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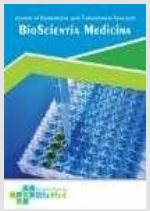

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Cystic Fibrosis Lung Disease: A Narrative Literature Review

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A B S T R A C T

Cystic fibrosis (CF) is caused by mutations in autosomal recessive genes that code for proteins cystic fibrosis transmembrane conductance regulator (CFTR) which is located on chromosome seven. The CFTR protein under normal conditions acts as a chloride channel and helps the movement of sufficient electrolytes and water across the membrane. Mutations in CFTR cause abnormalities in chloride ion transport through epithelial cells and impaired sodium and water transport resulting in viscous secretions with low water content. This thick and sticky secretion will inhibit the normal function of various organs, although pulmonary complications are the most common cause of death. Cystic fibrosis has wide genotypic and phenotypic variations. There are six categories of mutations based on their effect on the CFTR protein, where these categories are not only used to predict the phenotype but also to determine better therapeutic strategies based on the identified mutations.

1. Introduction

Cystic fibrosis is a genetic disease that is inherited in an autosomal recessive manner and is caused by mutations in the CFTR gene. Mutations in CFTR will disrupt chloride secretion, sodium reabsorption, and water transport, causing mucus hyperconcentration and decreased mucociliary clearance.[1] Cystic fibrosis can affect most organs, such as the lungs, pancreas, liver, and intestines, and is characterized by chronic bacterial infections of the respiratory tract, exocrine pancreatic insufficiency, intestinal dysfunction, and abnormal sweat gland function.[1,2] Data from Cystic Fibrosis Foundation (CFF) In 2022, there will be nearly 40,000 children and adults living with CF in the United States, and an estimated 105,000 people will have been diagnosed with CF in 94 countries.[3] The prevalence of CF varies across the fifty United States and the District of Columbia, ranging from 1.2/100,000 people in Hawaii to 24.6/100,000 people in Vermont. Cystic fibrosis affects more than 30,000 people in the United States and is one of the most common genetic diseases, especially in Caucasians.[3] Epidemiological data on CF in Indonesia itself is still not available at this time.

Long-term problems with CF in the airways occur because the CFTR protein becomes dysfunctional, causing the mucus to become thick and sticky and blocking the airways, making them more susceptible to infection.[1,2] Impaired mucus secretion can cause endobronchial infection and an excessive inflammatory response, resulting in severe bronchiectasis, fibrosis, and, ultimately, respiratory failure.[1] CF symptoms arise due to infectious and inflammatory processes in the lungs and digestive system disorders such as prolonged coughing, shortness of breath, excessive production of thick

phlegm, diarrhea, malnutrition, and disorders of the hepatobiliary system.[4] Cystic fibrosis is a genetic disease that cannot be cured. CF management only aims to treat symptoms and prevent further complications.[5,6] Median predicted survival among individuals born with CF in 2020 increased compared with the previous year when more than half of patients with CF living in the United States were adults.[7] This improvement in survival is due to earlier diagnosis, better understanding of the natural course of the disease, and better treatment.[6]

Cystic fibrosis

Cystic fibrosis is an autosomal recessive inherited disease caused by mutations in genes that code for the protein CFTR, which is located on chromosome seven (Figure 1).[2] The CFTR protein forms chloride channels that are important for efficient mucus transport. Mutations in CFTR will disrupt chloride secretion, sodium reabsorption, and water transport, causing viscous secretions and low water content. Thick and sticky secretions will inhibit the normal function of various organs, including the lungs.[1,2]

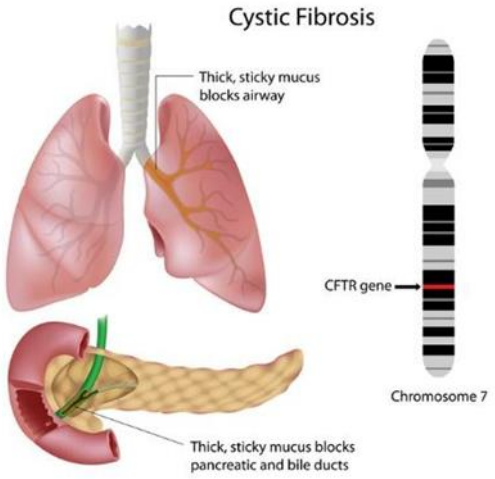

Figure 1. CFTR gene mutations in cystic fibrosis.

Epidemiology

Cystic Fibrosis can affect people from every racial and ethnic group, being most commonly found in Caucasians. According to data from the Cystic Fibrosis Foundation Patient Registry (CFFPR) in 2020, 91.6% of individuals included were of Caucasian descent, 3.5% were of African American descent, 2.3% were of other races, and 2.1% were Hispanic, 0.5% were Asian. About 1 in 25 people of European descent and one in 30 Caucasian Americans are carriers of the CF gene mutation. Ireland has the highest prevalence of CF in the world, with an incidence rate of 1:1353 individuals.[3,8] Cystic fibrosis is a genetic disease lethal in the white population. CF mortality rates vary with age, approximately 1-2% per year overall.[6] Newborns in the 1950s with CF rarely survived to the age of 1 year, but in the last 20 years, developments in knowledge and improvements in clinical care for CF patients have caused life expectancy for patients with CF to increase to 37 years and newborns with CF today predicted to live up to 50 years or even more.[3]

Etiology and risk factors

The etiology of CF is genetic, inherited in an autosomal recessive manner. The gene responsible for CF was identified in 1989 as the CFTR gene, which is located on the long arm of chromosome seven. Previous research has found more than 1,700 different mutations in the CFTR gene that can cause CF.[2] The CFTR protein is a cyclic adenosine monophosphate

(cAMP) regulated chloride channel, which has a molecular weight of 180 kDa when fully glycolized and is a single polypeptide chain containing 1,480 amino acids.[2,7] CFTR has multiple and complex functions in the lungs, sinuses, sweat glands, and epithelium of the reproductive, intestinal, liver, and renal organs. When CFTR function is impaired, organ-specific pathology occurs in all but the kidneys.[2,9] The risk factor for developing CF has two parents who carry the abnormal gene, which will give birth to children with CF at 25%, healthy at 25%, and 50% are carriers, as seen in Figure 2.[8]

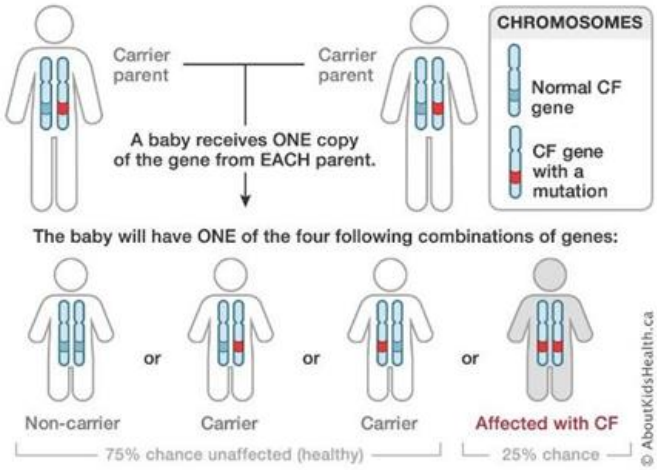

Figure 2. Genetic risk factors for cystic fibrosis.

Factors that influence the severity of CF are:[10] Genetic factors: namely, class I, II, and III gene mutations are generally more severe than class IV, V, and VI mutations. Environmental and lifestyle factors: CF patients need to consume large amounts of calories to maintain their weight and growth. Physical activity and not smoking are also important to help maintain lung health, as well as alcohol consumption needs to be avoided so as not to worsen liver problems. Age factor: The course of CF disease worsens with increasing age, and lung function will decrease every year.

Pathogenesis

Cystic fibrosis is caused by mutations in the CFTR protein located on chromosome seven.[2] The CFTR protein, under normal conditions, acts as a chloride channel and regulates the movement of sufficient electrolytes and water across the membrane.[8] Secretions from exocrine glands in the body (sweat, tears, saliva, digestive juice, and mucus) are normally thin and slippery.[6] Mutations cause abnormalities in chloride ion transport through epithelial cells and impaired sodium and water transport, resulting in viscous secretions and low water content.[10,11] CFTR's function, apart from being related to chloride channels, also plays a role in many other regulations, including inhibition of sodium transport through epithelial sodium channels, regulation of adenosine triphosphate (ATP), regulation of intracellular vesicle transport, acidification of intracellular organelles, and inhibition of endogenous calcium activation by chloride channels. CFTR is also involved in bicarbonate-chloride exchange. Deficiency in bicarbonate secretion causes low mucin solubility and results in mucin aggregation in the lumen.[10,12] The fully processed form of CFTR is found in the plasma membrane of normal epithelium.[2] There are 6 classes of mutations based on their effect on the CFTR protein, namely class I mutations, which result in defects in

protein production. Class II mutations for defects in maturation and processing protein, class III mutations for channel regulation defects, class IV mutations for changes in channel conductance, class V mutations for changes in protein stability, and class VI mutations associated with increased turnover of CFTR on the cell surface (Figure 3).[2,13]

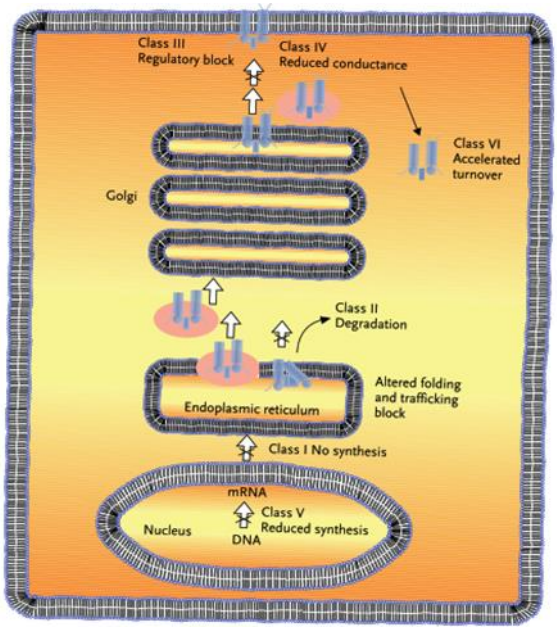

Figure 3. CFTR Mutation classes.

CFTR mutations, more than 2,000 different mutations have been reported to date. The F508del mutation is the most common (70% of all mutations).[13] Biochemical studies indicate that the F508del mutation causes processing defects and intracellular degradation of the CFTR protein. The absence of CFTR at the plasma membrane is central to the molecular pathophysiology of the F508del mutation and class I-II mutations. Classification of mutational defects and specific effects on CF are shown in Table 1.[2]

Table 1. CFTR mutation defects and their specific effects.[2]

Class	Mutation defects	Specific effects of mutation classes
I	Protein production defects	CFTR chloride channel function is absent
II	Defects in maturation and processing of protein	CFTR is destroyed in cells, CFTR does not reach the cell surface
III	Channel regulation defects	CFTR reaches the cell surface but is not well exposed to chloride transport
IV	Changes in channel conductance	CFTR function is poor, and chloride conduction is impaired
V	Changes in protein stability	decreased CFTR production
VI	increased turnover of CFTR on the cell surface	CFTR is functional but unstable on the cell surface and is removed and degraded

Pathophysiology

Efficient mucociliary clearance is essential for respiratory health.[6] The mucociliary cleansing apparatus consists of 2 hydrogels, namely the mucous layer and the periciliary layer. Effective mucociliary movement depends on good hydration of fluid at the surface of the airways. Mucociliary clearance will be impaired by abnormalities in ciliary movement or by changes in the composition of the mucus.[6,13] The airway epithelium in healthy people can secrete or absorb ions and water to maintain normal airway surface hydration.[6] The higher osmotic pressure of the periciliary layer in healthy people ensures that the airways are well hydrated, providing proper lubrication for ciliary activity and movement of the overlying mucus layer. A well-hydrated mucus layer will allow efficient transport from the distal airway to the trachea.[14] Abnormal concentrations of mucus in the airways of patients with CF reflect primary abnormalities of ion and water transport in the airway epithelium.[15] The airway epithelium in CF is susceptible to fluid hyperabsorption due to defects in CFTR-mediated secretion of chloride and bicarbonate anions. This abnormality in fluid absorption in the airway epithelium increases the osmotic pressure in the mucus layer, which will exceed the pressure in the pericillary layer. This condition will drain the airway surface fluid and cause the mucus to become hyper-concentrated (dehydration), disrupting mucus transport and mucus adhesion to the airway surface.[15] Increased mucin secretion, which is the main component of airway mucus, causes the formation of endobronchial mucous plaques.[15] This mucus plaque in the airways will allow bacterial colonization of the airways. The most common bacteria are *Pseudomonas aeruginosa, Haemophilus influenza,* and *Staphylococcus aureus.*[16] Based on the CFF report in 2016, the prevalence of pathogens that cause endobronchial infections in CF patients is the most common *Pseudomonas aeruginosa* (55% of isolated) followed by *Staphylococcus aureus, Haemophilus influenza, Achromobacter xylosoxidans* and several other bacteria.[14,16] Endobronchial infections that occur will induce an excessive inflammatory response characterized by increased levels of airway neutrophil elastase. This situation also causes excessive stickiness and cohesiveness of mucus in CF patients.[15,17] Repeated infections and chronic inflammation will result in damage to the structural integrity of the airways and lead to the development of bronchiectasis. This airway obstruction and recurrent bacterial infections are common features of CF lung disease.[2]

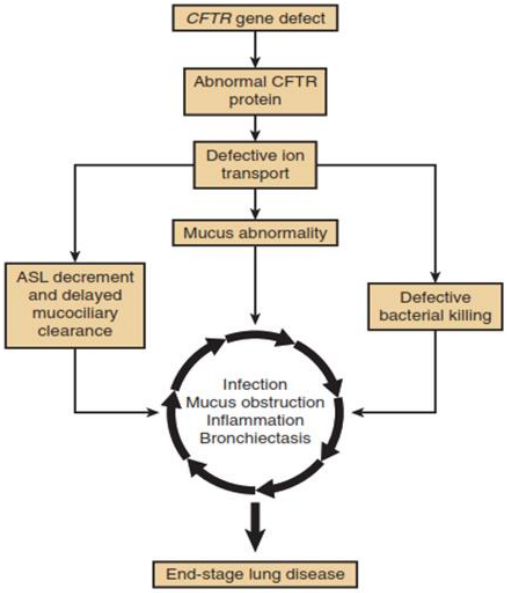

Figure 4. Pathophysiology of cystic fibrosis lung disease.

Diagnosis

The diagnosis of CF is based on suspicion, such as clinical manifestations, family history, or through newborn screening programs. Early detection through newborn screening leads to early recognition of the disease before the clinical characteristics become apparent. Cystic Fibrosis Foundation (CFF) published comprehensive diagnostic guidelines for infants and adults with suspected CF in 2008.[3,6]

Table 2. CF diagnosis criteria based on clinical phenotype and CFTR functional abnormalities.[6]

A diagnosis of CF is confirmed by the presence of:
Corresponding phenotypic clinical picture (one): Chronic sinopulmonary disease Chronic cough and sputum production by persistent infection with typical pathogens (*Staphylococcus aureus, Pseudomonas aeruginosa*, other gram-negative organisms Blood flow obstruction Chronic chest radiographic abnormalities sinus disease; nasal polyps Gastrointestinal and nutritional disorders Exocrine pancreatic insufficiency Recurrent pancreatitis Fat-soluble vitamin deficiency Meconium ileus; DIOS Obstructive azoospermia in men
Plus Laboratory evidence of CFTR dysfunction (one or more of the following): Sweat chloride increases Disease-causing mutations in the CFTR gene in both alleles Abnormalities in bioelectrical characteristics (potential differences) in the nasal epithelium Abnormal short-circuit current measurements in the intestine ex vivo

Cystic Fibrosis is diagnosed when a person has clinical manifestations of the disease and evidence of CFTR dysfunction. CFTR function tests are not always performed in this order but rather hierarchically to establish a diagnosis of CF. All individuals diagnosed with CF should undergo sweat testing and CFTR genetic analysis. Sweat chloride examination should be considered first, followed by genetic analysis of CFTR and then physiological examination of CFTR, as in the algorithm in Figure 5.

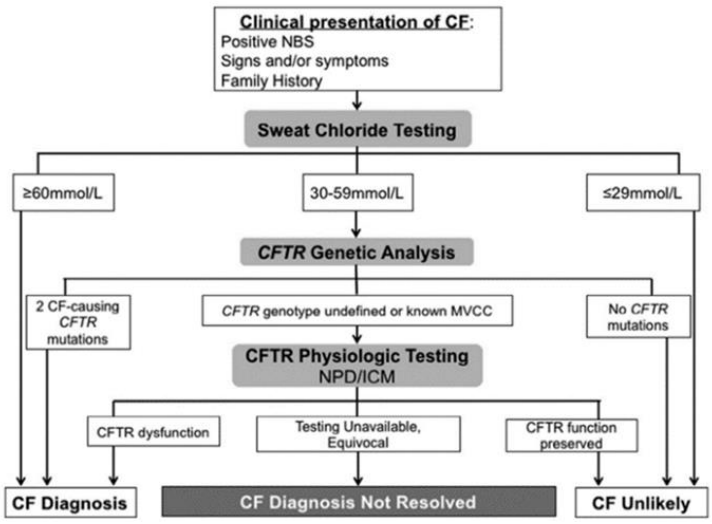

Figure 5. Cystic fibrosis diagnostic algorithm.

Sweat test

The most common presentation of CF is very high concentrations of sodium and chloride in sweat. Measurement of chloride concentration is recommended for clinical trials. The sweat test method currently used is the quantitative pilocarpine iontophoresis test (QPIT). Accurate results require 50-100 mg of sweat. The collection location must be from one part of the body and cannot be obtained from multiple locations.[17-20] This test can be inaccurate in very small babies and if the volume being examined is inadequate. The macro ductus collection method supports analysis with smaller sweat volumes. If collection is carried out in this way, sweat must be stimulated with an electrode using an inducer for 5 minutes. The minimum acceptable sample amount is 15 µL in 30 minutes.[7] Chloride and sodium levels in sweat vary with age, but values of >60 meq/L in CF sufferers can differentiate them from sufferers of other lung diseases.[3] For babies aged 3 months or less, chloride levels of 30-60 mEq/L are said to be on the border and require a repeat test because levels of 30-60 mEq/L can be within the range of sufferers and carriers. The sweat test should be performed more than once with a gap between tests of several weeks and should be repeated at the first positive test result or the first negative result with positive CF manifestations.[7]

Thoracic X-ray

Radiological features in people with mild pulmonary symptoms include mild hyperinflation and minimal peribronchial thickening. Radiographic findings become more markedly abnormal with the severity of the disease. Peribronchial thickening, especially in the upper lobes of the lung, occurs early in the course of the disease and then progresses to all lobes in later stages. Other features found in CF patients include ring shadows, cystic lesions, and nodular densities, such as bronchiectasis and atelectasis. The central pulmonary arteries often enlarge in the middle stages of the disease. Pulmonary artery dilatation and right ventricular hypertrophy are associated with cor pulmonale.[19]

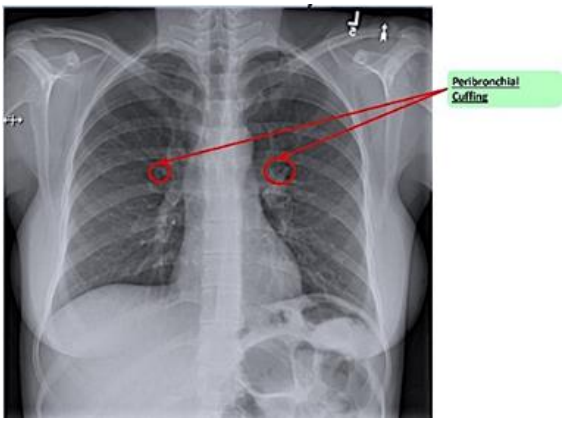

Figure 6. Chest X-ray image of CF, visible peribronchial cuffing.

High-resolution computed tomography (HRCT)

HRCT examination is not a routine diagnostic tool but is more sensitive than plain radiography. Common abnormalities seen in CF are bronchiectasis, peribronchial thickening, mosaic perfusion, air trapping, and mucus plug (Figure 7). Early bronchiectasis is easily detected on CT scans even when routine chest X-rays are normal. CT scan abnormalities can be detected before changes in pulmonary function tests.[19]

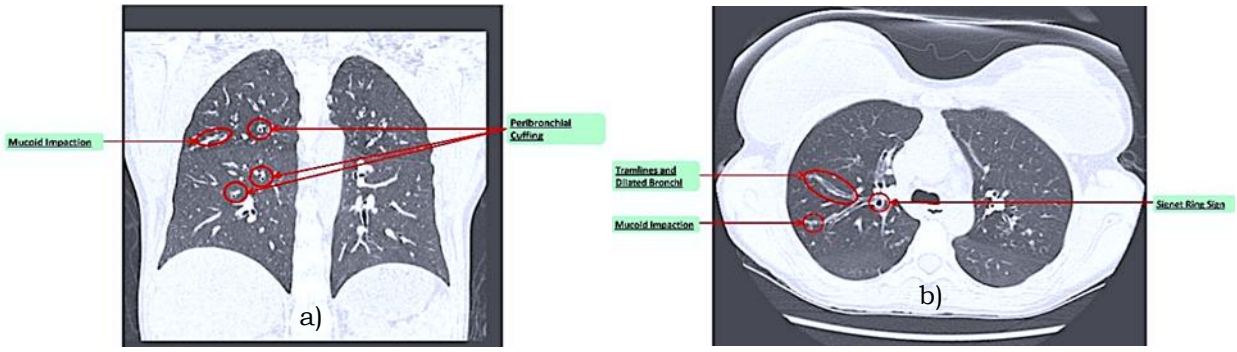

Figure 7. CT-scan image of CF a) Coronal section b) Axial section looks like peribronchial cuffing and mucoid impaction.

Genotyping

The genotyping examination is carried out using polymerase chain reaction (PCR) techniques, and findings of CFTR mutations related to clinical manifestations can be used to establish a diagnosis. This test can detect >98% of mutations that cause CF disorders in caucasians.[20]

Spirometry

Standard spirometry is not accurate for use in patients under 5 years of age. A replacement forced oscillation technique (FOT) that uses an impulse oscillometry system (IOS) can be used. The airway resistance measured by IOS corresponds to the airway resistance measured by body plethysmograph, and this technique has been successful in diagnosing lung function in children with CF.[7] Spirometry examination at the initial stage showed normal FEV1 results. FEF results of 25-75% decrease indicate small airway involvement; in line with worsening, FEV1 also decreases, and with hyperinflation, total capacity also increases. In end-stage patients, extensive lung changes accompanied by fibrosis are described by a decrease in total capacity and vital capacity.[7]

Bronchoalveolar lavage (BAL) and sputum microbiology

Airway inflammation is the main characteristic of CF sufferers. Dasenbrook's 2010 study showed inflammation can occur even in the absence of infection. Bronchoalveolar lavage shows high levels of neutrophils, and microbiological examination generally shows germs *Pseudomonas aeruginosa,* which supports the diagnosis of CF in atypical patients.[14]

Therapy

Cystic fibrosis has wide genotypic and phenotypic variations. Various studies have attempted to confirm the correlation between genotype and phenotype so as to not only clarify the pathogenesis but also select better therapeutic strategies based on the identified mutation classes. The drugs given to CF patients aim to suppress the occurrence of secondary manifestations.[15] Sports interventions carried out to improve health, such as jogging, gymnastics or light exercise, can routinely improve the body's immune system to help overcome CF. Exercises used in CF patients include a six-minute walking exercise. Six minutes of walking exercise is considered a very important measure during preparation for lung transplantation in CF patients.[20] Physiotherapy is one of the treatments for cleaning airway secretions in CF patients. The most common airway clearance technique is through postural drainage. Assessment of the effectiveness of physiotherapy is based on measuring sputum volume, lung function by spirometry, frequency of hospitalization, and quality of life.[23]

The anti-inflammatories used for CF patients are non-steroidal anti-inflammatories, especially ibuprofen. High doses of ibuprofen can slow lung disease in children and prevent worsening lung function.[15] N-acetylcysteine is a mucolytic with a

mechanism of increasing intracellular levels of the antioxidant glutathione, which can protect tissue from damage caused by neutrophils. N-acetylcysteine is given orally in high doses of 0.6 to 1.0 g three times a day for a month. These high doses have the potential to overcome the inflammation that occurs in CF.[9,15] Dornase alfa meghidrolysis deoxyribose nucleic acid (DNA), which is in mucus or phlegm and reduces the viscosity of mucus or phlegm so that it can increase airway clearance, thereby reducing exacerbations and improving lung function.[9,15] Inhalation therapy for CF uses hypertonic saline solution. This therapy is recommended for patients aged 6 years and over. The mechanism of action of the hypertonic saline solution increases airway surface hydration, induces mucus discharge, and improves mucociliary function so that it can improve function, reduce exacerbations, and improve quality of life.[20] The newest inhalation therapy uses hypertonic xylitol solution, where hypertonic xylitol solution for the treatment of CF exacerbations in hospitalized patients is well tolerated and has the same effectiveness as hypertonic saline solution.[15,19] Antibiotics in CF are used as prophylaxis, exacerbation, suppression, and eradication therapy. Pathogenic bacteria vary according to age and are found in the lungs of CF sufferers. The most common bacteria are found in infancy: *Staphylococcus aureus*, which increases in the child's time, and *Pseudomonas aeruginosa*, Most common in adolescence and adulthood. If left untreated, these opportunistic gram-negative bacteria will become chronic and can reduce or worsen lung function. CF therapy varies by country.[16] European countries recommend the use of anti-staphylococcal agents such as flucloxacillin, which can reduce pathogens *Staphylococcus aureus*. The most commonly used CF therapy in America is Tobramycin. Tobramycin is given at a dose of 300 mg or by inhalation at a dose of 112 mg twice a day and can also be given intravenously at a dose of 10 mg/kg/day. Other therapies, such as Aztreonam, can also be given, which can reduce *P. aeroginosa* pathogens and significantly improve lung function and body weight in patients. Amikacin liposomal formulation as a new alternative. This formula has a mechanism similar to tobramycin, which can improve lung function.[16,19]

CFTR therapy

There are six classifications of CFTR mutations, including class I mutations causing reduced production of functional CFTR as a result of premature termination codon (PTC). Class II mutations cause protein misfolding and failure trafficking to the cell surface. Class III mutations, especially gating mutations, fail to open response to intracellular signals. Class IV mutations cause a decrease in ion conduction. Class V mutations occur in splicing, which causes a decrease in the amount of CFTR protein. Class VI mutations decrease CFTR stability, which results in reduced patient survival.[16,19] A better understanding of CFTR mutations helps identify risk factors and can lead to therapies against several classes of mutations.[10] Pharmacological agents corrector is a term for agents that can correct protein processing and its expression. Meanwhile, agents who can have a positive influence on CFTR channel gating are often referred to as potentiators.[12,15]

The research concludes that the intracellular trafficking of F508del CFTR can be repaired with a number of pharmacological agents called correctors. Corrector is a term for agents that can correct protein processing and its expression. 4-phenylbutyrate agents are an example corrector, which, in high concentrations, has been proven to be able to improve intracellular trafficking in CF epithelial cells. Examples of corrector drugs are Lumacafter and Tezacaftor.[15,22] This therapy has the main target, namely the CFTR mutation, where the glycine has been replaced by aspartic acid at position 551 (G551D) and disrupts channel gating. The use of Ivacaftor can significantly improve FEV1 (10% absolute increase), 55% less chance of pulmonary exacerbations, increased body weight, and quality of life. Clinical trials have been carried out on children aged 2 to 5 years, and this drug is safe and can improve the CFTR biomarker. An example of a potentiator drug is

Ivacaftor.[22] Correctors such as Lumacafter and Tezacaftor help in processing and trafficking proteins to the cell surface, and Ivacaftor overcomes the gatting deficiency. The corrector acts by complementing and modifying primary defects in assembly errors, processing errors, and F508del CFTR mutations. When the corrector goes to the cell surface, the potentiator functions as a pathway opener to the CFTR channel. The newest combination therapy, namely ivacaftor plus tezacaftor plus lumacaftor, is a recommendation for current CF treatment so that combination therapy can improve FEV1 for CF patients, reduce exacerbations, and improve the patient's quality of life.[12,22] End-stage CF patients are recommended to undergo lung transplantation therapy. A retrospective study said that CF patients who had undergone lung transplantation therapy had good long-term survival, with the average survival being up to ten years. Lung transplant therapy can significantly reduce mortality in end-stage CF patients.[23]

2. Conclusion

Cystic fibrosis is a genetic disease caused by genetic mutations that form the CFTR protein located on chromosome seven and is found to be a multisystem disease. This disease is characterized by chronic bacterial infection of the respiratory tract, which will ultimately cause bronchiectasis and respiratory failure, exocrine pancreatic insufficiency, intestinal dysfunction, abnormal sweat gland function, and urogenital dysfunction. Most of the symptoms of CF are caused by thick, sticky mucus. Diagnostic examinations in CF cases include laboratory examinations, radiological examinations, and culture examinations. Management of CF cases is non-pharmacological, medical, and surgical.

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