She also noticed there were lesions on the pancreas that were very unusual. Upon these discoveries, she studied the past medical history of the patient and compared it with medical literature only to unearth a whole new disease. Dr. Andersen decided to focus on her living patients to further research the disease she called cystic fibrosis [1]. Dr. Anderson is also attributed with developing the sweat and chloride electrolyte test, the diagnostic tool that is still being used today, but struggled in finding ways to treat and cure the disease.

Today in North America, for every one in 3,000 live births there is a baby born diagnosed with CF. Up to 25 percent of the population are carriers of CF and each year 1,000 people are diagnosed with having the disease, averaging a total of 30,000 people. When the diagnosing of CF was first developed, children only lived to be a few years of age, but today they are living to see late adulthood [2]. The discoveries of the past and the developments of the future help CF patients continue to improve and live longer. This paper will examine the treatments for CF of the past, present, and future; as well as the options CF patients have in their plan of care. We will explore the ways cystic fibrosis patients survive longer today and the hopes of finding a cure.

### Discussion

Cystic fibrosis "is one of the most common lethal genetic diseases among whites in the United States" [2]. CF is a genetic disorder that occurs when a mutation of a protein, called cystic fibrosis Transmembrane Conductance Regulator (CFTR) is copied. This particular protein is responsible for transporting chloride ions to the cell membranes to allow secretions to be produced and maintained properly. Due to the mutation and lack of secretion control by the CFTR for CF patients, this causes a tremendous amount of breathing problems and persistent lung infections. Because the CFTR can be mutated over 1,000 different ways, this makes symptoms and treating cystic fibrosis

for each patient very divergent. CF patients tend to have complications with all organs that require exocrine functions, such as the sweat glands, the pancreas, and most commonly the lungs. CF patients have a hard time discarding salt from their sweat, giving them a more salty taste to their skin. Their pancreas cannot produce sufficient digestive enzymes making it hard for CF to digest proteins, carbohydrates, and fats in their diets. This leads to malnutrition and normally gives the person a slender physical looking body. Lastly, pulmonary complications are the leading cause of death in these types of patients [2]. The lungs of CF patients tend to produce copious amounts of mucus that is extremely thick and hard to expel from the lungs causing a large buildup that produces bacterial infections. The most common bacteria associated with CF, includes *S. Aureus*, *H. influenza*, and *Pseudomonas Aeruginosa*. If these infections are not treated immediately they can cause the airways to become obstructed leading to atelectasis, pneumonia, hyperinflation, lung damage, and eventually hypoxemia and respiratory distress.

## Diagnosis

CF testing can be done as early as 15 weeks of pregnancy through blood work, amniocentesis, or chorionic villus sampling. The blood testing is mainly to see if the parents are carriers of the cystic fibrosis gene. The amniocentesis and chorionic villus sampling are done by taking tissue or amniotic fluid from and around the placenta to be tested for genetic disorders. There is a 25 percent chance that CF can be passed onto the baby if both parents are carriers for the disease. If one parent is a carrier of the CF gene, then the baby has a 50 percent chance of inquiring that gene and becoming a carrier of the disease as well [3].

Testing for CF outside of the womb usually occurs when signs and symptoms of the disease occur or if the baby had a positive screening for the disease. Some signs and symptoms may include; a persistent cough with phlegm, poor growth and weight gain despite a good appetite, constant lung infections, salty tasting skin, greasy bowel movements, and persistent wheezing and shortness of breath [4]. The number one diagnostic tool for CF is the sweat chloride test. The sweat test is painless and is as simple as applying an odorless and colorless chemical, called pilocarpine to the skin, on an arm or leg, with the use of an electric stimulator to help the skin produce sweat. Once sweat is produced, it is collected on a piece of filter paper, gauze, or plastic coils and taken to the laboratory to have the amount of chloride produced in the sweat measured. If the results for cystic fibrosis are positive then the results will read 60mEq/L or greater [5].

## Treatment

Due to the deficiencies of digestive enzymes from the pancreas, 87 percent of CF patients have to take pancreatic enzyme supplements [6]. These pancreatic enzyme supplements are made into capsules and should be taken by mouth. They should also be taken before every meal and snack to help with digestion, as the enzymes only work for one hour after consumption. CF patients should work closely with a dietitian to help them understand the amounts that should be taken. Depending on the type of meal, increased intake of enzyme supplements may need to be taken. While other times it should be decreased, because taking too much enzyme can cause damage to the intestines and taking too little can cause malnutrition [6].

The majority of the medications taken by cystic fibrosis patients include bronchodilators, mucolytics, antibiotics, and anti-inflammatory drugs. Bronchodilators are drugs that tend to dilate the passages of the airways and decreases the resistance, allowing for easier movement of air through the airways. A mucolytic is a drug that helps thin out thick mucus that is stuck to the inside of the lungs, making it easier for the patient to expel the mucus. It is important to remove this mucus from the lungs as often as possible so that infections do not occur. Two very popular mucoactive drugs used by cystic fibrosis patients include: Pulmozyme and hypertonic saline. Both drugs are nebulized aerosols taken up to twice a day. The hypertonic saline shows the greatest outcomes with removal of sticky mucus from the lungs. The aerosol was first researched in Australia after surfers with cystic fibrosis stated that “their airways felt clearer after exposure to the salt spray” [7]. A study was done on 164 people in Australia at Royal Prince Alfred Hospital over a span of three years. Half of the people were given four milliliters of seven percent hyper tonic saline and the other half were given normal saline twice a day for 48 weeks. The results showed that participates who took the hyper tonic saline had fewer episodes and faster recovery rates with episodes versus participants who used only saline [7].

There are several new mucolytic drugs that are being studied to help improve airway clearance in CF patients. Those medications consist of: inhaled Mannitol, OligoG, VX-371, OrPro, and Spyryx. Inhaled Mannitol is an osmotic agent that tends to draw water into the lungs and helps the lungs stay moist. One study in the United Kingdom used a powder form inhaler of Mannitol with 390 participants over a span of 26 weeks. The first group of 141 were given 400 mg, max dose, of Mannitol and the second group of 102 were given a 50 mg controlled dose of Mannitol twice daily. Both groups showed improved lung function with pulmonary testing and a decrease in respiratory exacerbations. There were minimum adverse reactions with three percent having exacerbations with the max dose and two percent having exacerbations with the control dose [8]. This drug is still in phase three of its study and not yet approved for use in the United States, but has been approved for use in Australia and the United Kingdom as of September 25, 2014, [9]. OligoG is a drug used to help decrease the thickness of mucus and also aide in the effectiveness of antibiotics. This drug is in phase two of its study in Germany, United Kingdom, Sweden, Denmark, and Norway and has not been approved for use in the United States. VX-371 is another phase two drug study that has not yet been started, but is intended to block sodium channels and allow longer durations of fluid in the lungs. This drug is not yet approved for use in cystic fibrosis patients for airway clearance. OrPro and Spyryx are both still in the preclinical phase of their study in helping to remove mucus from the lungs and are not yet approved for use in cystic fibrosis patients for airway clearance.

Tobramycin is used to treat *Pseudomonas Aeruginosa* bacterial infections which is a frequent occurrence in CF patients. New studies show that Tobramycin in the new powder inhaler form works just as well as the nebulizer form and with a 70 percent decrease in treatment time if the patients FEV1 is between 25 - 80 percent of their lung function [10]. Cayston is an antibiotic that is made mainly for *pseudomonas aeruginosa* and has been an approved inhaled antibiotic since 2010. Azithromycin is an inhaled antibiotic made for chronic *pseudomonas aeruginosa*, but also works really well with other bacterial infections of the lungs. This particular drug showed improvement in lung functions, increased weight gain, and decreased hospitalization rates [11].

New and upcoming antibiotics indicated for use in CF patients are Levofloxacin, Liposomal Amikacin, Vancomycin inhaled powder, and Gallium. Levofloxacin was recently approved by the FDA on March 24, 2016 for use in treating pulmonary infections in cystic fibrosis patients [12]. Liposomal Amikacin inhalation medication is in the third phase of research, but a prior phase two study shows promising results for CF patients with *pseudomonas* bacterial infections, if taken once daily [13]. Vancomycin inhaled powder for the treatment of methicillin-resistant *staphylococcus aureus* (MRSA) is still being reviewed, but has also passed a phase two study. The phase two study showed a significance decrease of MRSA in the sputum collections of CF patients who took inhaled Vancomycin [14]. As of July 2016, the U.S National Institutes of Health are recruiting CF patients for evaluation of the new antibiotic Gallium for the treatment of pulmonary infections. Gallium has been approved by the Food and Drug Administration (FDA) for IV treatment for *pseudomonas*, but there has been no new updates on the use of this drug for treatment in CF at this time [15].

Ibuprofen is a commonly known anti-inflammatory medication, but to CF patients it is a daily must. Studies by the CF foundation have shown that taking Ibuprofen as early as thirteen years old helped tremendously more than those who started taking Ibuprofen at a later age [16]. CTX-4430 is another anti-inflammatory medication in the making for CF patients. CTX-4430 is in the second stage of the study by the CF foundation, and reduces the production of leukotriene B4 that causes inflammation in cystic fibrosis patients.

GS-5745 is an anti-inflammatory drug that is still in the second stage of studies as well, and is not yet approved for clinical use. The study consists of two different experiments: study one consists of using a high dose of the medication while the second study consists of using two lower doses of the medication. The results will be compared with pulmonary function testing on each patient [9]. JBT-101 is an anti-inflammatory drug that is in the second phase of studies and destroys inflammation molecules, while also producing an extra amount of molecules that continue to protect the lungs from inflammation. While the first phase studies showed improvement in the inflammation in the lungs within four hours, they are still hard at work to improve the drug and find ways to make it more efficient [17]. LAU-7B uses compounds related to that of vitamin A and will begin its testing for the use of decreasing inflammation in the lungs of CF patients starting in 2017 [18]. POL6014 is still in phase one of the studies and is currently being tested in Europe with hopes to continue

the studies in the United States. POL6014 works to prevent the protein called neutrophil elastase from forming in the lungs and decreasing the tissue break down [19].

### **Time management and compliance**

CF patients use multiple nebulizers for the treatment of their disease twice a day or more as needed. The amount of time it takes away from their lives can be a challenge. Some patients take up to five different nebulized drugs in one sitting using separate nebulizers to prevent drug interaction and infections. These nebulized treatments can take up to 30 minutes or more at a time. Maintaining a clean environment and nebulizers is very important and can get very expensive. There is currently no better alternative to nebulizer treatments for CF patients for topical lung deposition. It is very important that CF patients maintain compliance with nebulizer treatments as it can prevent them from having numerous exacerbations and further progression of the disease. One of the biggest problems with CF patients maintaining compliance is that they feel they do not need the treatments because they are breathing fine at the time [20]. We must encourage these patients to continue their home regimen treatments every day, even on days they feel great.

### **Airway clearance**

Airway clearance therapy (ACT) is a very important part of the treatment process for CF patients as it helps remove mucus buildup in their lungs. The use of ACT helps to mobilize and remove mucus in the lungs, prevent mucus plugs from occurring, and prevent unwanted pulmonary infections. There are several different methods that provide airway clearance including; chest physical therapy (CPT), coughing, positive expiratory pressure devices, and physical activity. The majority of CF patients use CPT and coughing techniques to keep their airways clear. CPT can consist of manual or electrical machines, such as the CPT vest that is commonly worn by CF patients during their nebulized treatments or as needed throughout the day. The CPT vest works in that it uses a constant vibration and shaking technique against the outside thoracic area at 20 to 30 hertz. This treatment may take up to 30 minutes or more. Using coughing techniques after nebulizer treatments or CPT allows a greater chance at removing secretions from the lungs. Positive expiratory pressure devices, such as the flutter valve, are other simple ways to provide mucus clearance from the lungs when time is limited. Lastly, staying active is important and an easy way to keep mucus from settling in the lungs, can improve lung capacity, and gives the person an overall positive quality of life experience. Manual CPT can be done with the help of another person. The person simply cups their hand and strikes the chest in a circular and waving type motion. Although this technique does work it is sometimes inconvenient and can be very tiring for the person performing the exercise.

One of the more recent airway clearance devices available is called the VibraLung. The VibraLung was created by a man named Art Hughes who initially came up with the idea in order to help his wife who had reoccurring pulmonary health problems. Art first designed the VibraLung using materials found around his home such as a can, a speaker, and a hollow tube to create a multi- vibrating frequency that helps break up mucus in the lungs. Art's wife Linda was only supposed to live for three months and required continuous oxygen, but after using the VibraLung, Linda no longer needed oxygen and lived for another six years [21]. The VibraLung uses increasing sound-waves from 5 to 1200 hertz over a ten minute treatment process during inhalation and exhalation. The VibraLung without insurance can be costly to purchase, as a VibraLung costs almost \$3,000 [22]. One of the biggest pros for this device is that it can be taken outside of the home, as the VibraLung runs off of batteries instead of air, oxygen, or electricity. Additionally, brief ten minute sessions may improve airway clearance treatment adherence.

### **CF clinics**

CF clinics can play a significant role in the lives of CF patients, in that it helps them find new treatment options and may help to decrease the number of hospitalizations each year. According to Scott Elder, RRT at The University of Tennessee Medical Center "many CF patients are unaware of all the options they can be provided with at a clinic". Before the UTMC opened their CF clinic the adult CF patients were having to drive all the way to Vanderbilt for these clinics. Scott Elder, RRT stated that "many patients would skip these appointments because the drive was too far and became too expensive for some". The UTMC opened its very first CF clinic in May of 2011 to help older

cystic fibrosis patient's transition from the pediatric world to the adult world. The CF clinic provides several services in a team-centered approach. Respiratory therapists may work with the patient to determine what types of therapy they are doing at home, what is working and what is not, assess their respiratory health status, and provide information/answer any questions they may have about their disease. CF patients are given pulmonary function testing every six months or after a treatment regimen is changed. Sometimes it may be that the CF patient shows up to the clinic having an exacerbation and can be quickly assessed, treated, and possibly admitted to the hospital.

### Lung transplants

A lung transplant is a surgical process in which the unhealthy or diseased lungs are removed and replaced with healthy donor lungs. Receiving a lung transplant can take years upon years to receive as there are more people needing replacement lungs than there are lungs to give [23]. With that being said there is a very long waiting list to be placed on in order to obtain a chance at receiving a lung transplant. Doctors may discuss a lung transplant with CF patients well before they are in need due to the extensive wait. According to the CF Foundation only patients who are expected to thrive after a lung transplant are kept on the waiting list [23]. Once a person demonstrates signs they may not survive the surgical procedure or that they can no longer properly provide quality care for themselves, are removed from the waiting list. Lung transplant patients are chosen by the urgency in which the person needs the lungs and can be evaluated by the lung allocation score. The lung allocation score is done by taking the person's age, body mass index, and results from medical tests and giving the person a number between zero and one hundred. The higher the score the more in need the person is to receive a lung transplant [23].

Before a CF patient has a lung transplant they should first look at the risks versus the benefits. Every person is different and no lung transplant is the same. When performing a lung transplant there are several things to consider, such as blood type, lung size, age, and gender. Once these things are taken into consideration then the transplant recipient can be matched. The benefits of a lung transplant may weigh heavier for some. Treatment regimens should continue as if the lungs still had CF. According to the Cystic Fibrosis Foundation 80 percent of people with CF who get a lung transplant are still living after one year, and 50 percent are still living after five years. Many people have reported to the Cystic Fibrosis Foundation they are able to breathe better, while others are able to go on to more extreme physical activity. Just like with any other surgical procedure there are risks associated with lung transplants. The risks of lung transplantation include but are not limited to: lung rejection, infections, increased airway problems, cancer, continued cystic fibrosis complications, increased risk for acquiring diabetes, kidney disease, and osteoporosis [23].

### Conclusion

Cystic fibrosis is a very complicated disease. Understanding the condition, how to treat it, where to go for help, knowing the options that are available, and helping find new advancements may allow for a better life for these patients. Although treatments can be time-consuming it is important to encourage CF patients to continue to take their nebulizers, perform airway clearance, attend doctor appointments and clinics, and help them weigh their options with lung transplantation. The future of CF could be very bright with continued studies on gene replacement therapy [24] and advancements in medication regimens.

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### Conflict of Interest

No conflict of interest is present for either co-author.

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