

Cystic Fibrosis: An Evaluation of Current Treatment Methods and Avenues for Future
Treatments

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Cystic Fibrosis: An Evaluation of Current Treatment Methods and Avenues for Future Treatments

Researchers have been working for decades to find a cure for the genetic disease cystic fibrosis (CF), and every year, new developments are taking them one step closer to finding the solution, the cure. Patients with the disease have a life expectancy of approximately thirty-seven years, which is a significant improvement from the initial recognition of the disease, at which time patients used to die almost immediately after diagnosis (Cohen-Cymerknoh, Shoseyov, & Kerem, 2011). With all of the research that has been done over the years, many treatments have evolved, making individual treatment plans as unique as the patients who relies on them for their lives. The National Institute of Allergy and Infectious Diseases (NIAID) commissioned this report for the purpose of evaluating current treatments and analyzing how effective these treatments are at treating the symptoms of CF. The NIAID also requested that the report contain information on research that proves how experimental treatments are performing in clinical trials in relation to the current treatments. Specifically focusing on whether these future treatments are going to be a feasible option, and whether there will be an increase in the level of efficacy shown in the most ideal circumstances; that is, in clinical trials.

In order to determine the effectiveness of current treatments, a decision matrix was created so that each treatment could be evaluated objectively and precisely. A separate matrix was developed for experimental treatments and the criteria were altered slightly to account for those treatments not yet being on the market. With each criterion given a certain weight, different treatments stood out in the sense that they only treated one symptom of the disease, proving that a combination of treatments would be necessary in order to effectively treat a patient. The treatment plans that are implemented today are created to treat the symptoms. For

example, a bacterial infection is treated with antibiotics, a build-up of mucus is treated with mucus clearers, and nutritional deficiency is treated with stool softeners, where one treatment lacks, another accounts for it. Many experimental treatments involve curing the disease at its source. All of these criteria were taken into account when deciding which treatment could be the most feasible for the future. Each treatment was scrutinized in how well it dealt with the most common characteristics of CF; then compared with other treatments. Unfortunately, there is not a simple answer to treating cystic fibrosis, but it is apparent that the treatments that are currently being used are providing a sufficient base for experimental treatments to build upon in the future.

Background

Cystic fibrosis is the most common lethal inherited disease in Caucasian population. At present, there are 70,000 cases worldwide, and at least 30,000 are Americans. Every year, about 1000 new cystic fibrosis cases are diagnosed in the US (Narasimhan & Cohen, 2011). Moreover, around one in twenty-five Caucasians are carriers of the defective recessive gene. In the 1940s, the life expectancy for people infected with CF was less than a year (Figure 1). However, due to a better understanding of the disease and more focused treatments, the life expectancy has significantly improved. Patients today can expect to live to their late 30s and up to their 60s, with the average life expectancy being thirty seven years (O'Sullivan & Freedman, 2009).

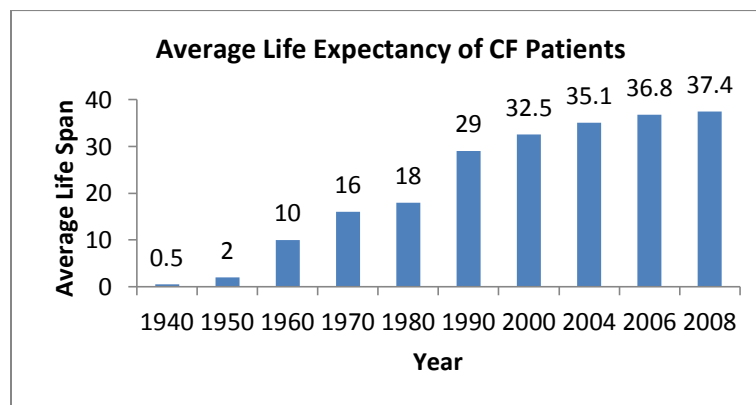


Figure 1: Average Life Expectancy of Patients with Cystic Fibrosis (Lobo, Rojas-Balcazar, & Noone, 2012)

The disease results from mutations in the cystic fibrosis transmembrane conductance regulator gene. These mutations are divided into six classes, among which Class I, II and III are of high morbidity and mortality. Though there are more than 1900 different mutations found, the most common mutation is the phe508del mutation, a class II and III mutation, which makes up approximately 86% of the cystic fibrosis population. This particular mutation is caused by the deletion of the phenylalanine amino acid at the position 508 of the encoded protein. The second most common mutation is the Gly551Asp mutation, a class III mutation, which approximately 5% of the CF population possesses (Thursfield & Davies, 2012). The individual classes are explained in Table 1, and shown in Figure 2.

CFTR gene mutation class	CFTR protein basic defect
I	Non-sense mutations: A premature termination codon leads to truncated protein with no function [eg. Trp1282X previously termed W1282X]
II	Trafficking mutations: Misfolded protein fails to traffic to the apical cell surface and instead is degraded by intracellular processes [eg. Phe508del, previously termed ΔF508]
III	Gating defect: Protein reaches the apical cell membrane in normal levels, but fails to open in response to intracellular signals [eg. Gly551Asp previously termed G551D]
IV	Decreased conductivity: Protein reaches the cell surface but the abnormal conformation of the pore leads to poor conductance of chloride ions [eg. Arg117His previously termed R117H]
V	Splicing defect: leads to decreased amount of CFTR protein at the cell surface [eg 3849+10 kb C>T]
VI	Functional but unstable with decreased half life at the cell surface [eg Gln1412X previously termed Q1412X]

Table 1: Classes of CFTR mutations (Thursfield & Davies, 2012)

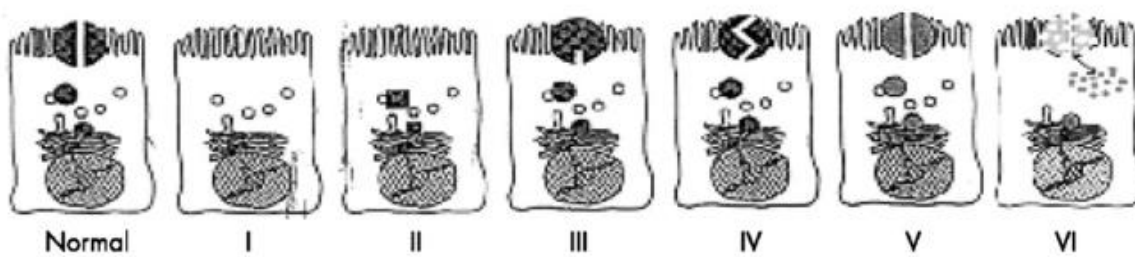


Figure 2: Classes of CFTR mutations (Thursfield & Davies, 2012)

The gene defect generates the abnormal protein product that causes a malfunction in the transportation of chloride ions into and out of epithelial cells, affecting multiple organ systems.

Specifically, the mutated gene leads to unusually thick and sticky mucus that cannot be evacuated easily. The mucus mainly interferes with respiratory, digestive, endocrine, and genital systems (Warwick & Elston, 2011).

The loss of proper chloride ion transport prevents water from properly passing into the airways connected to the lungs. This in turn causes a thinning of the airway surface liquid (ASL). The thinned ASL prevents the cilia of the airways from being able to remove mucus from the airways. This mucus, which is designed to catch and trap bacteria, then becomes infected with bacteria, most commonly with *Pseudomonas aeruginosa*, providing ideal growing conditions for the bacteria. The infection leads to an immune response, which causes inflammation in the tissue surrounding the infection. Because of the inability of the mucus to be cleared, this inflammatory response lasts too long. The long term inflammation causes permanent damage to the inflamed tissue. This damage to the tissue allows for future infections to develop more easily (Cantón & del Campo, 2010).

The repeated infections gradually reduce the lung function and destroy the lung. The final failure of lung function causes most deaths of cystic fibrosis today (Hoiby, 2011). Meanwhile, mucus also blocks the pancreatic duct, which is the path for enzymes to enter the digestive tract. This results in the poor digestion of fatty acid and protein, which leads to malnutrition. Moreover, insulin secretion from the pancreas is also influenced, thus about one in five cystic fibrosis patients have CF related diabetes (Krysa & Steger, 2007). The mucus also affects the genital ducts, therefore most male patients are infertile and female patients are of lower chance of pregnancy (Chan et al., 2009).

Treatments

Current Treatments

Treatments for the pancreas.

Pancreatic enzymes.

Within the digestive system, and specifically the pancreas, CF causes more viscous than normal secretions. More than 90% of infants with CF lose all exocrine pancreatic function and experience a lifetime of pancreatic insufficiency (Flume & Van Devanter, 2012). The pancreas is normally responsible for producing digestive enzymes that break down food and aid in its absorption. In cystic fibrosis the ducts which release these chemicals often become partially or completely blocked. This may result in impaired ability of patients to absorb nutrients such as fat-soluble vitamins A, D, E, and K. It is recommended that the presence of these vitamins be measured at the time of diagnosis and regularly monitored (Rustemovic et al., 2012).

In order to aid in proper digestion, cystic fibrosis patients are routinely prescribed pancreatic enzyme replacement therapy which provide these vital chemicals artificially. The necessity of this therapy can only be determined by examining symptoms, as no test exists which reveals the pancreatic exocrine output. Common symptoms include meteorism, diarrhea, steatorrhea, and weight loss. All pancreatin preparations must be enterically coated, so that they are not destroyed by gastric acid, mix well with gastric chyme, exit the stomach simultaneously with chyme, and release rapidly upon entering the duodenum. There have been no major, randomized comparative studies of various pancreatin preparations. The clinical preference is currently for enterically coated micropellets or minitablets with a diameter of two millimeters or less. Initial dosage is usually twenty thousand to forty thousand units of lipase taken once or twice per meal with some dose adjustment afterward (Mossner & Keim, 2010). As of April 2012,

the Food and Drug Administration has approved five artificial pancreatic enzyme products that meet the regulatory standards for quality, safety, and effectiveness. These are Creon, Zenpep, Pancreaze, Ultresa, and Viokace. Pancrecarb is another supplement set to enter the market shortly depending on FDA approval (Nakajima, Oshida, Muneyuki, & Kakei, 2012). Side effects include abdominal pain and nausea, but combined with a healthy, nutritious diet, pancreatic enzyme replacement therapy should satisfactorily eliminate the threat of malnutrition to most patients (Kalnins & Wilschanski, 2012).

Treatments for the bowel.

Stool softener.

With the mucus blocking the way for pancreatic enzymes to enter the digestive tracts, cystic fibrosis patients will always encounter problems with digestion and excretion (Littlewood, Wolfe, & Conway, 2006). In order to keep stool from blocking the bowel and causing abdominal pain, stool softeners are used as an assisting treatment for cystic fibrosis patients. Stool softeners are generally over the counter medications. Most stool softeners are taken orally, which means it is an easy treatment to administer. Minor side effects include stomach or intestinal cramps, stomach pain, nausea, throat irritation, vomiting, but serious side effects rarely occur. Stool softeners can greatly help improve patients' quality of life (Tariq, 2007).

Vitamins.

Another easy to administer treatment is vitamin supplement therapy. Because people suffering from cystic fibrosis are prone to infection due to the buildup of mucus, Vitamin A is extremely important for a patient to consume. Vitamin A helps strengthen the immune system, allowing it to fight infection more effectively ("The Importance of Vitamins and Minerals in CF," 2012). Because Vitamin A helps the immune system fight infection, it increases overall

lung function (Carr, 2000). Vitamin E is important for patients because it helps to maintain the health of the gastrointestinal tract. Vitamin E is also important because, like Vitamin A, it aids in fighting infection ("The Importance of Vitamins and Minerals in CF," 2012). Thirty-eight percent of infants with CF have low vitamin E, and thirty-five percent of infants with CF already have low vitamin D levels (Carr, 2000). Vitamin D strengthens bones, which is especially important for cystic fibrosis patients as bone problems are a symptom of this disease ("The Importance of Vitamins and Minerals in CF," 2012).

Diet.

Another treatment option for cystic fibrosis patients is maintaining a good diet. Because the mucus in the digestive tract negatively affects the absorption of nutrients, in most cases people with cystic fibrosis need to consume twenty to fifty percent more calories than the average person (McKenna, 2006). Studies have shown that in cystic fibrosis patients, a higher body weight generally means better lung function. A healthy diet also helps to develop and maintain a stronger immune system, which allows infections to be more easily fought off (McKenna, 2006).

Feeding Tubes.

Feeding tubes are another treatment option to help cystic fibrosis patients maintain nutritional health. For patients who have trouble gaining weight despite their current daytime eating habits, doctors will generally recommend nocturnal feedings of a calorie rich formula via a gastrostomy tube or nasogastrostomy tube. A nasogastrostomy tube is inserted through the nose until it enters the stomach, while a gastrostomy tube is surgically inserted into the stomach with the adaptor valve always present on the outer abdomen. In either case, the tube is then hooked up to a formula bag on an IV pole and an enteral pump which continuously releases small amounts

of nutrient paste into the patient's stomach throughout the night. This treatment supplements a patient's diet with an additional 1500 to 2000 kcal while the patient sleeps (Steinkamp & von der Hardt, 1994).

Studies show this supplemental treatment dramatically improves the nutritional status of malnourished patients. After 36 months of gastrostomy tube-feeding, the mean weight percentile for patients generally shows an increase from 2% to 19% for their age group (Rosenfeld, Casey, Pepe, & Ramsey, 1999). This weight gain also leads to an increase in energy for patients, as well as an improvement in lung function without any major side effects (Steinkamp & von der Hardt, 1994).

Bowel Surgery.

Static mucus causes bacteria to overgrow in the bowel, causing blockage. For about 10% of newborns with cystic fibrosis, this symptom occurs and surgery is often needed to remove the blockage. Another common case is the intussusception, where a section of bowel has folded in on itself. Different levels of surgical repair are needed to fix this problem. Both cases are accompanied with abdominal pain (de Becdelievre et al., 2011). If not treated in a timely manner, these bowel problems can greatly influence the quality of life of patients, and even threaten their lives. The cost of a bowel surgery is greater than \$4000, not including the cost of recovery and further medical care. The risk of the surgery is relatively high when compared to other non-surgical treatments. However, not all patients require bowel surgery, only those with a blockage or intussusception of the bowel (Masoomi et al., 2012).

Treatments for lungs.***Mechanical clearers.***

Mechanical clearing is an effective, yet short term way for patients to clear the mucus out of the lungs. Mechanical clearing, also known as chest physical therapy, loosens the mucus in the lungs and makes it easier for the patient to expel (Staff, 2012). There are many different devices which are designed to help loosen the mucus, but the basic function is to vibrate the chest in some fashion to relax the mucus in the lungs so it can be expelled more easily (Perry, 2011).

There are two main techniques involved in mechanical clearing. The first procedure is chest percussion, which is the physical beating on a person's chest to loosen pulmonary secretions. The percussion should be done over the wall of the chest in which the area needs to be cleared of mucus. Each area is usually percussed up to one minute, and the procedure should be performed several times a day. Vibration, the second technique, is essentially the same premise as chest percussion, except vibrations are performed by a mechanical device for a similar effect. After five minutes of treatment, the patient will cough to expel the dislodged mucus (Perry, 2011).

Antibiotics.

Antibiotics are taken to kill or slow the growth of bacteria. Even though antibiotics have been available for decades, there have been issues with finding a solution to antibiotic resistance (Hoiby, 2011). Antibiotics that are taken for suppressing the bacteria in the lungs are usually inhaled. There are local side effects when taking a drug through a nebulizer, such as inflammation, allergy, and coughing (Hoiby, 2011). When taken with a nebulizer, local concentrations of the antibiotic can be controlled (Touw, Brimicombe, Hodson, Heijerman, &

Bakker, 1995). The size of the droplets can be controlled, which is important for regulating the location of the droplets in the lungs (Hoiby, 2011).

Taking antibiotics not only helps clear the bacteria, but it also indirectly treats other symptoms of cystic fibrosis. A decrease in the amount of bacteria in the lungs will result in less inflammation, which would make it easier for a patient to breath. Infection and inflammation are the greatest causes of mortality for patients with cystic fibrosis, so treating the bacteria increases life expectancy. Patients who regularly take antibiotics have improved lung function and spend fewer days in the hospital (Hoiby, 2011).

Lung transplant.

In the past five years, about 150 to 200 cystic fibrosis patients have received lung transplants per year. Like all organ transplants, this is overseen by the United Network of Organ Sharing (UNOS). Prior to 2005, patients received lung donations based solely on time spent on the waitlist. In the spring of 2005, UNOS began of policy of periodic patient evaluations to determine need and began redistributing organs based on this. Need is based on disease diagnosis, lung function, health factors such as diabetes, the use of oxygen or a ventilator, and other factors. Evaluations are carried out every six months. Those desiring a transplant must live within a few hours of a transplant center so that they can arrive at the transplant center as soon as a pair of lungs becomes available ("Lung Transplantation," 2012).

All CF patients must receive a bilateral lung transplant due to the likelihood of infections transferring from one lung to the other. At one time it was necessary to transplant the heart as well as the lungs, but this is no longer necessary. Hospitalization time following the surgery can vary from days to months depending on the patient's recovery. As the new lungs do not have CF, they will function normally in this regard. However, the patient must take prescribed

immunosuppressant drugs for the rest of his or her life, so that the body does not reject the new organs. As this can interfere with the body's ability to fight infections in the upper respiratory tract which will still occur due to CF ("Lung Transplantation," 2012).

In 2008, the Health Resource and Services Administration provided the statistics, shown in Table 1, regarding patient survival rates following a lung transplant.

3 Months	1 Year	3 Years	5 Years	10 Years
92.3%	83.3%	66.2%	54.4%	28.6%

Table 2: Survival rates after lung transplant ("Unadjusted Graft and Patient Survival ", 2009)

Inhaled mucus clearers.

While antibiotics alone may seem at first the most effective means of preventing, eradicating, and controlling bacterial infections in cystic fibrosis patients, they are most effective in combination with mucus clearers. Mucolytic drugs and hypertonic saline solutions seek to further control infection by easing the removal process of mucus that has resulted from infection. Clearing the airways of viscous mucus improves quality of lung function and reduces the risk of exacerbated infection and inflammation all in a cost efficient, easy-to-treat manner that is considered to be relatively safe and can be applied to a majority of the cystic fibrosis population (Ramsey et al., 1999).

In comparison with other costly treatments, inhaled mucus clearers are non-invasive and inexpensive. The treatment is also one of the most recommended by clinicians following the diagnosis of cystic fibrosis. As no cure yet exists, the comfort of the patient takes priority upon diagnosis and mucus clearers work to remove excess mucus and improve breathing quality. Given that 70% of patients with cystic fibrosis die of lung infection, this treatment, especially in

combination with antibiotics is effective in preventing the bacterial infection, eradicating already existing infection, and controlling exacerbated infections (Cantón & del Campo, 2010).

Nasal polyp remover.

Cystic fibrosis patients can undergo endoscopic sinus surgery to help relieve some of the symptoms that are associated with CF. The increase in inflammation in the nasal passages can cause polyps to form in the nasal lining. Polyps are small, sac-like, inflamed areas of the nasal tissues. Between thirty-five and fifty percent of CF patients world-wide are infected with these nasal polyps (Rickert S, 2010). Side effects of these polyps include nasal blockage, sinus infections, and loss of sense of smell ("Cystic Fibrosis: Nasal Polyps ", 2012). In order to remove these polyps, patients are undergoing endoscopic sinus surgery. Patients are also being recommended to have the surgery to decrease the density of bacterial colonization in their nasal passages (Rickert S, 2010).

In many cases, the polyps are too large to be treated with medication, so surgery becomes the next viable treatment. The surgery consists of a doctor inserting an endoscope, a thin camera rod with a light at the end to provide a magnified view of the nasal passages, into the nostrils. The surgeon will then remove the polyps and any other obstructions in the nasal passages. Most patients are able to go home the same day as the surgery, with the risk of side effects being minimal: bleeding, poor sense of smell, and infections (Flume & Van Devanter, 2012). Doctors agree that the procedure is safe and effective at treating the nasal polyps. Patients with severe polyposis are more likely to need revision surgery than patients with less chronic cases (Rickert S, 2010). Patients with CF are also reporting less hospital day in the six months after surgery. Studies have shown that sinus surgery to remove polyps has little effect on lung function and the ability for patients to gain weight (Rosbe, Jones, Rahbar, Lahiri, & Auerbach, 2001).

Oxygen therapy.

Scarring of the lungs frequently plagues individuals with cystic fibrosis and inhibits breathing ability. Oxygen therapy is a commonly utilized method of treatment for cystic fibrosis that involves providing extra oxygen to the lungs through the use of an oxygen tank. The oxygen can be delivered through a nasal cannula, which consists of two small prongs that fit in the nose, a face mask that fits over the face and mouth, or through trans-tracheal oxygen therapy, involving a small tube feeding into an incision in the neck. In comparison to most treatments, oxygen therapy is relatively inexpensive, tank price ranging from about \$50 to \$100 (Munhoz et al., 2011). Several studies have suggested that oxygen therapy primarily targets and improves pulmonary and lung function. Oxygen therapy, while useful, should be used in combination with many other forms of treatment for cystic fibrosis, seeing as it does little to affect the overall symptoms of the disease (Galli et al., 2012). Research suggests that oxygen therapy is a safe form of treatment for cystic fibrosis, however, patients should keep the oxygen tanks away from open flame because the oxygen rich mixtures are more flammable than atmospheric air (George et al., 2011).

Treatments for the entire body.***Exercise.***

Exercise can also reduce the symptoms that cystic fibrosis causes. Exercise increases lung function as well as the ability to fight lung infections for the majority of patients. Healthier lung function allows patients to live a more normal everyday life. It is not healthy for all patients to participate in exercise depending on the extent of their symptoms. For example, it is not recommended for cystic fibrosis patients with cor pulmonale, pulmonary hypertension, an

exacerbation, or a respiratory infection to partake in physical activity. All patients should be tested by a doctor to establish if it is healthy to work out. More chloride and sodium is lost in the sweat of a cystic fibrosis patient, versus a person without this disease, so the people that suffer from cystic fibrosis need to drink more fluids that replace these electrolytes when working out (Cerny, 2009).

Anti-inflammatory.

Chronic bacterial infection in cystic fibrosis leads to a vicious cycle of infection, inflammation, and airway blockage. In order to prevent damage to lung tissues due to chronic inflammation, anti-inflammatory drugs are often administered. As in most cases of inflammation, ibuprofen is often the first drug to be prescribed to treat the symptoms of cystic fibrosis patients. As an over the counter drug, ibuprofen is very effective in treating inflammation without any major side effects, even in high doses (Fennell et al., 2007).

In cases of severe inflammation or inflammation which causes airway blockage, corticosteroids are prescribed. Corticosteroids are extremely effective in reducing inflammation in the lungs and are somewhat effective in clearing mucus to make it easier for the patient to breathe. Corticosteroids can be administered as either a pill or an inhalant. Side effects of extended use of oral steroids include osteoporosis, high blood pressure, bruising, cataracts, growth delay, and glucose metabolism complications. Side effects of inhalable corticosteroids include sore throat, coughing and spasms of the large airways, fungal infections in the mouth, delayed growth in children, osteoporosis, cataracts, and glaucoma (Heijerman, Westerman, Conway, & Touw, 2009). However, these side effects tend to only occur when an incorrect dosage is taken. Inhalable steroids are more commonly prescribed for patients requiring extended steroid treatment, as the side effects of the drug are more tolerable and less frequent.

Potentiator.

The current forefront of cystic fibrosis treatment is small molecule drugs. Two types of small molecule chemicals which are used to treat cystic fibrosis are potentiators and correctors. Potentiators help to promote proper activity of the CFTR protein in proteins which are at the cell wall, but exhibit a class III defect (Cuthbert, 2011).

Among potentiators, the most clinically successful is VX-770, which has been developed into an orally delivered drug known as Kalydeco (generic: Ivacaftor), which is produced and sold by Vertex Pharmaceuticals for \$294,000 per year, for a bi-daily pill. In a large scale phase III clinical trial which lasted for 48 weeks, VX-770 led to a 17% improvement past the baseline in lung function. Negative side effects were less prevalent in the treatment group than in the control group. There were however some side effects unique to the treatment group; these included rash, headache, URTI, and nasal congestion. Kalydeco is very nearly a complete treatment for patients who have only class III defect in their CFTR protein, as it deals with the protein itself rather than symptoms of the protein's defect (Thursfield & Davies, 2012).

Experimental treatments**Treatments for the lungs.*****ENaC inhibitor.***

Due to the mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, the protein product which works as the most important chloride channel in exocrine epithelia loses its function and results in abnormal chloride transportation. The chloride ions and sodium ions are two of the important ions involved in the balance of water in human bodies. When the protein loses its function, the balance of the salt and water is interrupted and the

body's secretions become dehydrated; which causes sticky mucus in the airway and ducts (Cantón & del Campo, 2010).

The defect of the chloride channel is the root of all the symptoms of the disease. The abnormal chloride transportation influences the sodium transportation and causes the imbalance of salt and water. An ENaC inhibitor, the epithelial Na(+) channel inhibitor, provides a solution from another side of the problem. It controls the level of sodium ions to influence the chloride ion. ENaC inhibitors work to inhibit the epithelial Na(+) channel, thus reducing the Cl(-) absorption. As the level of sodium chloride decreases, less water is reabsorbed by the body, thinning the mucus to allow it to be cleared more easily (Di Grande et al., 2010).

There are several kinds of existing ENaC inhibitors and their generic versions in the market, such as Amiloride and Triamterene, costing about one to three dollars per day. The medicine deals with reducing mucus, which helps improve many symptoms of the disease such as bacteria growth, infection, and pancreatic defect. It is effective in every patient. Side effects include increased urination, high potassium, and low sodium, as the drug interferes the normal salt transportation in the body ("ENaC Inhibitors (Epithelial sodium channel inhibitors)," 2012).

Cl⁻ promoter via Ca⁺/Cl⁻ transport system.

Another treatment for CF is to bypass the CFTR protein altogether and use alternative chloride transport pathways. One such compound is Denufosal Tetrasodium which causes a Ca⁺/Cl⁻ pump to be more active than normal, thereby compensating for the lack of activity by the CFTR protein, this leads to a rehydration of the ASL due to proper Na⁺/Cl⁻ balances in the epithelia of the airways and an increase in cilia beat frequency. These combined help to clear mucus from the airways. There are however problems with the delivery of the drug, namely the effects are very short lived (Accurso et al., 2011).

In theory this treatment would be applicable to all cystic fibrosis patients. A phase III trial was conducted over 24 weeks, with 352 participants. All participants had normal to mildly impaired lung function (prior tests have shown this treatment to be less effective for cases where lungs are severely damaged). The trial used FEV as a measure of success. The placebo group improved by .003L, and the treatment group improved by .048L. The final findings of the trial were that lung function increased as measured by FEV, but that there were no other measurable changes (Accurso et al., 2011).

Treatments for the entire body.

Corrector.

Correctors are another type of small molecule drug (along with potentiators). Correctors help class II defective CFTR proteins get to the cell membrane. Among correctors, the most clinically successful is VX-809, which, in vitro, showed improvements in chloride transport to 14 % of non-cystic fibrosis levels. And which, in a four week phase II study containing 89 patients, showed a 7mmol/L reduction in sweat chloride, which was a statistically significant amount. The trial did not however show a clinical improvement. The main problem with correctors is that most mutated proteins, which are incapable of making it to the cell membrane, are also incapable of operating once they reach the cell membrane. This means that while a corrector may do its job, getting the protein to the cell membrane, the protein will still be incapable of functioning once it reaches the membrane (Thursfield & Davies, 2012).

Gene Therapy.

In addition to current treatments, scientists have been working for years and still currently are working on new potential treatments and cures for cystic fibrosis. When the gene causing cystic fibrosis was first discovered and cloned, scientist had a large amount of optimism that this

finding would allow scientist to cure this disease using the cloned gene(Griesenbach, 2011). However, this confidence has faded throughout the years, as the cure of cystic fibrosis through gene therapy has proven to be more complex than originally anticipated. Although small groups are still working on other future treatments, the number of scientists still developing gene therapies has significantly dropped in more recent years. One of the reasons that gene therapy has not been completely successful is that scientists are having difficulty discovering the best system to transport the normal cystic fibrosis transmembrane conductance regulator gene, the gene that was found to cause cystic fibrosis. Scientists need to determine the duration and frequency gene therapy should be applied in order to be an effective cure to cystic fibrosis. Establishing the life span of the lung cells affected by the gene is another problem scientists are encountering (Griesenbach, 2011). This is a good potential treatment because if these problems are solved and gene therapy is operational, then gene therapy will attack the disease at the source of the problem and present a cure. Unlike current treatments gene therapy will not only alleviate some of the symptoms but it will end the disease in general.

Potentiator/corrector .

For the approximately 85% of cystic fibrosis patients that have the phe508del mutation, a class II mutation with class III characteristics, neither a corrector nor a potentiator alone can effectively treat the cystic fibrosis (Cantón & del Campo, 2010; Thursfield & Davies, 2012). A combination therapy of both drugs can, however. In a phase II trial sponsored by Vertex Pharmaceuticals, Kalydeco and VX-809 were administered as a dual therapy to patients who possessed the phe508del mutation. By day 21 of the trial, this led to a decrease in sweat chloride levels of 13 mmol/L, which was measured alongside a 6.1% increase in lung function from the start of the trial and an 8.6% increase in lung function when compared to the control group.

Larger scale trials are scheduled to begin in 2013. This treatment could effectively treat approximately 85% of patients with cystic fibrosis, and because the treatments treat the CFTR protein itself the treatment would be a complete treatment for that population of cystic fibrosis patients ("Final Data from Phase 2 Combination Study of VX-809 and KALYDECO™ (ivacaftor) Showed Statistically Significant Improvements in Lung Function in People with Cystic Fibrosis Who Have Two Copies of the F508del Mutation," 2012; Thursfield & Davies, 2012). As Kalydeco alone is \$294,000 per year for treatment, the dual therapy would likely be very expensive.

Framework

Decision Matrix

A decision matrix was used to determine which current treatments are most effective and which future treatments hold the most promise. The completed matrix for the current treatments can be found in Table 10 and the completed matrix for future treatments can be found in Table 11. The matrices take a series of weighted criteria and rankings for each treatment, multiply them together (product shown in grey) and add up all of the products for each treatment. The individual rankings for each treatments for each criteria is assigned a color based on how ideal the treatment is within the scope of that criteria (red is equal to 0 on a gradient to 5 being equal to dark green). The final scores are for each treatment are colored in a similar fashion. This coloring is designed to aid in identification of the holes present in treatments and to allow easy visual comparison.

The criteria for current treatments are weighted in such a fashion as to focus on the problem of determining the most effective treatment. As such the criteria of 'improvement in life expectancy' and 'improvement in quality of life' are weighted the highest.

The criteria for experimental treatments are similarly weighted to those of current treatments, but with the omission of the cost criteria, as experimental treatments do not have a well-defined cost to administer, and the addition of a ‘difficulty to achieve governmental approval’ and a ‘time to bring to market’ criteria, as these are factors that affect the feasibility of experimental treatments.

It should be noted that all ratings are done on a scale of 0-5, with 5 being most ideal. More specifically cost ratings are shown in Table 3. It should be noted that for treatments which appear as a one time (ex: surgery) cost, the treatment’s cost is taken over the period of its effect, along with secondary costs (additional doctors’ visits, long term medication, etc...). The rating scale for improvement in life expectancy, improvement in quality of life, effectiveness at clearing mucus, effectiveness at helping nutrient absorption, effectiveness at bacteria removal, and effectiveness at reducing inflammation is shown in Table 4. The ratings for affected population, ease of treatment, and side effects/risk factors, can be found in Table 5, Table 6, and Table 7 respectively. For experimental treatments difficulty to achieve governmental approval and time to bring to market were included in the overall scoring of treatments, the ratings for these can be found in Table 8 and Table 9.

Rating	Cost (\$ annually)
0	100,001+
1	80,001-100,000
2	60,001-80,000
3	40,001-60,000
4	20,001-40,000
5	0-20,000

Table 3: Cost ratings

Rating	Improvement in life expectancy, improvement in quality of life, effectiveness at clearing mucus, effectiveness at helping nutrient absorption, effectiveness at bacteria removal, effectiveness at reducing inflammation
0	No improvement
1	Very small improvement
3	Some improvement
5	Significant improvement

Table 4: Improvement in life expectancy, improvement in quality of life, effectiveness at clearing mucus, effectiveness at helping nutrient absorption, effectiveness at bacteria removal, effectiveness at reducing inflammation ratings

Rating	Affected population (%)
0	0
1	1-20
2	21-40
3	41-60
4	61-80
5	81-100

Table 5: Affected population ratings

Rating	Ease of treatment
0	A treatment with similar difficulty to a major invasive surgery
1	A treatment with similar difficulty to perform as an outpatient surgery
3	A treatment which requires some additional equipment to perform
5	Pill or similarly simple to administer treatment

Table 6: Ease of treatment ratings

Rating	Side effects/risk factors
0	A treatment which carries a significant chance of death
1	High risk treatment
3	Moderate risk treatment
5	Very safe/low risk treatment

Table 7: Side effects/risk factors

Rating	Difficulty to achieve governmental approval
0	No chance of receiving governmental approval
1	Possible but not likely
3	Moderately easy
5	Very easy

Table 8: Difficulty to achieve governmental approval

Rating	Time to bring to market
0	A treatment which is not likely to ever make it to market
1	A treatment which could make it to the market
3	A treatment which is likely to make it to the market
5	A treatment which is nearly on the market

Table 9: Time to bring to market

The rankings for each criterion, for each individual treatment are based on the data presented elsewhere in this paper. The well-defined rating system allows for a consistent and clear method of rating without the necessity of explicitly explaining each rating.

The results of the matrix calculations lead to the conclusion that for current treatments there is no single treatment which can by itself effectively manage all of symptoms associated with cystic fibrosis. The color coding of results allows easy visibility of the holes of different treatments. The highest ranked treatment, the potentiator, with a score of 4.7 out of 5, has major holes in cost and the affected population categories. While it is a near fix all for 5% of the cystic fibrosis population, it is not a final solution for all patients. The other high ranking treatments are pancreatic enzymes (3.28), antibiotics (3.34), inhaled mucus clearers (3.69), nasal polyp removal (3.44), and ENaC inhibitors (3.5). However, looking at the complete matrix, it can be easily seen that none of them is a complete solution. As such, any complete therapy must include multiple individual components. An ideal therapy fills the holes of one treatment with the additional treatments which it adds on. For example, if antibiotics, inhaled mucus clearers, and pancreatic enzymes are overlaid then visually the result would be green across most of the matrix,

indicating that those three treatments would together create a valuable combined treatment, and in fact this is the core of the most common treatment. Although some treatments received low overall scores, they should not necessarily be discredited. The matrix allows for easy recognition of the strengths and weaknesses of the treatments which it shows. For example, vitamins score poorly and only somewhat help with nutrition; however their level of safety and low cost makes them viable even with the small improvement which they effect in the patient.

For experimental treatments, the potentiator/corrector combination therapy scores the highest with 4.7 out of 5. This is because it targets the CFTR protein and repairs the defect in the majority of patients to a high enough degree to allow near normal functioning of the patients' bodily functions, leading to very high rankings across the matrix.

Completed Matrix for Current Treatments

	cost	improvement in life expectancy	improvement in quality of life	ease of treatment	side effects/Risk factors	affected population	effectiveness at clearing mucus	effectiveness at nutrient absorption	effectiveness at bacteria removal	effectiveness at reducing inflammation	1.00
WEIGHT:	0.02	0.26	0.20	0.05	0.10	0.05	0.08	0.08	0.08	0.08	1.00
pancreatic enzymes	5.00	3.00	5.00	5.00	5.00	5.00	0.00	5.00	0.00	0.00	3.28
feeding tubes	4.00	1.00	3.00	1.00	3.00	3.00	0.00	3.00	0.00	0.00	1.84
bowel surgery	4.00	3.00	5.00	0.00	1.00	1.00	0.00	5.00	0.00	0.00	2.41
stool softner	5.00	0.78	3.00	5.00	5.00	2.00	0.00	0.40	0.00	0.00	1.63
vitamins	5.00	1.00	1.00	3.00	5.00	5.00	0.00	1.00	0.00	0.00	1.64
diet	5.00	0.26	0.20	0.25	0.50	0.25	0.00	0.08	0.00	0.00	1.84
exercise	5.00	1.00	1.00	1.00	3.00	4.00	1.00	1.00	1.00	0.00	1.27
mechanical clearing	5.00	1.00	3.00	3.00	5.00	5.00	5.00	5.00	5.00	1.00	2.74
antibiotics	4.00	3.00	5.00	5.00	3.00	3.00	0.00	1.00	5.00	3.00	3.38
inhaled mucus clearers	5.00	0.78	1.00	0.25	0.30	0.25	0.00	0.08	0.40	0.24	3.62
nasal polyp removal	5.00	3.00	5.00	1.00	3.00	2.00	5.00	0.00	0.40	0.24	3.37
lung transplant	0.00	5.00	5.00	0.00	0.00	1.00	3.00	0.00	3.00	3.00	3.07
oxygen therapy	5.00	3.00	3.00	3.00	5.00	4.00	0.00	0.00	0.00	1.00	2.41
anti inflammatory	5.00	3.00	3.00	5.00	3.00	5.00	1.00	0.00	1.00	5.00	2.84
enac inhibitor	5.00	3.00	3.00	5.00	5.00	5.00	5.00	1.00	3.00	3.00	3.44
potentiator	0.00	5.00	5.00	5.00	5.00	1.00	5.00	5.00	5.00	5.00	4.70

Table 10: Decision Matrix for current treatments

Completed Matrix for Experimental Treatments

	expected improvement in life expectancy	improvement in quality of life	side effects	affected population	efficacy of clearing mucus	efficacy of helping nutrient absorption	efficacy of bacteria removal	efficacy of reducing inflammation	difficulty to achieve Governmental approval	time to bring to market	1.00
WEIGHT:	0.26	0.21	0.10	0.05	0.07	0.07	0.07	0.07	0.05	0.05	
potentiator/corrector	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	3.00	3.00	4.80
gene therapy	1.30	1.05	0.50	0.25	0.35	0.35	0.35	0.35	0.15	0.15	4.30
Cl- promoter via Ca+/Cl- transport systems	5.00	5.00	3.00	5.00	5.00	5.00	5.00	5.00	0.00	0.00	3.10
Cl- promoter via Ca+/Cl- transport systems	1.30	1.05	0.30	0.25	0.35	0.35	0.35	0.35	0.00	0.00	3.10
Cl- promoter via Ca+/Cl- transport systems	3.00	3.00	3.00	5.00	3.00	3.00	3.00	3.00	3.00	3.00	3.10
Cl- promoter via Ca+/Cl- transport systems	0.78	0.63	0.30	0.25	0.21	0.21	0.21	0.21	0.15	0.15	1.00
corrector	1.00	1.00	5.00	5.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
corrector	0.26	0.21	0.50	0.25	0.07	0.07	0.07	0.07	0.05	0.05	1.00

Table 11: Decision Matrix for experimental treatments

Closer Look at Lung Treatments

Because the majority of deaths from CF today are caused by complications arising from the lungs and airways, treatments affecting this area of the body were investigated in more detail.

Antibiotics

As proven in the decision matrix, antibiotics are extremely important in the treatment plan for any patient with cystic fibrosis. Antibiotics are taken to help control and prevent the growth of bacteria in the lungs. Without any treatment that focuses on controlling the bacteria, lung deterioration is inevitable and is the main cause of death for patients with cystic fibrosis (Cantón & del Campo, 2010). Chronic lung function can be delayed if the bacteria is treated early and not given the opportunity to colonize with high density. The farther along the bacteria has colonized, the harder it is to eradicate it, eventually impossible (Fernández-Olmos et al., 2012) This is why doctors who are developing treatment plans for cystic fibrosis find it necessary to prescribe an antibiotic to treat the bacteria as early as possible. The three most common antibiotics that are prescribed today are amoxicillin, azithromycin, and tobramycin ("Cystic Fibrosis Foundation ", 2012).

Amoxicillin.

Amoxicillin is a drug that is not necessarily identified with treating cystic fibrosis, but it stops the growth of bacteria that causes pneumonia, gonorrhea, and lung infections (Cantón & del Campo, 2010). It is considered to be a penicillin-like antibiotic which makes it prone to causing allergic reactions. People with cystic fibrosis are more likely to have an allergic reaction to an antibiotic than people without the disease. These reactions are most likely going to be late reactions with a mean of 9.1 days after having taken the antibiotic. These late reactions can manifest as rashes, nausea, diarrhea, myalgia, amongst other side effects (Parmar & Nasser,

2005). For treating cystic fibrosis, this antibiotic is not the most commonly prescribed. This is due to the common allergic reactions in patients and its questionable effectiveness in treating the bacteria. Because this antibiotic is taken daily, the bacteria will eventually develop resistance to it and the antibiotic will no longer have any effect. The most common bacteria associated with cystic fibrosis, *Pseudomonas aeruginosa*, also happens to be the most common bacteria that can develop resistance to several antibiotics ("Bacteria and Antibiotic Resistance," 2012).

Azithromycin.

A more common drug used for cystic fibrosis patients is azithromycin. It was approved by the FDA in 1991 and has been prescribed by doctors to help cure the symptoms associated with cystic fibrosis. It is currently being used by 15,000 people in the United States who are infected with cystic fibrosis ("Cystic Fibrosis Foundation ", 2012). Azithromycin has a long half-life and is able to stay in the body longer than most antibiotics (M. B. C. M.-H. N. Saiman L & et al., 2003).

Studies have been done on patients infected with and without *Pseudomonas aeruginosa*. This bacterium infects eighty percent of patients with cystic fibrosis over the age of 18. Even though azithromycin has been approved for patients as young as six, it cannot be fully utilized until the patient begins to develop the chronic bacteria. In 2003, a randomized, double-blind, placebo-controlled, multicenter trial was initiated for CF patients who were infected with *P aeruginosa*. After twenty-four weeks, patients in the azithromycin group showed improvements in their overall forced expiratory volume (FEV) while they were taking the drug; four weeks after the drug was discontinued, the FEV returned to normal. The only side effects that differed from the placebo group were nausea, diarrhea, and wheezing. There was little difference between the azithromycin and placebo groups in reference to the emergence or eradication of *P*

aeruginosa. However, there was a slight decrease (0.3 log) in *P aeruginosa* density, and a slight increase in the placebo group (0.5 log). Patients in the active drug group were able to gain weight more than the placebo group which infers that the drug has some effect on increasing the nutrition absorption of CF patients. Patients with the live drug also scored higher on the physical function section of the CF Quality of Life Questionnaire. There was also a slight decrease in inflammation for patients with the azithromycin drug than the placebo group (M. B. C. M.-H. N. Saiman L & et al., 2003).

A very similar twenty-four week trial was conducted seven years later with patients who were not infected with *P aeruginosa*. In general, these are mostly children under the age of 18 who have not yet developed the chronic bacteria. The azithromycin group had a 50% reduction in pulmonary exacerbations, gained weight, and had a reduction in the introduction of new antibiotics. These differences were not enough for the researchers to conclude that azithromycin can improve lung function for patients without *P aeruginosa*. Azithromycin is beneficial for patients who are infected with the bacteria *P aeruginosa* but not for those without. Cystic fibrosis is diagnosed at a very young age, and if those patients are not infected with the bacteria, the drug will not be useful until their condition deteriorates with age (A. M. M.-H. N. Saiman L & et al., 2010).

Tobramycin.

The most common antibiotic that cystic fibrosis patients are using is tobramycin. TOBI® is the only FDA approved drug that is an inhaled version of tobramycin. This drug has been known to greatly decrease and even completely eradicate the *P aeruginosa* bacterium. It is most commonly inhaled with a nebulizer; this is appealing versus taking it orally because it can be delivered in high concentrations directly to the site of infection. This does cause local side

effects, such as coughing and difficulty breathing. It is administered twice a day for twenty-eight days followed by twenty-eight days off. This makes it less likely for the bacterium to develop resistance to the antibiotic. The cost for a twenty-eight day supply is \$4,500 which makes it well over \$20,000 for a year's supply ("TOBI," 2012).

In 2000, a study was done to prove the effectiveness of tobramycin. The study followed a similar schedule of administering the drug for four weeks and continuing observation for a two week period. At all points in the experiment, the levels of *P aeruginosa* were significantly less in patients who were taking tobramycin. At the end of the study, about two-thirds (62%) of the patients receiving the tobramycin were considered to have improved medically. Women were twice as likely to have been effected by the drug as men were. A few of the patients developed immunity to the drug over the course of the trial, showing that not everyone can avoid developing resistance to the antibiotic. However, patients who did not develop a resistance had increased lung function, decreased *P aeruginosa* density, and a decreased number of hospital visits (BARKER et al., 2000).

A similar study was done in 2002 with subjects under the age of six. Young children with cystic fibrosis are less likely to be infected with *P aeruginosa* than adults are, yet the bacterium can still exist in smaller quantities. The drug was administered as an inhalant with direct access to the infection site. After twenty-eight days of trials, the results marked a significant decrease in *P aeruginosa* density. Compared to the patients' original bacteria density, younger patients showed a greater decrease in the percentage of bacteria than the older CF patients. This is because the younger patients had minimal symptoms and normal lung function. The study showed that beginning antibiotic treatment at a younger age, gives a heightened chance of bacteria control and possible eradication (Gibson et al., 2003).

Mucus Clearers

Among the most efficient means of treatment for cystic fibrosis, inhaled mucus clearers are necessary for the overall improvement of lung function in patients. The most effective inhaled mucus clearers come in the form of mucolytic drugs. Though certainly not a cure, these drugs have a significant impact on the quality and longevity of life for patients with cystic fibrosis.

Dornase Alfa.

One of the most common mucolytic drugs prescribed to cystic fibrosis patients is sold under the brand name, Pulmozyme. The drug, recombinant human deoxyribonuclease (rhDNase or Dornase Alfa) was introduced in 1994 as the first drug in thirty years to significantly improve the quality of life in patients. These mucolytic drugs are clinically designed to thin excess extracellular DNA left behind after white blood cells or antibiotics attack bacterial infection in the lungs. Though the drug doesn't destroy or remove the mucus that plagues patients' airways entirely, the mucolytic drug allows the patients to more easily cough up mucus and thereby improve their ability to breathe (Frederiksen, Pressler, Hansen, Koch, & Høiby, 2006).

From a monetary standpoint, the cost of Pulmozyme runs at about \$27 per 2.5 mg ampule (the recommended daily dose). This price comes to be around \$9,855 annually and should be covered by both private and governmental insurance plans. This is relatively inexpensive when compared to the cost of hospital admission, invasive surgical procedures, and more innovative experimental treatments for cystic fibrosis. The drug is simple enough to use, though as it is an aerosol, additional equipment is required to administer it. These kinds of equipment come in the form of nebulizers and compressors that can be used in a variety of environments, including the home (Castile, 2005).

With regards to safety, Dornase Alfa was approved by the FDA in 1994 and is currently undergoing trials for approval for use in children under the age of 5 (Castile et al. 2005.) Side effects of the drug include inflammation of the airway, pharyngitis, laryngitis, rash, chest pain, conjunctivitis, and voice alteration. Though generally mild and temporary, patients are advised to consult their physician upon the appearance of these symptoms. The drug can be used to treat almost all patients with cystic fibrosis, assuming they are not allergic to the ingredients or undergoing therapies that might counteract with or create adverse reactions to the drug (Elphick, 2009)

Overall the DNase drug works to reduce viscosity of mucus and aid patients in improving lung function. This being said, the drug is not as effective in alleviating other symptoms associated with cystic fibrosis, namely, poor nutrient absorption, and inflammation. While the drug does work in combination with antibiotics to remove bacterial infection that often results in a decrease of inflammation, these results are not a primary side effect of Dornase Alfa nor are they consequential enough for the mucolytic drug to be credited for them.

Hypertonic saline.

Another common therapy used by cystic fibrosis patients for mucus clearing involves the inhalation of hypertonic saline solution. The dysfunction of the CFTR gene in cystic fibrosis patients results in a failure of chloride transport through cell membranes in the airway and thus, dehydrates the airway surface liquid. The hypertonic saline increases the ion concentration of the airway surface liquid leading to an osmotic gradient, which draws fluid in the airway, thereby accelerating mucus clearance. This treatment has been effective in promoting sustained mucus clearance, increased respiratory function, and quality of life, though it has yet to be proven as effective as the mucolytic drug, Dornase Alfa. Economically, hypertonic saline is very

inexpensive. The typical dosage is 10 mL of 7% solution twice daily (Like the mucolytic drug, hypertonic saline solution is inhaled via nebulizer and can be administered in the comfort of patients' home (Nicholson et al. 2007).

Almost any patient can use hypertonic saline solution and it is most effective with the use of a bronchodilator. It has been proven to not be effective in patients under the age of 6. Side effects of the drug include coughing, chest tightness, pharyngitis, and salty taste (Nicholson et al. 2007).

Mannitol.

An inhaled dry powder called Mannitol is another inhaled mucus clearer currently being experimented with. Studies have found that the drug shows better lung function and fewer respiratory symptoms after 2 weeks but not to a significant extent (Figuroa et al. 2012).

Final Recommendations

Current Treatments

Cystic Fibrosis is a lethal disease that, at this point in time, has no definitive cure. This makes a doctor's task of creating an effective treatment plan difficult. Using the decision matrices, found in Table 10 and Table 11, both current and possible future treatments were analyzed. Because CF has no absolute cure, any current effective treatment strategy must be multi-faceted.

From the results of the decision matrix, there are three types of treatments a physician should consider when dealing with CF patients. The first type would be long-term treatments that could either have permanent effects or be given continually to combat symptoms. The second type would be specified short-term treatments that deal with symptoms or malfunctions when they become an issue for the patient. The last type of treatment would be the closest thing to a

cure. These treatments would alter the physiological malfunction that is occurring and are on the borderline between being a treatment and a cure.

Initially, anti-inflammatory drugs and antibiotics should be prescribed to the afflicted. These are in the middle of the rankings of the matrix and combat many of the various symptoms patients have, including inflammation and bacterial infections. Another mid-range treatment is pancreatic enzymes. Pancreatic enzymes should be given to solve a majority of the issues that occur in the pancreas. These treatments receive mid-range rankings because they are important and helpful in treating symptoms but do not affect or solve the malfunction with the CFTR protein or the CFTR gene. Inhaled mucus clearers and stool softeners are other long-term treatments that can be taken orally continually to relieve the targeted symptoms. Certain patients with different CFTR mutations and differing genetic makeup may not need identical treatments. However, antibiotics, anti-inflammatories, pancreatic enzymes, and inhaled mucus clearers, which all scored medium-high, should be considered standard for all patients with CF because of the major symptoms they target. Some of the lowest scoring treatments still need to be used such as diet, exercise, and vitamins. This is because although they don't solve direct issues, long term application of these three recommendations has the possibility of improving quality of life, at a generally low cost.

If the disease manifests itself further in certain aspects, additional short-term treatment measures should be taken case by case. These short-term methods also scored mid-level because they only address the symptoms associated with CF and not the source itself. When necessary, the doctor would need to perform endoscopic sinus surgery on a patient for nasal polyp removal or bowel surgery. These surgeries should be a last resort if the symptoms become too severe.

The final type of treatment is one that is approaching the nature of a cure and doesn't treat the symptoms of CF but rather addresses the cause. This treatment would be a potentiator, which directly deals with the CFTR protein itself. This small molecule drug is very effective at assisting in regulation of CFTR; however, it applies to a small population of CF patients. If applicable to the patient, this newly approved drug should be prescribed. Acknowledging the success of this new treatment, future funding should be given to developing other small molecule drugs.

Future Treatments

Experimental treatments were ranked on the decision matrix, with slightly different criteria than the treatments that are currently in use. The experimental treatments were not ranked according to cost or ease of treatment because they are not currently in use. For experimental treatments, the criteria of difficulty to achieve government approval and the time to bring to market were also taken into account.

According to rankings from the decision matrix, found in Table 10 and Table 11, the combined treatment of potentiators and correctors have the most potential to cure cystic fibrosis. When in use, these experimental chemicals will not just treat secondary symptoms of cystic fibrosis, like current treatments, but instead treat the disease closer to the source, the CFTR protein itself. The only problem with this treatment and the reason it is not currently in use is because it is not presently on the market; however, it is entering its final trials. Because this chemical has a high efficacy and feasibility to come into use as a treatment of cystic fibrosis, a large majority of resources should go into getting this drug to market.

The next best ranking experimental treatment is gene therapy. Like potentiators and correctors, this therapy does not only treat the secondary symptoms of cystic fibrosis but it is a

more permanent solution to the disease. It has the potential to have a high efficacy, but this treatment did not rank as high on the decision matrix because there are significant issues with the feasibility of mechanisms for the delivery of the drug. As such, there is a low feasibility that this treatment will get onto the market. Gene therapy is not the best treatment to put resources and time into; it has had a large amount of resources already put into it, and the major problem of drug delivery has yet to be solved.

The lowest ranked experimental treatment being currently studied is Cl⁻ promoter through Ca⁺/Cl⁻ transport systems. This treatment bypasses the CFTR protein and it affects the entire population of people with CF. The problem with this treatment is that it only treats the secondary symptoms and does not cure the disease like the other future treatments mentioned. In addition, there are issues with drug delivery. This is why the disease was ranked very low according to the decision matrix and very few resources should go into this kind of treatment.

The evaluation of current treatment methods exposes the holes in where treatment plans are failing for patients suffering with cystic fibrosis. The expectation for the future is that the most promising experimental treatments will one day become a viable option for these patients and a cure will be attainable rather than forgotten.

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