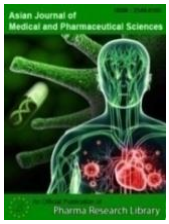

Asian Journal of Medical and Pharmaceutical Sciences
Home Page: https://pharmaresearchlibrary.org/journals/index.php/ajmps
ISSN (Online): 2348-0165 | Publisher: Pharma Research Library
A. J. Med. Pharm, Sci., 2025, 13(2): 103-109
DOI: https://doi.org/10.30904/j.ajmps.2025.4863

A Review on Clinical Diagnosis, Novel Therapeutic Strategies and Future Approaches for Management of Cystic Fibrosis

CH. A. L. Kalyani*[1], Kandula Anitha Reddy[2], Eraparaju Bhavani[2], Yeddula Sireesha Reddy[2], Gangine Palli Koushik Reddy[2]

[1]Associate Professor, Department of Pharmaceutical Analysis and Quality assurance, Saastra College of Pharmaceutical Education & Research, Totapalli Gudur (M), Varigonda(V), Nellore-524311, A.P, India

[2]IVth Year B.Pharm, Saastra College of Pharmaceutical Education & Research, Totapalli Gudur (M), Varigonda(V), Nellore-524311, A.P, India

A B S T R A C T

Cystic fibrosis (CF) is agenetic disorder inherited in an autosomal recessive manner that impairs the normal clearance of mucus from the lungs, which facilitates the colonization and infection of the lungs by bacteria, notably Staphylococcus aureus. CF is a rare genetic disorder that affects mostly the lungs, but also the pancreas, liver, kidneys, and intestine. The hallmark feature of CF is the accumulation of thick mucus in different organs. Long-term issues include difficulty breathing and coughing up mucus as a result of frequent lung infections. 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 symptoms. CF gets worse over time and needs daily care, but people with CF usually can attend school and work. They often have a better quality of life than people with CF had in past decades. Better screening and treatments mean that people with CF now may live into their mid- to late 50s or longer, and some are being diagnosed later in life. The gene therapies will continue to be an important strategy for CF as well as other genetic diseases, and organoid-based regenerative medicine designed with gene engineering technologies can provide an enormous innovation for CF therapy in the next years.

Keywords: Cystic fibrosis, sinus infections, screening, treatments, diagnosis, gene therapies.

A R T I C L E I N F O

Corresponding Author
CH. A. L. Kalyani
Associate Professor, Department of Pharmaceutical Analysis & Quality Assurance, Saastra College of Pharmaceutical Education & Research, Varigonda, Nellore-524311, A.P, India

Article History:
Received 12 Aug 2025
Revised 31 Aug 2025
Accepted 21 Sep 2025
Published 10 Oct 2025

Citation: CH. A. L. Kalyani, *et al.* A Review on Clinical Diagnosis, Novel Therapeutic Strategies and Future Approaches for Management of Cystic Fibrosis. A. J. Med. Pharm, Sci.,2025; 13(2): 103-109.

C O N T E N T S

1. Introduction

Cystic fibrosis is inherited in an autosomal recessive manner. It is caused by the presence of mutations in both copies (alleles) of the gene coding the cystic fibrosis trans membrane 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 that are usually thin instead become thick. The condition is diagnosed by a sweat test and genetic testing. The sweat test measures sodium concentration, as people with cystic fibrosis have abnormally salty sweat, which can often be tasted by

parents kissing their children. Screening of infants at birth takes place in some areas of the world[1-5]. 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 may 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, with a median of 40.7 years. Lung problems are responsible for death in 70% of people with cystic fibrosis. CF is most common among people of Northern European ancestry, for whom it affects about 1 out of 3,000 newborns, and among which around 1 out of 25 people is a carrier. It is least common in Africans and Asians, though it does occur in all races. It was first recognized as a specific disease by Dorothy Andersenin 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. Cystic fibrosis is a chronic genetic disorder that has affected children and adults since ancient times, primarily affecting the respiratory, digestive, and reproductive systems[7-14].

Incidence

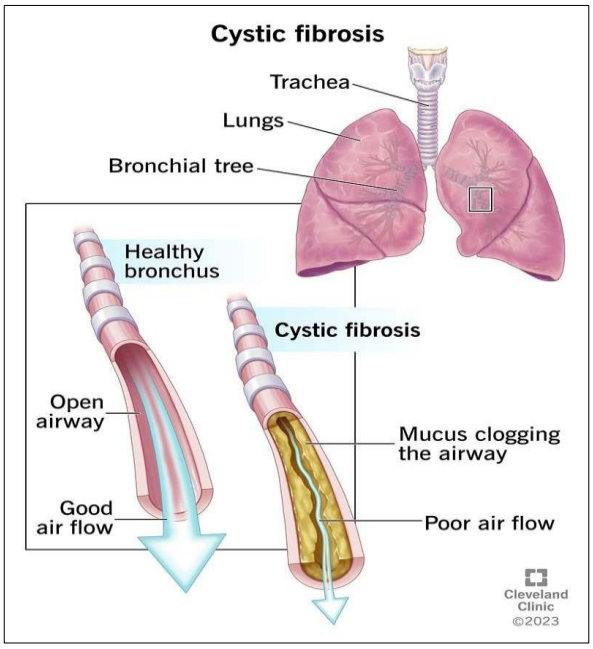

Fig.1: Cystic Fibrosis Affects Lungs

The incidence of CF has traditionally been estimated at 1/2500 live births in a populations of European descent. However, data from newborn screening (NBS) programs for CF reveal that the incidence appears to be lower than in the past. Today, the incidence of CF is estimated, on average, between 1/3000 and 1/6000 in such populations, which corresponds to carrier rates of 1/28 and 1/40, respectively. Time trends in the incidence of CF have been investigated in several studies, most of which reported a decline but not all. This was the case for example in two American states: in Colorado which observed no decline in incidence over a 24-year period (1983–2006) and in Wisconsin, which analyzed time trends over an 18-year period (1994–2011) and even observed a trending (but not significant) increase in incidence in recent years (in different genotype groups and in all ethnic groups). In Brittany (western France), we analyzed time trends in the incidence of CF over a 35-year period and observed a significant decline (from 1/1983 in the late 1970s to 1/3268 over the 2005–2009 period) but also a clear breakpoint at the end of the 1980s, which seemed consecutive to the availability of prenatal diagnosis[15-20].

Cystic Fibrosis (CF) is primarily categorized into classical CF and mild CF, though these are not strict types but rather a spectrum of severity. The severity of CF depends on the specific mutations in the CFTR gene, which affect the CFTR protein's function. These mutations are broadly classified into five classes based on their effect on protein production, processing, and function.

CFTR Mutation Classes

Class I: Defective protein production (no CFTR protein is made).

Class II: Misfolded CFTR protein is produced and degraded before reaching the cell surface.

Class III: CFTR protein reaches the cell surface but the ion channel doesn't open properly (gating defect).

Class IV: CFTR protein reaches the cell surface, but the ion channel conducts ions poorly (conductance defect).

Class V: Reduced quantity of CFTR protein at the cell surface.

2. Etiology

Changes to the CFTR gene called variants or mutations cause cystic fibrosis. CFTR makes a protein that works as an ion channel on the surface of a cell. Ion channels are like gates in a cell’s membrane that allow certain molecules to pass through. CFTR usually makes a gate for chloride ions, a type of mineral with a negative electrical charge. Chloride moves out of the cell, taking water with it, which thins out mucus and makes it more slippery. In people with CF, gene mutations in CFTR prevent this from happening, so the mucus stays sticky and thick[21-25]. This gene is the cystic fibrosis transmembrane conductance regulator (CFTR) gene. It affects the cells that make mucus, sweat and digestive juices. When the CFTR protein doesn't work as it should, the result is thick, sticky mucus in the respiratory, digestive and reproductive systems, as well as extra salt in sweat. Changes in the CFTR gene that cause CF are divided into several different groups based on the problems they cause. Different groups of gene changes affect how much CFTR protein is made and how well it works.

Risk factors

Because cystic fibrosis is a condition passed down in families, family history is a risk factor. CF occurs in all

races, but it's most common in white people of Northern European ancestry. Because it's less common in people who are Black, Hispanic, Middle Eastern, Native American or Asian, this might lead to a much later diagnosis[22-29].

Signs and symptoms

- Frequent lung infections
- Loose or oily poop (stool).
- Trouble breathing.
- Frequent wheezing.
- Frequent sinus infections.
- A nagging cough.
- Slow growth.
- Failure to thrive (inability to gain weight despite having a good appetite and taking in enough calories).

Atypical cystic fibrosis symptoms

- Chronic sinusitis
- Nasal polyps.
- Dehydration
- heat stroke from abnormal electrolyte levels
- Diarrhea
- Pancreatitis.
- Unintended weight loss.

3. Pathophysiology

CF is caused by a mutation in the CF trans membrane conductance regulator (CFTR) gene. The CFTR protein produced by this gene regulates the movement of chloride and sodium ions across epithelial cell membranes. When mutations occur in one or both copies of the gene, ion transport is defective, and results in a buildup of thick mucus throughout the body, leading to respiratory insufficiency, along with many other systemic obstructions and abnormalities. A combination of decreased mucociliary clearance and an altered ion transport allow for bacterial colonization of the respiratory tract, most commonly Pseudomonas, Haemophilus influenza, and Staphylococcus aureus. These pathogens cause an overwhelming inflammatory response. Ultimately, chronic infection and this repetitive inflammatory response can lead to airway destruction. The CFTR protein lets chloride to pass through the mucus producing cells after which the water follows and mucus becomes thin. However, defective CFTR results in thick and sticky mucus obstructing the pathways, leading to serious lung infections especially pseudomonas. There is massive neutrophil infiltration releasing elastase, which overpowers the lung antiproteases contributing to tissue destruction. Additionally, degranulating neutrophils release large quantities of nucleic acids and cytosol matrix proteins contributing to the mucus hyper-viscosity. In the GIT, the mucous plugs obstruct the canaliculi of pancreas and gall bladder duct preventing enzyme and bile flow into duodenum triggering malabsorption and digestion abnormalities. Additionally, Distal Intestinal Obstruction Syndrome (DIOS), which is distinctive to CF, may occur especially in those with pancreatic insufficiency[30-36]. This is characterized by ileocecal obstruction of inspissated intestinal contents. There is also imbalance of minerals in blood due to loss of extra salt in sweat leading to dehydration, arrhythmias, fatigue, weakness, heat stroke and rarely death.

Diagnosis

Newborn screening: Few drops of blood from the baby's heel. A lab checks the blood sample for higher levels than expected of a chemical called immunoreactive trypsinogen (IRT). IRT is released by the pancreas and may suggest CF. A newborn's IRT levels also may be high because of premature birth or a stressful delivery. For that reason, other tests may be needed to confirm a diagnosis of cystic fibrosis.

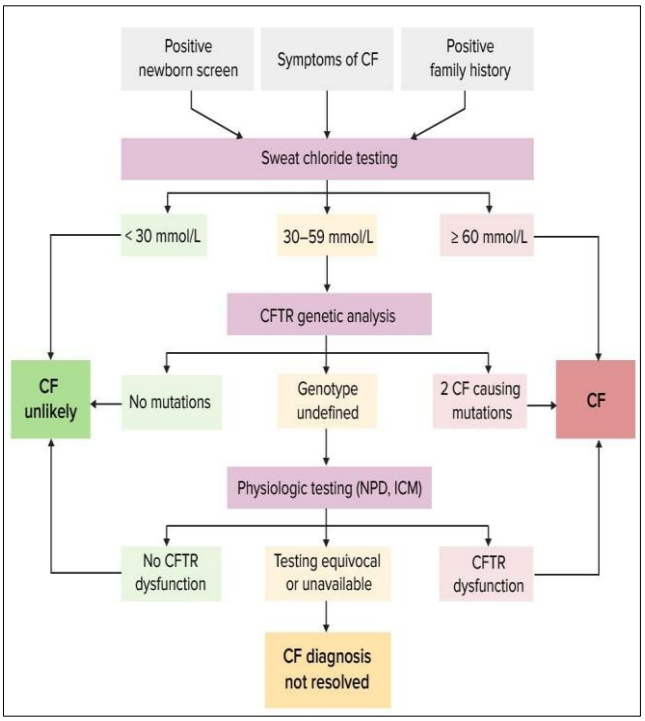

Fig.2: Diagnosis of Cystic Fibrosis

Sweat test:

To check if a baby has CF, a sweat test is done once the baby is at least 2 weeks old. A chemical that causes the skin to sweat is put on a small area of skin. Then the sweat is collected to test it and see if it's saltier than typical. Testing done at a care centre accredited by the Cystic Fibrosis Foundation helps ensure results that can be trusted. Genetic testing: Healthcare professionals also may recommend genetic testing to look for specific changes on the gene responsible for CF. Genetic testing may be used along with IRT levels to confirm the diagnosis[37-40].

4. Management of cystic fibrosis

There is no cure for cystic fibrosis, but treatment can ease symptoms, lessen complications and improve quality of life. Close monitoring and early, aggressive intervention is recommended to slow the worsening of CF over time. This can lead to a longer life. Managing CF is complicated, so it's best to get treatment at a center with a multispecialty team of doctors and other healthcare professionals trained in CF. They can evaluate and treat condition.

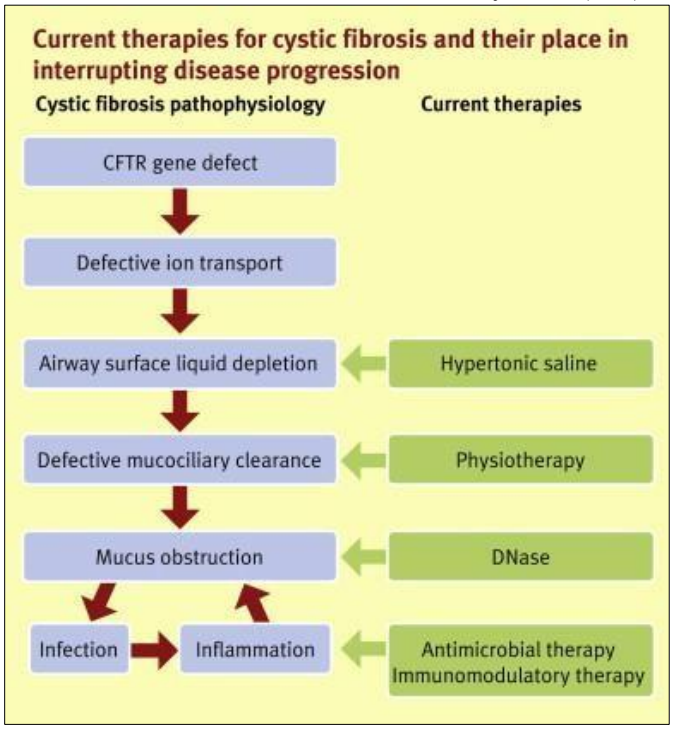

Fig.3: Current therapies for fibrosis

5. Prevention

- Patients with CF are cared for by different nurses when possible.
- Patients with CF are not allowed to be in the room of another patient with CF.
- Patients with CF are not allowed to be in communal areas, such as playrooms or the gym, at the same time.
- Patients with CF are cared for using Contact Precautions.
- Health care providers wear gowns and gloves while in the presence of a patient with CF.
- Patients are hospitalized in a single room.

The goals of treatment include:

- Preventing and controlling Infections that occur in the lungs.
- Removing and loosening mucus from the lungs.
- Treating and preventing intestinal blockage.
- Getting enough nutrition.

Therapy

Medicines that target gene changes and improve how the CFTR protein works.

These are called cystic fibrosis transmembrane conductance regulator (CTFR) modulators.

- Antibiotics
- Anti-inflammatory
- Mucus thinning medicines
- Stool softeners

Airway clearance techniques

Airway clearance techniques, also called chest physical therapy, can help get rid of mucus blocking the airways. It also can help to lessen infection and inflammation in the airways. Airway clearance techniques loosen the thick mucus in the lungs, making it easier to cough up. Surgery is also performed in critical conditions. Which include; nasal and sinus surgery, oxygen therapy, bowel surgery, lung transplant, liver transplant etc.

Complications

- Cardiovascular disease
- Diabetes
- Colorectal cancer
- Pneumonia
- Infertility
- Pneumothorax
- Malnutrition

Future therapies for management of cystic fibrosis

Molecular therapies for CF

The first therapeutic drug that has demonstrated significant clinical effects is Ivacaftor (Kalydeco®). Developed by Vertex Pharmaceuticals, it is the first of its kind to target the underlying gene defect. It works by modulating inefficient CFTR channels at the cell surface causing them to open. The main target is the G551D mutation, a Class III defect and the most prevalent gating mutation. Several completed studies highlight the significant improvements in percent predicted forced expiratory volume in one second ($ppFEV_1$) and other clinical outcomes in class III and IV mutations. The main drawback of Ivacaftor is that there is no supportive evidence that it is effective for those with a F508del mutation, which accounts for the majority of cases in Europe and North America. This Class II mutation causes ineffective protein folding. To target this, Vertex has designed Lumacaftor which acts as a chaperone during protein folding, increasing the number of efficient CFTR proteins at the cell surface. Evidence shows that as a monotherapy, it is ineffective at providing significant improvements in lung function, but may have potential for use in combination with other drugs. To fully combat the F508del mutation, Vertex has created co-formulated combinations aimed at maximizing the number of effective CFTR channels.

The first of these is Ivacaftor/Lumacaftor (Orkambi®), which utilizes the dual action of both drugs by helping the protein fold correctly and then modulating the channel after it has reached the cell membrane. Some Phase III studies involving Orkambi® have demonstrated significant improvements in $ppFEV_1$, although others have not identified such significance[41-43]. Another combination treatment is Tezacaftor/Ivacaftor (Symdeko® in US, Symkevi® in EU). Tezacaftor has been designed to facilitate the processing and trafficking of the CTFR protein towards the cell surface. In the two biggest completed Phase III studies, EVOLVE and EXPAND, the Tezacaftor/Ivacaftor group showed significant improvements in $ppFEV_1$, although a smaller study showed no significant increase in $ppFEV_1$.Vertex has recently produced a triple combination therapy consisting of a combination of Elexacaftor/ Tezacaftor/ Ivacaftor (Trikafta® in US, Kaftrio® in EU) that is used in a combination regimen with ivacaftor. Elexacaftor, like

Tezacaftor, is a CFTR corrector but binds to a different site and facilitates the cellular processing and trafficking of the CFTR protein to the cell surface. Significant reductions in sweat chloride concentration have also been shown compared to trials involving the other dual therapies.

Lung transplantation

Due to the absence of a cure, there may be a point where conventional treatments no longer work. In this scenario, medical staff may then have to decide whether a lung transplant is the most viable option. Other organs such as the liver or pancreas are also examined for possible transplantation, but only if necessary. There is no way to determine how long a patient will have to wait for a transplant. This would depend upon how the transplant team have evaluated their condition, but also on the availability of a donor that is a good match for the patient.

Emerging molecular therapies

There is ongoing development on a variety of new potentiators and correctors. Alongside this, entirely new classes of CFTR modulators are in development, primarily read-through agents and CFTR amplifiers. ABBV-3067 (formerly known as GLPG-3067) has completed Phase I clinical trials and preliminary results seem to indicate that the drug was well tolerated. Phase II clinical trials alone and in combination with ABBV-2222 (formerly known as GLPG-2222), a corrector that demonstrated advantages over the first-generation correctors Lumacaftor and Tezacaftor in preclinical studies.

ENaC as an alternative target

There is also potential to target other channels that contribute to the pathogenesis of CF. Due to the heavy role that ENaC plays in the dehydration of ASL in CF, there has been a focus on the potential for ENaC as a therapeutic target, for which there are no current therapeutics. Theoretically, the therapeutic inhibition of ENaC can reduce the hyperabsorption of sodium ions seen in CF, therefore rehydrating the ASL. A variety of strategies can potentially be used to target ENaC. One established strategy is to simply directly inhibit ENaC, for which particular attention is being given to BI 1265162, a highly potent ENaC inhibitor that has shown efficacy in preclinical testing. Phase I clinical trials also demonstrated that the molecule was safe and well tolerated. It is currently the only ENaC inhibitor in Phase II clinical trials, in which it must now demonstrate clinical efficacy

Gene delivery approaches

In contrast to a mutation specific approach, genetic manipulation has the potential to treat CF patients with mutations in any class. This strategy involves introducing the correct copies of *CFTR* DNA into the epithelial cells in the airways. There are two components that are required for this. The first is a normal copy of the *CFTR* gene, along with the required regulatory constructs, and the second is a transfer agent capable of efficient transfection.

The biggest challenge with this therapy will be how best to deliver the genetic material to the target cells. Lung cell turnover and the immune response have prevented many proposed vectors from delivering the *CFTR* gene into the epithelial cells. Focus was previously placed on viral approaches such as adenoviruses, adeno-associated viruses and Sendai virus, but these have proved ineffective due to the inefficient transduction of the *CFTR* gene.

Lentiviruses look more favourable, as they have shown sufficient capacity for a *CFTR* expression cassette and greater transducing capabilities. Additionally, unlike adenoviral vectors, lentiviral vectors display low immunogenicity and are more amenable to repeated dosing. In individuals with severe lung disease who may not respond to existing prescribed CFTR modulators, such as those with nonsense mutations, lentiviral vectors may offer certain advantages.

However, lentiviruses do not naturally possess the surface proteins capable of recognizing receptors on respiratory epithelia. To get around this, the UK CF Gene Therapy Consortium has created a simian immunodeficiency virus (SIV) pseudo typed with F and HN envelope proteins taken from a Sendai virus. Currently, the Consortium is trying to design a Phase I/IIa trial using nasal epithelium as a surrogate organ, which will allow for easy monitoring of gene expression and safety. As well as the lungs, *CFTR* is expressed in other organs and viruses may have potential in targeting these. This is because viruses can only deliver DNA to specific cell types. The subsequent positive effects in nutritional and metabolic requirements are likely to reduce clinical problems and significantly improve quality of life[44-47].

6. Conclusion

Cystic fibrosis remains a challenging multisystem disease requiring a comprehensive and individualized care approach. Significant progress in CFTR modulators, gene therapy, and various surgical interventions has greatly improved the management and prognosis of CF patients. Pulmonary rehabilitation, incorporating exercise, airway clearance, and psychological support, plays a crucial role in maintaining lung function and enhancing quality of life. Despite these advancements, ongoing research and personalized treatment strategies are essential to further optimize outcomes and extend survival for individuals living with cystic fibrosis. Advances in screening and treatment have greatly improved patients outcomes, allowing many people with CF to live longer and achieve a better quality of life than in the past. CF treatment usually depends on the identification of the underlying genetic defect. Although the clinical outcome is mostly similar, CF patients differ from each other in terms of mutation type and disease progress. The mutation-specific treatment and personalized therapy was an achievable goal for CF. CFTR modulators have become a remarkable step in terms of personalized treatment in CF. The gene therapies will continue to be an important strategy for CF as well as other genetic diseases, and organoid-based regenerative medicine designed with gene engineering technologies can provide an enormous innovation for CF therapy in the next years.

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Source of Support: Nil.