

Cystic Fibrosis Study of

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Abstract: Cystic fibrosis (CF) is a hereditary, multisystemic disease caused by different mutations in the CFTR gene encoding CF transmembrane conductance regulator. CF is mainly characterized by pulmonary dysfunction as a result of deterioration in the mucociliary clearance and anion transport of airways. Mortality is mostly caused by bronchiectasis, bronchiole obstruction, and progressive respiratory dysfunction in the early years of life. Over the last decade, new therapeutic strategies rather than symptomatic treatment have been superposed, such as the small molecule approach, ion channel therapy, and pulmonary gene therapy. Due to considerable progress in the treatment options, CF has become an adult disease rather than a paediatric disease in recent years. Pulmonary gene therapy has gained special attention due to its mutation type independent aspect, therefore being applicable to all CF patients. On the other hand, the major obstacle for cystic fibrosis treatment is to predict the drug response of patients due to genetic complexity and heterogeneity. The advancement of 3D culture systems has made it possible to extrapolate the disease modelling and individual drug response in vitro by making mini adult organs called “organoids” obtained from rectal cell biopsies. In this review, we summarize the advances in the novel therapeutic approaches, clinical interventions, and precision medicine concept for disease.

Keywords: Cystic fibrosis; cystic fibrosis transmembrane conductance regulator (CFTR), gene editing; nanocarriers

❖ INTRODUCTION

Cystic fibrosis (CF), the most common lethal autosomal recessive disorder in the US, and caused by mutation in the gene encoding the CF transmembrane conductance regulator (CFTR). The major clinical manifestations of CF include exocrine pancreatic insufficiency, male infertility, and chronic pulmonary disease (1-4). Pulmonary disease is a main cause of morbidity and mortality. Pulmonary disease is the main cause of morbidity and mortality. The CF airway is marked by chronic bacterial colonization and persistent neutrophilic inflammation. Bacterial colonization of the airways generally occurs within the first year after birth. There is a predisposition to subsequent chronic infection with *Pseudomonas aeruginosa*, an organism whose presence in the Cystic fibrosis lung is associated with progressive respiratory compromise. By adulthood, 80–90% of patients with CF suffer from chronic bronchial infection with mucoid strains of *P. aeruginosa*. Infection is associated with an exuberant response dominated by neutrophils and the potent inflammatory mediators that are released by activated neutrophils. The end result of this mix of infection and inflammation is progressive, bronchiectasis destruction of the lung (1-3). Continued advances in the management and treatment of cystic fibrosis (CF) have resulted in significantly improved life expectancy. In many countries, the median predicted survival for CF patients is now between 30 and 40 years, representing a 10-year improvement compared with only a decade ago. Signs and symptoms of cystic fibrosis, the most common cause of death. No means for correcting the genetic defect has been available; current medical treatments are palliative. A nonsense mutation is a single point alteration in Cystic fibrosis results from mutations in the gene that encodes the cystic fibrosis transmembrane conductance regulator (CFTR), an apical cell-surface epithelial chloride channel that promotes chloride efflux and secondarily inhibits constitutive sodium influx via the epithelial sodium channel (ENaC).¹ Dysfunction of this regulator leads to epithelial mucous dehydration and viscous secretion, which often cause chronic neutrophilic inflammation of respiratory airways. Obstruction of pancreatic ducts, the biliary tract, and the vas deferens can occur. Patients typically develop progressive respiratory dysfunction and persistent pulmonary infections and often have pancreatic insufficiency, diminished bodyweight, chronic hepatic to biliary inflammation, and male infertility. Respiratory failure is DNA that results in the inappropriate presence of a UAA, UAG, or UGA stop codon in the protein-coding region of the corresponding messenger RNA (mRNA) transcript. Such a stop codon causes premature cessation of translation, with protein truncation leading to loss of function and consequent disease. Nonsense mutations are responsible for about 10% of cystic fibrosis cases worldwide.² However, in Israel, nonsense mutations are the cause of cystic fibrosis in most patients.³ Because people with such mutations produce little functional CFTR, these patients usually have a phenotype of severe cystic fibrosis.⁴ Certain aminoglycoside antibiotics (e.g., gentamicin) can induce ribosomes to read through a premature stop codon in mRNA, resulting in incorporation of an amino acid and continuation

of translation to produce a complete protein.⁵ We have previously shown that topical application of gentamicin drops to the nasal mucosa can cause a local increase in CFTR-mediated chloride transport as assessed by nasal transepithelial potential. Cystic fibrosis (CF) is an autosomal recessive multi-organ disease affecting approximately 75,000 individuals worldwide [1]. The main clinical features are exocrine pancreatic insufficiency and bronchiectasis with chronic airway infection leading to respiratory failure and premature death. The disease was described in 1938 [2] and although the biochemical basis of CF was not identified for 50 years, the disease was known to be associated with abnormalities of chloride and sodium transport in several epithelia [3,4]. In 1989, the cystic fibrosis transmembrane conductance regulator (CFTR) gene was cloned [5] and the CFTR protein identified as chloride channel [6]. This led to a growing research output on the basic defect in CF: the CFTR gene and mutations, and the CFTR protein's maturation, structure, function and interaction with other ion channels. The mainstay of treatment in CF is symptomatic and focused on compensating for exocrine pancreatic insufficiency with pancreatic enzymes, fat-soluble vitamins and high caloric intake; and slowing lung disease progression with inhaled and physical therapies that improve airway clearance, and antibiotic therapy [7]. The goal of new approaches to therapy includes the development of drugs that correct the basic defect in CF that might delay the progression or prevent respiratory disease if given early enough in life.

Cystic fibrosis (CF) is a rare genetic disorder that affects mostly the lung, but also the pancreas, liver, kidneys, and intestine. Long-term issues include difficulty breathing and coughing up mucus as a result of frequent lung infection. Other signs and symptoms may include sinus infections, poor growth, fatty stool, clubbing of the fingers and toes, and infertility in most males. Different people may have different degrees of symptom. Cystic fibrosis is inherited in an autosomal recessive manner. It is caused by the presence of mutations in both copies of the gene for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Those with a single working copy are carriers and otherwise mostly healthy. CFTR is involved in the production of sweat, digestive fluids, and mucus. When the CFTR is not functional, secretions which are usually thin instead become thick. The condition is diagnosed by a sweat test and genetic testing. Screening of infant at birth takes place in some areas of the world. There is no known cure for cystic fibrosis. Lung infections are treated with antibiotics which may be given intravenously, inhaled, or by mouth. Sometimes, the antibiotic azithromycin is used long term. Inhaled hypertonic saline and salbutamol may also be useful. Lung transplantation may be an option if lung function continues to worsen. Pancreatic enzyme replacement and fat-soluble vitamin supplementation are important, especially in the young. Airway clearance techniques such as chest physiotherapy have some short-term benefit, but long-term effects are unclear. The average life expectancy is between 42 and 50 years in the developed world. Lung problems are responsible for death in 80% of people with cystic fibrosis.

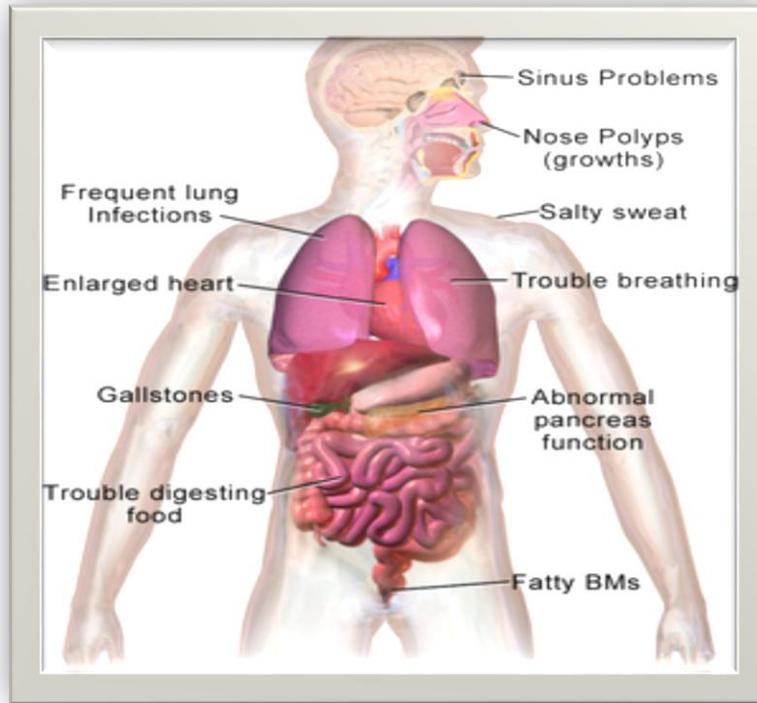
CF is most common among people of Northern European ancestry and affects about one out of every 3,000 new-borns. About one in 25 people is a carrier. It is least common in Africans and Asians. It was first recognized as a specific disease by Dorothy Andersen in 1938, with descriptions that fit the condition occurring at least as far back as 1595. The name "cystic fibrosis" refers to the characteristic fibrosis and cysts that form within the pancreas.

- **Signs and symptoms**

Cystic fibrosis typically manifests early in life. New-born and infant with cystic fibrosis tend to have frequent, large, greasy stool (a result of malabsorption) and are underweight for their age. 15–20% of new-borns have their small intestine blocked by meconium, often requiring surgery to correct. New-borns occasionally have neonatal jaundice due to blockage of the bile duct. Children with cystic fibrosis lose excessive salt in their sweat, and parents often notice salt crystallizing on the skin, or a salty taste when they kiss their child.

The primary cause of the morbidity and death in people with cystic fibrosis is progressive lung disease, which eventually leads to respiratory failure. This typically begins as prolonged respiratory infection that continues until treated with antibiotics. Chronic infection of the respiratory tract is nearly universal in people with cystic fibrosis, with *Pseudomonas aeruginosa*, fungi, and mycobacteria all increasingly common over time. Inflammation of the upper airway results in frequent runny nose and nasal obstruction. Runny nose is common, particularly in children and teenagers. As the disease progresses, people tend to have shortness of breath, and a chronic cough that produces sputum. Breathing problems make it increasingly challenging to exercise, and prolonged illness causes those affected to be underweight for their age. In late adolescence or adulthood, people begin to develop several signs of lung disease and wheezing, digital clubbing, coughing up blood, pulmonary heart diseases, and collapsed lung (atelectasis or pneumothorax).

In rare cases, cystic fibrosis can manifest itself as a coagulation disorder. Vitamin K is normally absorbed from the breast, formula, and later, solid and food. This absorption is impaired in some CF patients. Young children are especially sensitive to a vitamin K malabsorptive disorder because only a very small amount of vitamin K crosses the placenta, leaving the child with very low reserves and limited ability to absorb vitamin K from dietary sources after the birth. Because clotting factors II, VII, IX, and X are vitamin K-dependent, low levels of the vitamin K can result in a coagulation problem. Consequently, when a child presents with unexplained bruising, a coagulation evaluation may be warranted to determine whether an underlying disease is present.



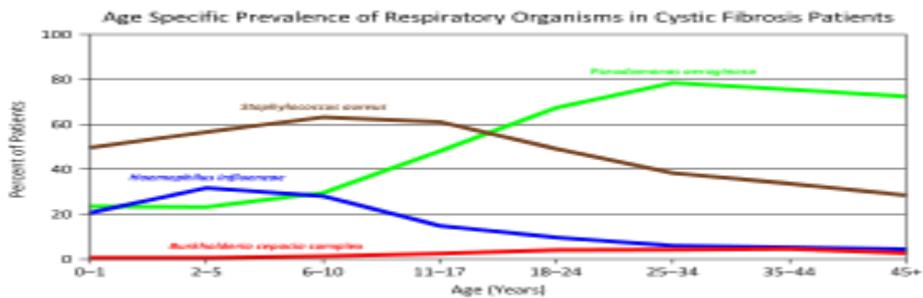
- Health problems associated with cystic fibrosis

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Lungs and sinuses[edit]



Respiratory infections in CF vary according to age.

Green = *Pseudomonas aeruginosa*
 Brown = *Staphylococcus aureus*

Blue = *Haemophilus influenzae*

Red = Burkholder cepacia complex

Lung disease results from clogging of the airway due to mucus build-up, decreased mucociliary clearance, and resulting inflammation. In later stage, change in the architecture of the lung, such as pathology in the major airway (bronchiectasis), further exacerbate difficulties in breathing. Other signs include high blood pressure in the lung (pulmonary hypertension), heart failure, difficulties getting enough oxygen to the body (hypoxia), and respiratory failure requiring support with breathing mask, such as bilevel positive airway pressure machines or ventilators. *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* are the three most common organisms causing lung infections in CF patients. In addition, opportunistic infection due to Burkholder and cepacia complex can occur, especially through transmission from patient to patient. Mucus in the paranasal sinuses is equally thick and may also cause blockage of the sinus passage, leading to infection. This may cause facial pain, fever, nasal drainage, and headaches. Individuals with CF may develop overgrowth of the nasal tissue (nasal polyps) due to inflammation from chronic sinus in addition to typical bacterial infection, people with CF more commonly develop other types of lung diseases. Among these is allergic bronchopulmonary aspergillosis, in which the body's response to the common fungus *Aspergillus fumigatus* causes worsening of breathing problems. Another is infection with *Mycobacterium avium* complex, a group of bacteria related to tuberculosis, which can cause lung damage and do not respond to common antibiotics. Recurrent sino-nasal polyp can occur in 10% to 25% of CF patients. These polyps can block the nasal passage and increase breathing difficulty. Cardiorespiratory complications are the most common cause of death (about 80%) in patients at most CF centers in the United States.

- **Gastrointestinal**

In addition, protrusion of internal rectal membranes (rectal prolapse) is more common, occurring in as many as 10% of children with CF and it is caused by increased fecal volume, malnutrition, and increased intra-abdominal pressure due to coughing.

The thick mucus seen in the lung has a counterpart in thickened secretion from the pancreas, an organ responsible for providing digestive juice that helps break down food. These secretions block the exocrine movement of the digestive enzyme into the duodenum and result in irreversible damage to the pancreas, often with painful inflammation (pancreatitis). The pancreatic ducts are totally plugged in more advanced cases, usually seen in older children or adolescents. This causes atrophy of the exocrine gland and progressive fibrosis. Individuals with CF also have difficulty in absorbing the fat-soluble vitamins A, D, E, and K.

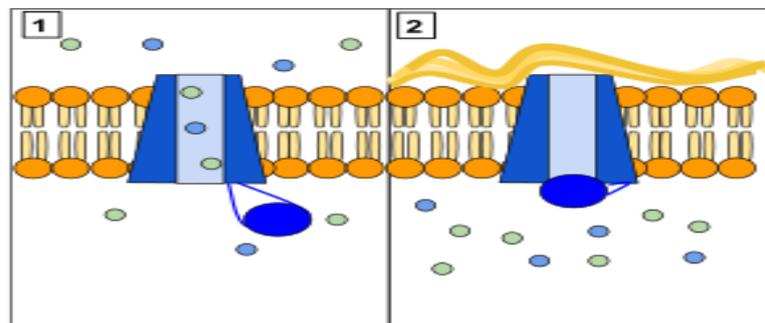
In addition to the pancreas problem, people with CF experience more heartburn, intestinal blockage by intussusception, and constipation. Older individuals with CF may develop distal intestinal obstruction syndrome, which occurs when the colon becomes thick with mucus (inspissated) and can cause bloating, pain, and incomplete and complete bowel obstruction.

Exocrine pancreatic insufficiency occurs in the majority of (90%) of patients with CF. It is mainly associated with "severe" CFTR mutation, where both alleles are completely non-functional (e.g., $\Delta F508/\Delta F508$). It occurs in 10% to 15% of patients with one "severe" and one "mild" CFTR mutation where little CFTR activity still occurs, or where two "mild" CFTR mutations exist. In these milder cases, sufficient pancreatic exocrine function is still present so that enzyme supplementation is not required. Usually, no other GI complications occur in pancreas-sufficient phenotypes, and in general, such individuals usually have excellent growth and development. Despite this, chronic pancreatitis can occur in a subset of pancreas-sufficient individuals with CF, and is associated with recurrent abdominal pain and life-threatening complications.

Thickened secretions also may cause liver problems in patients with CF. Bile secreted by the liver to aid in digestion may block the bile ducts, leading to liver damage. Impaired digestion or absorption of lipids can result in steatorrhea. Over time, this can lead to scarring and nodularity (cirrhosis). The liver fails to rid the blood of toxins and does not make important proteins, such as those responsible for blood clotting. Liver disease is the third-most common cause of death associated with Cystic Fibrosis.

Around 5–7% of people experience liver damage severe enough to cause symptoms typically gallstones causing biliary colic.

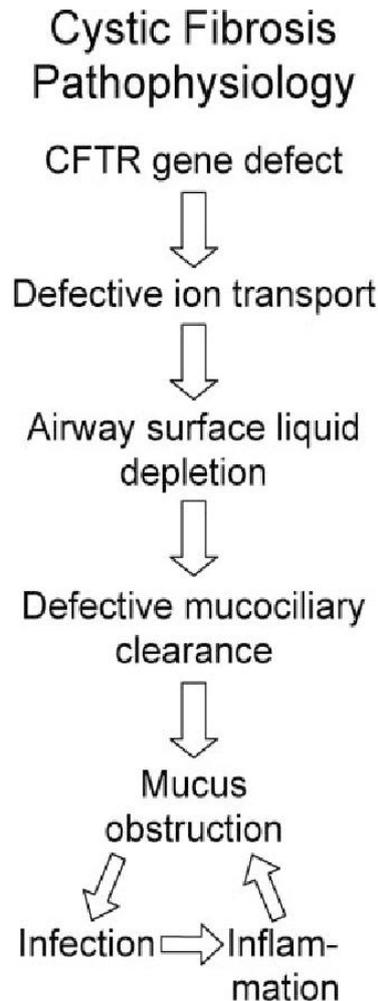
- Pathophysiology



The CFTR protein is a channel protein that controls the flow of H_2O and Cl^- ions in and out of the cell inside the lung. When the CFTR protein is working correctly, ions freely flow in and out of the cell. However, when the CFTR protein is malfunctioning, these ions cannot flow out of the cell due to a blocked channel. This causes cystic fibrosis, characterized by the build-up of thick mucus in the lung.

Several mutations in the CFTR gene can occur, and different mutations cause different defects in the CFTR protein, sometimes causing a milder or more severe disease. These protein defects are also targets for drugs which can sometimes restore their function. $\Delta F508$ -CFTR gene mutation, which occurs in >90% of patients in the U.S., creates a protein that does not fold normally and is not appropriately transported to the cell membrane, resulting in its degradation.

Other mutations result in proteins that are too short because production is ended prematurely. Other mutations produce proteins that do not use energy (in the form of ATP) normally, do not allow chloride, iodide, and thiocyanate to cross the membrane appropriately, and degrade at a faster rate than normal. Mutations may also lead to fewer copies of the CFTR protein being produced.



The protein created by this gene is anchored to the outer membrane of cells in the sweat glands, lungs, pancreas, and all other remaining the exocrine glands in the body. The protein span this membrane and acts as a channel connecting the inner part of the cell (cytoplasm) to the surrounding fluid. This channel is primarily responsible for controlling the movement of halide anion from inside to outside of the cell however, in the sweat ducts, it facilitates the movement of chloride from the sweat duct into the cytoplasm. When the CFTR protein does not resorb ions in sweat ducts, chloride and thiocyanate released from sweat glands are trapped inside the ducts and pumped in to the skin.

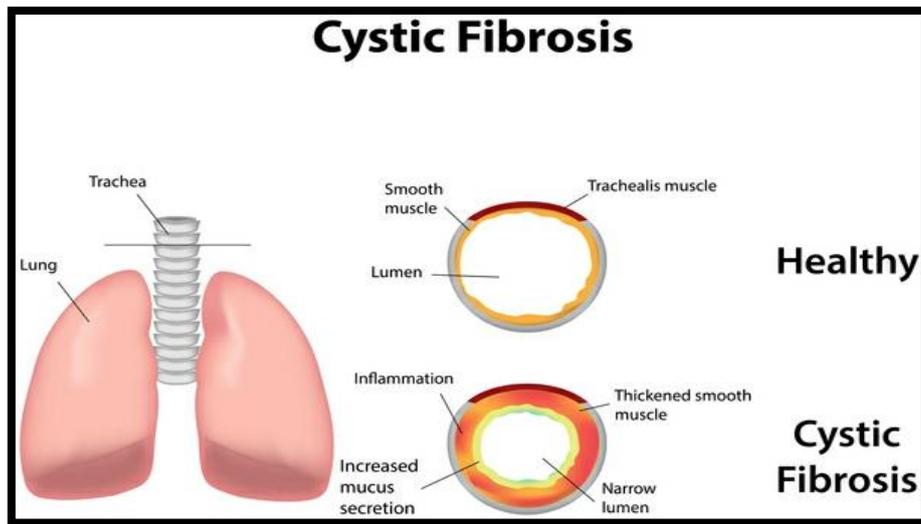
Additionally, hypothiocyanite, OSCN, cannot be produced by the immune defence system. Because chloride is negatively charged, this modifies the electrical potential inside and outside the cell that normally causes cations to cross into the cell. Sodium is the most common cation in the extracellular space. The excess chloride within sweat ducts prevents sodium resorption by epithelial sodium channel and the combination of sodium and chloride create the salt, which is lost in high amount in the sweat of individual with CF. This lost salt forms the basis for the sweat test.

Most of the damage in CF is due to the blockage of the narrow passages of affected organs with the thickened secretion. These blockages lead to remodelling and infection in the lung, damage by the accumulated digestive enzymes in the pancreas, blockage of the intestines by thick faeces, etc. Several theories have been posited on how the defects in the protein and cellular function cause the clinical effect. The most current theory suggests that defective ion transport leads to the dehydration in the airway epithelia, thickening mucus.

airway epithelial cells, the cilia exist in between the cell's apical surface and mucus in a layer known as airway surface liquid (ASL). The flow of ions from the cell and into this layer is determined by ion channels such as CFTR. CFTR not only allows chloride ions to be drawn from the cell and into the ASL, but it also regulates another channel called Enact, which allows sodium ions to leave the ASL and enter the respiratory epithelium. CFTR normally inhibits this channel, but if the CFTR is defective, then sodium flows freely from the ASL and into the cell

❖ History of cystic fibrosis

Cystic fibrosis – The disease in 2014 Cystic fibrosis (CF) is the most common life shortening condition in the Caucasians and affect approximately 70,000 people around the globe including ~30,000 in North America and more than 30,000 in Europe (31). CF is an autosomal recessive disease which is caused by the mutation in each of the 2 CFTR gene. almost 2,000 different mutation have been reported to the original CFTR mutation repository (32). F508del is by far the most common mutation. It is found on about 70% of CF chromosomes worldwide and it is present in ~85% of patient on at least one an allele. prevalence is broadly similar in



the population which had their origin from northern of Europe, there are considerable variation in through Europe from as high as 1 in 1,400 live births in Ireland, 1 in 4,200 in Italy and 1 in 25,000 in Finland (33,34). Prevalence rate are much lower in non-Caucasian population (e.g., 1 in 4000-10000 in Latin Americans, 1 in 15000-30000 in Africans and ~1 in >100000 in people of Asian origin) (36, 37). Cystic fibrosis is a multisystem disease affecting organ and tissues where CFTR is expressed. The most common clinical manifestation are related to impact of the defect gene on the airways (upper and lower respiratory tract), gastrointestinal tract including the biliary system and the reproductive tract (Table 1). About 85% of patients with the CF have pancreatic insufficiency associated with nutrient malabsorption and often under-nutrition. Decreased reabsorption of chloride ions via CFTR channel in the sweat duct can lead to salt loss syndrome. Increased concentration of chloride ion in sweat (>60 mmol/L), remain the best diagnostic test for CF. Therapies are complex and involve pancreatic enzyme supplementation, fat soluble vitamins, mucolytic (e.g., dornase-alpha) and hydrator therapies (e.g., hypertonic saline, mannitol), airway clearance, and frequent an often-repeated course of antibiotic. The vast majority of morbidity and mortality results from pulmonary disease associated with chronic bronchial infection and bronchiectasis. Lung disease remains a progressive condition and the burden of therapy is very significant for the patient, his family and the health care system. When initially described in the 1930s, CF was universally fatal in infancy or early childhood. Until recently the majority of people with CF were children, though in the past decade in many part of the world there are now more adult than children (38-40).

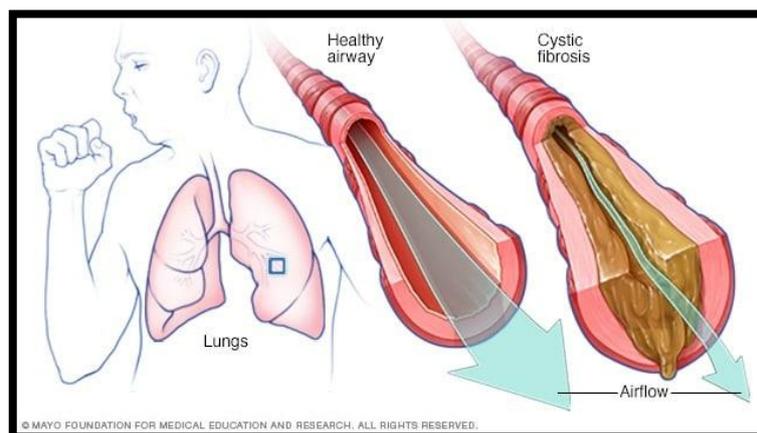
❖ DESCRIPTION OF THE DISEASE

Cystic fibrosis (CF) was first recognized as the separate disease entity in 1938 when autopsy studies of the malnourished infants distinguished a disease of the mucus plugging of the glandular duct, termed "cystic fibrosis of the pancreas," from others with celiac syndrome (1). This disease was characterized by malabsorption of fat and protein, steatorrhea, growth failure, and pulmonary infection.

❖ Respiratory signs and symptoms

The thick and sticky mucus associated with cystic fibrosis clog the tubes that carry air in and out of your lungs. This can cause signs and symptoms such as:

- A persistent cough that produces thick mucus (sputum)
- Wheezing
- Exercise intolerance
- Repeated lung infection
- Inflamed nasal passages or a stuffy nose
- Recurrent Sinusitis



Digestive signs and symptoms

The thick mucus can also block tubes that carry digestive enzymes from your pancreas to your small intestine. Without these digestive enzymes, your intestines are not able to completely absorb the nutrients in the food you eat.

- Foul-smelling, greasy stools
- Poor weight gain and growth
- Intestinal blockage, particularly in new-borns (meconium ileus)
- Chronic or severe constipation, which may include frequent straining while trying to pass stool, eventually causing part of the rectum to protrude outside the anus (rectal prolapse).

Respiratory system complications

- **Damaged airways (bronchiectasis).** Cystic fibrosis is one of the leading causes of bronchiectasis, a chronic lung condition with abnormal widening and scarring of the airway (bronchial tubes). This makes it harder to move air in and out of the lungs and clear mucus from the bronchial tubes.
- **Chronic infections.** Thick mucus in the lungs and sinuses provides an ideal breeding ground for bacteria and fungi. People with cystic fibrosis may often have sinus infections, bronchitis or pneumonia. Infection with bacteria that is resistant to antibiotics and difficult to treat is common.
- **Growths in the nose (nasal polyps).** Because the lining inside the nose is inflamed and swollen, it can develop soft, fleshy growths (polyps).
- **Coughing up blood (haemoptysis).** Bronchiectasis can occur next to blood vessels in the lungs. The combination of airway damage and infection can result in coughing up blood. Often this is only a small amount of blood, but it can also be life-threatening.
- **Pneumothorax.** In this condition, air leaks into the space that separates the lung from the chest wall, and part or all of a lung collapse. This is more common in the adult with cystic fibrosis. Pneumothorax can cause sudden chest pain and breathlessness. People often feel a bubbling sensation in the chest.

Respiratory failure. Over time, cystic fibrosis can damage lung tissue so badly that it no longer works. Lung function usually worsens gradually, and it eventually can become life-threatening. Respiratory failure is the most common cause of death.

❖ Causes of Respiratory system complications

- In cystic fibrosis, a defect (mutation) in a gene — the cystic fibrosis transmembrane conductance regulator (CFTR) gene — changes a protein that regulates the movement of salt in and out of cells. The result is thick, sticky mucus in the respiratory, digestive and reproductive systems, as well as increased salt in sweat.
- Many different defects can occur in the gene. The type of gene mutation is associated with the severity of the condition.
- Children need to inherit one copy of the gene from each parent in order to have the disease. If children inherit only one copy, they won't develop cystic fibrosis. However, they will be carriers and could pass the gene to their own children.

Digestive system complications

Nutritional deficiencies. Thick mucus can block the tube that carry digestive enzymes from your pancreas to your intestines. Without these enzymes, our body can't absorb protein, fats or fat-soluble vitamins, so you can't get enough nutrients. This can result in delayed growth, weight loss or inflammation of the pancreas.

Diabetes. The pancreas produces insulin, which your body needs to use sugar. Cystic fibrosis increases the risk of diabetes. About 20% of teenagers and 40% to 50% of adults with CF develop diabetes.

- ❖ **Liver disease.** The tube that carries bile from your liver and gallbladder to your small intestine may become blocked and inflamed. This can lead to liver problems, such as jaundice, fatty liver disease and cirrhosis and sometimes gallstones.
- ❖ **Intestinal obstruction.** Intestinal blockage can happen to people with cystic fibrosis at all ages. Intussusception, a condition in which a segment of the intestine slides inside an adjacent section of the intestine like a collapsible telescope, also can occur.
- ❖ **Distal intestinal obstruction syndrome (DIOS).** DIOS is partial or complete obstruction where the small intestine meets the large intestine. DIOS requires urgent treatment
- ❖ **Other complications**
 - **Thinning of the bones (osteoporosis).** People with cystic fibrosis are at higher risk of developing a dangerous thinning of bones. They may also experience joint pain, arthritis and muscle pain.
 - **Electrolyte imbalances and dehydration.** Because people with cystic fibrosis have saltier sweat, the balance of minerals in their blood may be upset. This makes them prone to dehydration, especially with exercise or in hot weather. Signs and symptoms include increased heart rate, fatigue, weakness and low blood pressure.
 - **Mental health problems.** Dealing with a chronic illness that has no cure may cause fear, depression and anxiety.

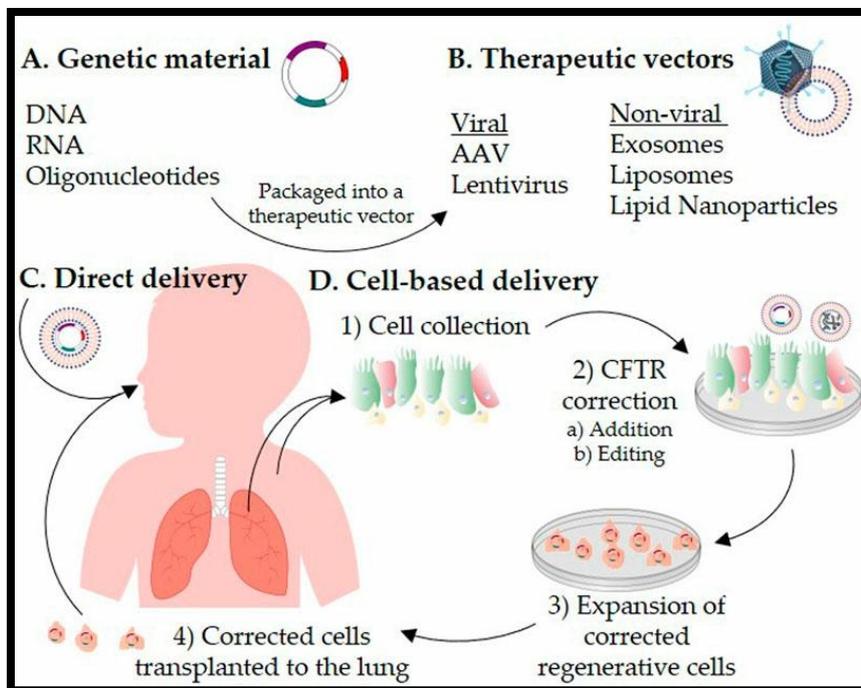
Pathogenesis of cystic fibrosis

- Genetics.
- Cystic fibrosis is caused by mutations in the CFTR gene which is located on chromosome band .
- Whereas a 3-base-pair deletion (F508del) occurs approximately 70% of cystic fibrosis chromosomes worldwide, nearly 2,000 mutations in the CFTR gene have been found to date and are collected in the Cystic Fibrosis Mutation Database. For a large number of CFTR mutations, no inference can be made as to the effect of this alteration on gene expression, the function of the protein product or a clinical phenotype.
- **Pathophysiology of CF Lung Disease**

- CF lung disease is distinct from other organ system manifestations in CF because (1) lung disease is the cause of premature death in about 95% of patients, and (2) only the lung develops a chronic infection phenotype with an associated intense inflammatory response. Further discussion of the pathophysiologic processes that contribute to CF lung disease is therefore warranted. Current evidence suggests that the CF lung is free of infection and not inflamed at the time of birth [17, 18]. Over the course of months to years, however, stigmata of first recurrent and then chronic infection begin to appear. Microbiologic studies reveal a fairly typical evolution of pathogen, with respiratory virus, Haemophilus influenzae and Staphylococcus aureus, predominating early in life. With time, more problematic and increasingly resistant pathogens, including Pseudomonas aeruginosa and other Gram-negative bacteria (e.g., Burkholderia cepacia complex, Stenotrophomonas maltophilia, xylophilids), often dominate the clinical picture. Direct tests of systemic immunity, which are normal, and the absence of an infectious phenotype outside the respiratory tract suggest that a local defect in lung defence is responsible for the development of CF lung disease. In fact, the intense neutrophilic inflammatory response to airway infections is arguably more robust and persistent than in non-CF conditions [19–22], yet the CF lung ultimately fails to clear bacterial pathogens once they become established. It is this defect in innate airway defence that has been the focus of intense investigation and the recent target for therapies aimed at preventing or slowing the cascade of pathogenic events that culminate in progressive lung destruction.

This channel is primarily responsible for controlling the movement of halide anion from inside to outside of the cell however, in the sweat duct, it facilitates the movement of The CFTR protein is a channel protein that controls the flow of H₂O and Cl⁻ ions in and out of cells inside the lungs. When the CFTR protein is working correctly, ions freely flow in and out of the cells. However, when the CFTR protein is malfunctioning, these ions cannot flow out of the cell due to a blocked channel. This causes cystic fibrosis, characterized by the build-up of thick mucus in the lungs. Several mutations in the CFTR gene can occur, and different mutations cause different defects in the CFTR protein, sometimes causing a milder or more severe disease. These protein defects are also targets for drugs which can sometimes restore their function. ΔF508-CFTR gene mutation, which occurs in >90% of patients in the U.S., creates a protein that does not fold normally and is not appropriately transported to the cell membrane, resulting in its degradation. Other mutations result in proteins that are too short (truncated) because production is ended prematurely. Other mutations produce proteins that do not use energy (in the form of ATP) normally, do not allow chloride, iodide, and thiocyanate to cross the membrane appropriately and degrade at a faster rate than normal. Mutations may also lead to fewer copies of the CFTR protein being produced., lungs, pancreas, and all other remaining exocrine glands in the body. The protein spasms this membrane and acts as a channel connecting the inner part of the cell (cytoplasm) to the surrounding fluid chloride from the sweat duct into the cytoplasm. When the protein created by this gene is anchored to the outer membrane of cells in the sweat gland the CFTR protein does not resorb ions in sweat ducts, chloride and thiocyanate released from sweat gland are trapped inside the duct and pumped to the skin.

❖ Characteristics of cystic fibrosis



- Airway disease It is remarkable that the airways of most people are clean and sterile, even though the air we breathe contains viruses and bacteria, along with many sorts of particulate matter. Just how the airways can remain clean and sterile under these conditions is still not completely understood, but much new information has accrued in recent years as progress is made towards the complete picture of the defence mechanisms. It is also known that in cystic fibrosis (CF) airway defences are severely compromised. In CF, problems affecting the airways are the major causes of morbidity and mortality, so the major therapeutic challenge is directed to improving airway function. It is now 21 years since the CF gene was discovered (Riordan et al., 1989) and around 1700 different mutations are now known. The CF gene codes for a membrane protein, the

cystic fibrosis transmembrane conductance regulator (CFTR; channel nomenclature follows Alexander et al., 2009) that acts as an anion channel, regulated by cAMP-dependent protein kinase A (PKA) and requiring ATP to cycle between open and closed states (Tsai et al., 2010). Thus, in CF epithelial anion transport fail, causing functional disruption in a number of organs besides the airways, including the alimentary canal, exocrine pancreas, gall bladder, reproductive tract and sweat ducts.

- TREATMENT

- In the mid-1950s, patients with CF began to assemble into center for care, so physicians became familiar with the clinical manifestations of the disease and gained experience with treatment. In 1954, at the CF center in Cleveland, Leroy Matthew instituted a comprehensive program of care that attacked every complication aggressively. Matthews and co-workers established three pillars of treatment: nutritional repletion, relief of airway obstruction, and antibiotic therapy of the lung infection. Over the next few years, results were dramatic. Survival and quality of life improved, all without knowledge of the CF basic defect. Although the details have changed, aggressive treatment remains the foundation of care today. In 1955, the Cystic Fibrosis Foundation was founded. One of its greatest achievements has been the establishment, accreditation, and support of a network of centers that are committed to high-quality, evidence-based care. Moreover, the foundation supports a center network for clinical research to obtain the clinical evidence necessary to make good therapeutic decision.

- ❖ Anti-inflammatory agents

- Due to the importance of inflammation within the CF airway, this has long been a therapeutic target. Ibuprofen has been shown to slow the progression of lung disease in children, (5) but concerns over side effects have limited its widespread uptake. A recent pilot study looking at novel biomarkers of kidney injury suggest that ibuprofen can be used safely within a selected patient group (>6 years, ≥60%) although still recommended to be temporarily ceased when the patient is also receiving intravenous aminoglycoside. (6) Another drug, azithromycin, is thought to work at least in part as an anti-inflammatory agent and has proven efficacy in patients with and without chronic Pa infection. A current study is looking at the efficacy of azithromycin in infants with CF, specifically its effect on the development of bronchiectasis. Glutathione is a major antioxidant, level of which are decreased in CF lung. A recent trial of inhaled glutathione in children over 8 years and adult reported no improvement in lung function or exacerbation rates. (7)

- ❖ Anti-infective treatments

- There is no newly identified antibiotic, but there have been many trials investigating alternative delivery method. The advantages of inhaled drugs are increased airway concentration in ventilated regions of the lung and minimisation of systemic side effects.[8] The most common pathogen in older children and adults is *Pseudomonas aeruginosa* (PA); chronic infection is associated with increased rates of decline in lung function, morbidity and mortality. Tobramycin, used for several years as a nebulised solution tobramycin inhaled solution (TIS), can now be delivered more quickly as a dry powder tobramycin inhalation powder (TIP), via a Podhale. It was found to be comparable in terms of lung function changes and PA sputum density changes to the nebulised solution.[9] It can be used by children aged 6 years and older but was associated with higher rates of cough and dysphonia than TIS. Similarly, a new dry powder formulation of colomycin (Colobreathe) administered via a Turbos pin device has been developed for patients at least 6 years old. In a phase III randomised open-label trial, there were no difference in lung function, colistin resistance or adverse events over a 24-week period, confirming non-inferiority to TIS and patients preferred the dry powder. Aztreonam is available in a nebulised form, aztreonam for inhalation solution (AZLI). An 18-month open-label placebo-controlled study (28 day on/off cycles) compared twice and three times daily dose.[10] There was a greater improvement in lung function on three times daily, but in all patients the lung function had fallen back to baseline by the end of the 'off' period. There was a decrease in bacterial density sustained over the total duration of the study and a sustained weight gain. Another study examined the same primary and secondary outcomes in patients with FEV1 >75% predicted. Over 50% of participants were aged 6–18 years.[11] Results were similar but somewhat less pronounced, likely due to the milder disease. A comparison study, over 3×28-day treatment courses, between TIS and AZLI in patients 6 years and over with an FEV1 <75% has shown AZLI to be superior in terms of increased lung function and decreased exacerbation rates.[12]

- Transplantation

Lung transplantation may become necessary for individual with CF as lung function and exercise and tolerance decline. Although single lung transplantation is possible in other disease, individual with CF must have both lungs are replaced because the remaining lung might contain bacteria that could infect the transplanted lung. A pancreatic or liver transplant may be performed at the same time to alleviate liver disease and/or diabetes. Lung transplantation is considered when lung function declines to the point where assistance from mechanical devices is required or someone's survival is threatened. According to Merck Manual, "bilateral lung transplantation for severe lung disease is becoming more routine and more successful with experience and improved techniques. Among adults with CF, median survival posttransplant is about 9 years."

- ❖ Mucolytics

Sputum in CF contains considerable amounts of neutrophil in addition to bacteria, and is thick and viscous. Dornase alfa (recombinant human DNase) breaks down the large amounts of the DNA in CF sputum and reduces sputum viscosity, improves pulmonary function and decreases the number of exacerbations.[31,32] It is firmly established in the treatment regimen of many patients; however, careful assessment of an initial therapeutic trial is mandatory, as individual patient response is highly variable.[33] Acetylcysteine has been investigated as a treatment because it may affect the rheological properties of sputum. However, studies of both oral and inhaled acetylcysteine have not shown evidence of clinical benefit in CF. [34]

❖ Improving Airway Hydration

In CF, the ASL is depleted through the imbalance of defective chloride secretion and increased sodium absorption. Replenishing the ASL is another therapeutic target, either through drugs that influence ion channels or osmotic agents that may replenish the ASL.

➤ Osmotic Agents

Nebulized 7% hypertonic saline is now established as part of the treatment regimen for many patients with CF, following the recent publication of two clinical study demonstrating beneficial effects in increased rates of mucus clearance[19] and improvements in lung function and a reduction in pulmonary exacerbation rates with use of hypertonic saline.[20] A drypowder preparation for inhalation of the osmotic agent mannitol (Bronchioles) is currently being evaluated for the treatment of CF lung disease. In a 2-week crossover trial in 39 patients with mild to moderate CF lung diseases, inhaled mannitol 420 mg twice daily demonstrated improvement in lung function parameters with a mean FEV1 increase of 7% above baseline.[21] As with all inhaled treatments, there should be the close supervision of the initial test dose by a specialist physiotherapist experienced in CF care. In a study of 38 children with CF, 9 (24%) had a decrease in FEV1 of 15% during a bronchial provocation challenge to mannitol.[22] The phase III study of this dry-powder preparation of mannitol for the treatment of CF lung disease has recently been completed, the full result of which are awaited.[23]

❖ Exocrine Pancreatic Insufficiency

One of the characteristics of CF is exocrine pancreatic insufficiency, affecting roughly 85–90% of patients. The current treatment for exocrine pancreatic insufficiency is porcine derived exocrine pancreatic enzyme preparations. For many patients, this involves taking a considerable number of capsules with each meal and even then, normal absorption is not always achieved. Phase II studies have been completed for one porcine-free recombinant pancreatic replacement enzyme, Merispace [24] and another, Tristen is presently being evaluated in a phase III study. [25]

❖ Treatments for Other Complications

With increased life expectancy, other problem is being more frequently encountered, such as low bone mineral density and CF-related diabetes mellitus. Clinical trial is required to identify the optimal treatment policies for these conditions.

❖ Challenges:

The number of hopeful drugs for the treatment of CF is increasing, and at . declining in FEV1 and this has been shown to be predictive of survival.[26] However, the decline in FEV1 has been noticeably slowed by improvements with current clinical care [2] and increasing numbers of trial participants are required to demonstrate statistically significant differences in FEV1 change for phase III clinical studies. New substitute markers of lung disease, such as the lung clearance index [27,28] and high-resolution CT scan changes,[29] are being explored as potential suitable endpoints for clinical trials. Dimensions of biological and physiological markers such as changes in nasal potential differences, sweat sodium levels, and cellular CFTR expression with agents that modify CFTR function or ion channels, may be included as outcome measures in studies. There remains a need to ensure that these measurements are sufficiently standardized and to establish how they correlate with clinical outcome. World-wide clinical trial networks are being formed to assist and organise the evaluation of new treatments for CF. [30]

The current and future therapeutic targets are mainly focused on correcting structural and functional aberrations of CFTR protein. Additionally, some agents for indicative improvement are also in pipeline.

❖ CFTR modulators

- A new group of drugs called CFTR modulators are available which are able to correct the basic imperfection in CF, i.e., protein itself though the exact apparatus is not fully explicated.

❖ Ivacaftor

- Developed by vertex medications and approved by FDA in 2012 for children ≥ 6 years having rare mutation, G551D (class III), ivacaftor (Kalydeco) [14] was the first successful medicine to rectify the defective protein and has proven to be very effective in two large multicentric trials, STRIVE and ENVISION [15, 16]. Marked enhancement in FEV, body weight and superiority of life were observed. Now FDA has expanded its use in other mutations and also children aged 2–5 years based on the results of KIWI trial [17]. Additionally, a phase IV study (GOAL) also reported improvements in FEV1 and FVC, BMI, quality of life and decreased sweat chloride absorption in patients carrying at least one G551D allele. More than 72% patients in this trial also carried F508del as subsequent allele [18]. The G551D mutation causes the channel to act like a locked gate, preventing the trans-conductance of chloride and fluid. The location of channel is proper but the function is impaired. Ivacaftor the time of channel in open state. But the main limitation of this therapy is that G551D mutation is present in only 2.3% patients [18]. It is not found to be effective in the most common F508del (class II) mutation because of decreased convenience of protein. Additionally, the high cost of healing may also be a limiting factor (ICER: £335,000–£1,274,000/QALYs gained [17]).

• Other aspects

Intracytoplasmic sperm injection can be used to provide fertility for men with cystic fibrosis New-borns with intestinal obstruction typically require surgery, whereas adults with distal intestinal obstruction syndrome typically do not. Treatment of pancreatic insufficiency by replacement of missing digestive enzymes allows the duodenum to properly absorb nutrients and vitamins that would otherwise be lost in the faces. However, the best dosage and form of pancreatic enzyme replacement is unclear, as are the risks and long-term effectiveness of this treatment. So far, no large-scale research involving the incidence of atherosclerosis and coronary heart disease in adults with cystic fibrosis has been conducted. This is likely because the vast majority of people with cystic fibrosis do not live long enough to develop clinically significant atherosclerosis or coronary heart disease.

Diabetes is the most common no pulmonary complication of CF. It mix landscapes of type 1 and type 2 diabetes, and is standard as a distinct entity, cystic fibrosis-related diabetes While oral antidiabetic drugs are sometimes used, the recommended treatment is the use of insulin injections or an insulin pump and, unlike in type 1 and 2 diabetes, dietary boundaries are not recommended While *Stenotrophomonas melophilia* is relatively common in people with cystic fibrosis, the evidence about the success of antibiotics for *S. melophilia* is uncertain.

Bisphosphonates taken by mouth or intravenously can be used to improve the bone mineral density in people with cystic fibrosis When taking bisphosphates intravenously, adverse effects such as pain and flu-like symptoms can be an issue. The adverse effects of bisphosphates taken by opening on the gastrointestinal tract are not known

Poor growth may be avoided by insertion of a feeding tube for increasing food energy through added feeds or by administration of injected growth hormone.

Sinus infections are treated by protracted courses of antibiotics. The development of nasal polyps or other chronic changes within the nasal passages may severely limit airflow through the nose, and over time reduce the person's sense of smell. Sinus surgery is often used to alleviate nasal obstruction and to limit extra infections. Nasal steroids such as fluticasone propionate are used to decrease nasal inflammation.

Female infertility may be overcome by assisted imitation technology, particularly embryo transfer techniques. Male infertility caused by absence of the vas deferens may be overcome with testicular sperm extraction, collecting sperm cells directly from the testicles. If the collected sample contains too few sperm cells to likely have a spontaneous fertilization, intracytoplasmic sperm injection can be completed. Third party imitation is also a likelihood for women with CF. Whether taking antioxidants affects outcomes is unclear.

Conclusion-

Nowadays, the majority of patients with cystic fibrosis survive into adulthood and in doing so enter the remit of Ault gastroenterologists. A wide range of hepatobiliary and gastrointestinal manifestations are common in cystic fibrosis, and with in each patient there is variability in disease severity and course. Adult patients with cystic fibrosis also have an increase risk of gastrointestinal and pancreatic-biliary tract malignancy in contrast to therapeutic option for a pulmonary complication in cystic fibrosis.

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