IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 5, Issue 3, January 2025

A Review on Cystic Fibrosis Disease

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Abstract: *Cystic fibrosis is a monogenic disease considered to affect at least 100 000 people worldwide. Mutations in CFTR, the gene encoding the epithelial ion channel that normally transports chloride and bicarbonate, lead to impaired mucus hydration and clearance. Classical cystic fibrosis is thus characterised by chronic pulmonary infection and inflammation, pancreatic exocrine insufficiency, male infertility, and might include several comorbidities such as cystic fibrosis-related diabetes or cystic fibrosis liver disease. This autosomal recessive disease is diagnosed in many regions following newborn screening, whereas in other regions, diagnosis is based on a group of recognised multiorgan clinical manifestations, raised sweat chloride concentrations, or CFTR mutations. Disease that is less easily diagnosed, and in some cases affecting only one organ, can be seen in the context of gene variants leading to residual protein function. Management strategies, including augmenting mucociliary clearance and aggressively treating infections, have gradually improved life expectancy for people with cystic fibrosis. However, restoration of CFTR function via new small molecule modulator drugs is transforming the disease for many patients. Clinical trial pipelines are actively exploring many other approaches, which will be increasingly needed as survival improves and as the population of adults with cystic fibrosis increases. Here, we present the current understanding of CFTR mutations, protein function, and disease pathophysiology, consider strengths and limitations of current management strategies, and look to the future of multidisciplinary care for those with cystic fibrosis.*

Keywords: Cystic fibrosis

I. INTRODUCTION

Cystic fibrosis (CF); is an autosomal recessive multi-system condition characterized by recurrent respiratory tract infections, pancreatic malabsorption and male infertility. It is caused by defects of the gene that encodes the CF transmembrane regulator (CFTR); a glycoprotein found on epithelial cells throughout the body. CFTR is a chloride channel that regulates fluid and electrolyte transport both directly and through interactions with other apical membrane proteins involved in conductance pathways. In the lungs, defective CFTR results in depletion of the airway surface liquid (ASL) height and impairment of the mucociliary transport mechanism.[1]

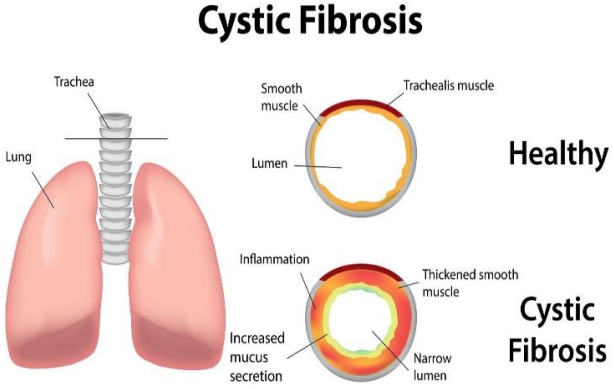

Figure no.1

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ISSN (Online) 2581-9429
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Cystic fibrosis is an inheritedlife-threatening disorder that damages the lungs and digestive system.

Cystic fibrosis affects the cells that produce mucus, sweat and digestive juices. A genetic defect in the cystic fibrosis transmembrane conductance regulator(CFTR) protein disrupts transport of salts into and out of the cell, resulting in a thick, sticky mucus.

The most prominent effect of the disease is obstruction of airways in the lungs and loss of defensive action against some bacteria leading to infection.

The disease affects many other tissue and organs of the body, and leads to a significantly shortened lifespan.

CF is the most common inherited disease of whites, occurring in approximately 1 in 3,000 live births sin the United States and Europe and resulting from mutations in the **CF** transmembrane conductance regulator (CFTR).[2]Prevalent **CF** pathogens include Staphylococcus aureus and Pseudomonas aeruginosa; later in the disease course, some patients become infected with more unusual and difficult to treat pathogens like Burkholderia cepacia, Achromobacter xylosoxidans, Stenotrophomonas maltophilia and mycobacteria. However, complications can occur in nearly every organ and increase with age, including: liver disease, **CF**-related diabetes, nasal polyps, intestinesobstructions, haemoptysis and allergic bronchopulmonary aspergillosis and many more.[3]

Lower airway mucus accumulation is a key component of cystic fibrosis (CF) lung disease and is thought to be directly related to the impaired function of the CF transmembrane regulator (CFTR) protein. The limited ability for epithelial cells to secrete chloride (Cl) through the cAMP stimulated chloride channel CFTR, in combination with excessive absorption of sodium (Na+), results in a decreased water content of the periciliary fluid. The lack of a supporting fluid layer causes respiratory cilia to collapse with consecutive breakdown of mucociliary transport.[4] This leads to mucus retention, which is thought to favor chronic airway infection with Pseudomonas aeruginosa and other Gram-negative organisms. CF lung disease is also characterized by neutrophilic airway inflammation and together, infection and inflammation lead to bronchiectasis,progressive pulmonary function decline and eventually respiratory

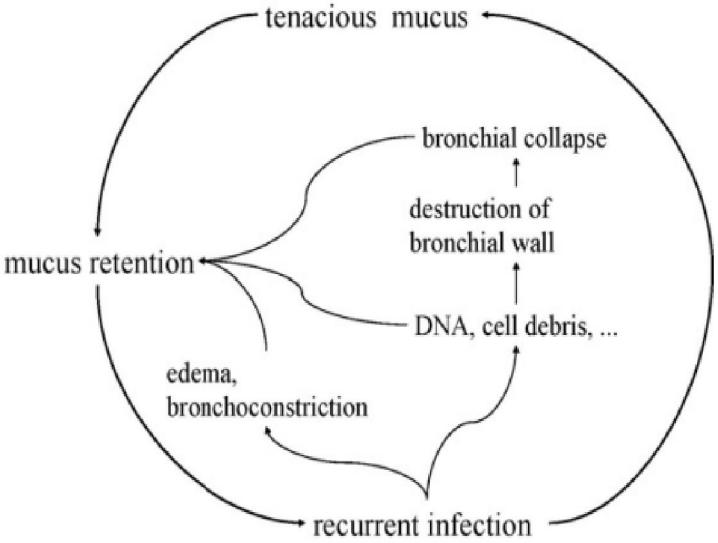

Figure.No.2

(Vicious cycle of tenacious mucus retention and recurrent infections.)

CAUSES OF CYSTIC FIBROSIS.

1) Cystic fibrosis (CF) is caused by mutations in cystic fibrosis transmembrane conductance regulator (CFTR). It leads to severe morbidity and mortality from lung disease that is characterized by small airway obstruction due to mucus accumulation, inflammation, repeated infections, and bronchiectasis.

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2) Cystic fibrosis is caused by impaired ion transport due to mutated cystic fibrosis transmembrane conductance regulator, accompanied by elevated activity of the amiloride-sensitive epithelial Na+ channel(Enac).
3) Respiratory failure is the most common causes of death.[5]

PATHOPHYSIOLOGY OF CYSTIC FIBROSIS.

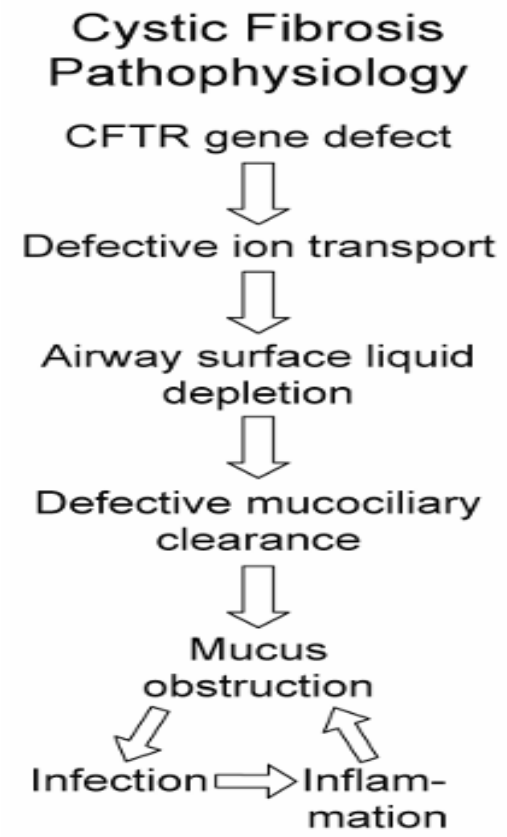

Figure. No.3 (Cascade of pathophysiology in cystic fibrosis lung disease.)

Translate into new and potentially more causative treatment approaches. As in many areas of research, more de tailed studies of the molecular structure and function of the CF transmembrane regulator (CFTR) protein have shown us that its functions and interactions may be much more complex than initially anticipated. Therefore, while many aspects of CF pathophysiology have been clarified, there are still multiple areas of ongoing debate that need to beclarified. Resolving these controversies will be important to identifying the most promising treatment strategies. This review will summarize the current knowledge on how CF gene mutations cause disease and will focus largely on the respiratory tract. In addition, new therapeutic targets and compounds that have arisen from this improved understanding will be discussed.

Abrief and simplified cascade of the current concept of howlung disease evolves in CF is summarized in Figure 1. The CF gene defect leads to an absent or malfunctioning CFTRprotein, which results in abnormal chloride conductance on the apical membrane of the epithelial cell. In the lung this results in airway surface liquid depletion and, since airway surface liquid is essential to support ciliary stability and functioning, ciliary collapse and decreased mucociliary transport. The consequence of this is a vicious circle of phlegm retention, infection, and inflammation. Though this broad concept is largely undisputed, controversies exist on multiple aspects of this cascade. Topics that have specific relevance to the development of new therapies.

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DIAGNOSIS OF CYSTIC FIBROSIS

Sweat chloride test:

Sweat chloride testing is the main diagnostic test for cystic fibrosis with high sensitivity (99%) and specificity (93%) and has established guidelines for technical quality and accuracy at specialized cystic fibrosis centers.[6]
demonstration of high sweat chloride values in a clinical setting or identification of two mutations or demonstration of high transnasal potential difference.

Mutation analysis:

Cloning of the gene responsible for CF and identification of disease-producing mutations have raised the possibility that DNA testing may be substituted for the sweat test in certain circumstances. Considerable evidence for the deleterious consequences of a number of CF mutations has accumulated. Alterations in the CFTR gene, designated as CFcausing mutations, should fulfill at least one of the following criteria. The mutation has been shown to: (1) cause a change in the amino acid sequence that severely affects CFTR synthesis and/or function, (2)introduce a premature termination signal (insertion, deletion nonsense mutations), (3) alter the "invariant" nucleotide site.

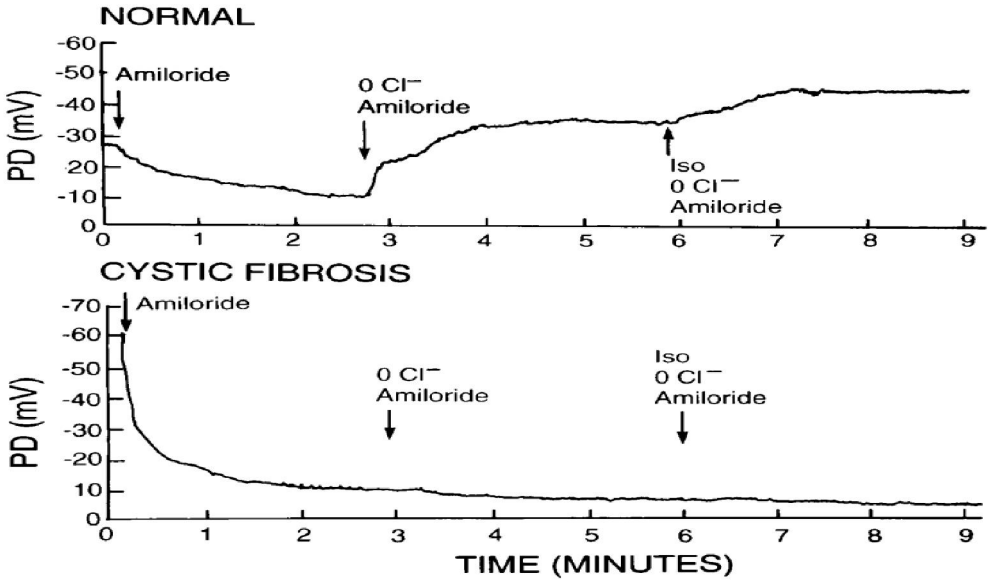

Figure.4. Nasal PD tracing in a normal subject (top panel) and a patient with CF (bottom panel). Tracings illustrate response of PD to perfusion with amiloride (10–4 mol/L), addition of a Cl– -free solution (gluconate buffer) to amiloride, and addition of isoproterenol (10–5 mol/L) to the Cl– -free solution containing amiloride (see text)

Ancillary tests to assess the patient's phenotype: In patients who initially have an "atypical" phenotype, it is important to carry out a comprehensive clinical, radiographic, and laboratory evaluation (Table 1) for features known to be consistent with the CF phenotype or for alternative diagnoses.

Assessment of Exocrine Pancreatic Function: The vast majority of patients with CF, including those without obvious steatorrhea, have abnormal pancreatic acinar and ductular function.[7]The exocrine pancreas has a large functional capacity; more than 98% of the pancreatic capacity to secrete enzyme must be lost before signs and symptoms of maldigestion are evident.[8]Thus there is no "ideal" test. Direct tests are highly specific and capable of evaluating the entire range of pancreatic function. They are of great value for identifying aspects of pancreatic fluid and anion secretion in patients with a questionable diagnosis of CF. However, these tests require special skill to perform and interpret, and their invasive nature precludes their use for routine clinical purpose.

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DRUG PROFILE OR TREATMENT.

Long-term Therapies:

For patients with cystic fibrosis, at least quarterly visits with a specialized, multidisciplinary team, including physicians, nurses, social workers, anddietitians, are recommended tomonitor for disease progression and treat multiorgan manifestations.[9]

Annual screening for psychosocial health concerns is recommended in children aged 12 years or older.[10] Monitoring for comorbidities includes annual oral glucose tolerance testing (10 years) for cystic fibrosis–related diabetes,[11] dual-energy x-ray absorptiometry scanning every 2 to 5 years (>8 years) for bone density, and colonoscopy every 5 years (40 years) for colorectal cancer.[12] Exacerbations manifest as an acute worsening of respiratory symptoms and lung function (percent predicted FEV1 [ppFEV1] and usually require oral or intravenous antibiotic treatments specific for respiratory microbiology, increased airway clearance therapies (eg, high-frequency oscillatory percussive devices), and high-calorie, high-protein diets to limit permanent loss of lung function.[13]

long-term pharmacological pulmonary therapies such as mucolytics to thin secretions to facilitate clearance from the upper and lower airways (such as dornase alfa), airway surface liquid hydration (inhaled hypertonic saline, mannitol), and anti-inflammatory drugs (azithromycin, ibuprofen) have been based on phase 3 randomized, placebo-controlled clinical trials (Table 2).

Therapy	Mechanism of action	Indication	Mode of administration and frequency
Mucociliary clearance			
Airway clearance techniques such as chest physiotherapy and oscillating devices	Augmented mucociliary clearance of the lung and facilitate cough to remove mucus obstruction from airways; mechanical loosening of airway secretions	Mechanical exercise and devices to relieve retained airway secretions in conjunction with standard maintenance nebulized therapies	Maintenance typically 2/d and increases with pulmonary exacerbations[27]
Dornase alfa	Reduced viscosity of airway secretions through cleaving of extracellular DNA in sputum	Recombinant DNase enzyme used in conjunction with maintenance airway clearance techniques	Recommended as part of maintenance therapy: 2.5-mg nebulized 1/d[29,30]
Inhaled hypertonic saline	Not established. Proposed mechanisms include airway surface hydration through improved sputum rheological properties and antimicrobial properties	Concentrated saline solution inhaled used in conjunction with standard maintenance airway clearance therapies	Recommended as part of maintenance therapy[29] 7%: 4 mL-nebulized 2/d; Bronchodilator pretreatment recommended to reduce symptoms of cough and wheeze associated with administration
Mannitol	Not directly established; proposed mechanisms are to act as a hyperosmolar agent to rehydrate the airway surface and improve sputum viscosity	Nebulized sugar alcohol as add-on maintenance therapy to manage patients who have passed a tolerance test Mannitol was approved in 2019 for age ≥18 y in the US	400-mg inhaled 2/d
Anti-inflammatory			
Azithromycin	Proposed anti-inflammatory mechanisms include reducing IL-4 and IL-8, suppressing neutrophil activity, and decreasing production of tumor necrosis factor[37]	Macrolide antibiotic as add-on maintenance therapy for patients who are chronically infected with *Pseudomonas aeruginosa* and consideration of use for those without *P aeruginosa*[29,30]	Limited data, but largest trials have used <40 kg: 250 mg 3/wk and ≥40 kg: 500 g 3/wk[38]

[Table.1]

CFTR Modulator Therapies:CFTR modulator therapies act by 2 mechanisms to enhance CFTR function. Potentiators, like ivacaftor, increase the probability that the protein channel is open, so chloride or bicarbonate can flow more easily

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through the cell membrane (Figure 5).Correctors, like lumacaftor, tezacaftor, and elexacaftor, improve channel quantity at the cell surface by helping the protein fold properly, enabling transport to the cell surface (Figure5). Severe variants such as F508del need both potentiators and correctors to improve channel function.

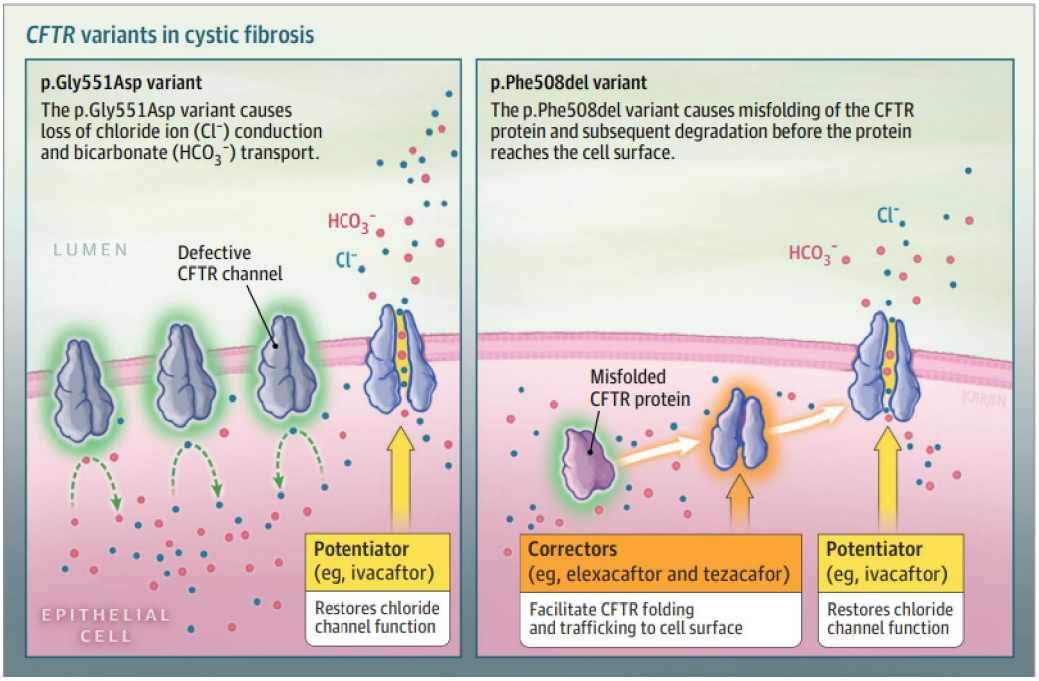

Figure No.5

Ivacaftor is available as a monotherapy, and lumacaftor-ivacaftor, tezacaftor-ivacaftor, and elexacaftortezacaftor-ivacaftor are available as combination therapies. Ivacaftor (formerly VX-770) was the first CFTRmodulator tested in randomized clinical trials of patients with cystic fibrosis in 2006. Ivacaftor was tested first for patients with cystic fibrosis who have a G551D-CFTR variant where the CFTR protein is transported to the cell membrane, but the CFTR channel does not open properly. In a randomized clinical trial of 161 patients with at least 1 copy of G551D, compared with placebo, patients at 24 weeks' follow-up had improved ppFEV1 (10.1% vs −0.4%; mean difference, 10.5%; 95% CI, 8.5%-12.5%), a 55% reduction in pulmonary exacerbations (28 vs 44; rate ratio, 0.43; 95% CI, 0.27-0.68), and increased weight (3.1 kg vs 0.4 kg; mean difference, 2.7 kg; 95% CI, 1.3-4.1 kg).[14]

Airway Rehydration: Inadequate airway surface liquid is thought to be an important factor in the development of CF lung disease, so one treatment approach is to increase the airway fluid layer with an inhaled osmotic agent (Fig. 4).[15] Hyper tonic saline was initially used as an irritant to obtain sputum samples in patients with airway diseases, butstudies also found positive effect on mucociliary trans port and lung function,[16] which was thought to be largely due to the acute effects of inducing cough and hydrating the mucus, but recent evidence suggests that hypertonic saline also increases the depth of the airway surface liquid in CF.[17]A multicenter trial in Australia found a relatively modest improvement in lung function but a more remarkable reduction in pulmonary exacerbations in the treated patients.[18] Inhaled powdered mannitol is being tested as an alternative to hypertonic saline, and a phase-2studyfoundbenefittolungfunction.[19]Aphase-3study is in preparation.

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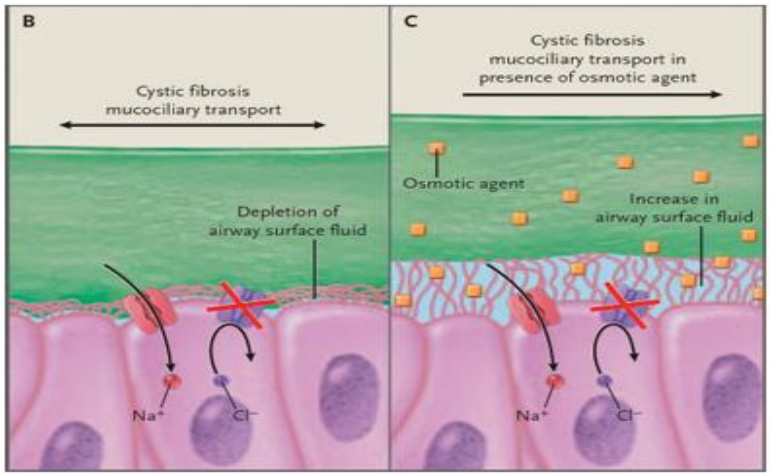

Figure no.6

(Proposed mechanism of action of osmotic agents such as hypertonic saline in cystic fibrosis.) (From Reference 19, with permission.)

Chronic Suppressive Antibiotic Therapy: Chronic suppressive antibiotic therapy often is employed because the treatment of pulmonary exacerbations will not eradicate the lung infection. Aerosolized tobramycin (TOBI) has been the most thoroughly studied chronic suppressive therapy. In two large, multicenter, double-blind, placebo-controlled trials conducted over a 24-week period, treatment with TOBI was found to produce significant improvement in pulmonary function, to de crease the density of P aeruginosa in sputum, and to decrease the number of days that subjects were hospitalized.[20]These studies included patients with moderate-to-severe pulmonary disease, which was defined as an FEV1 between 25% and 75% of predicted. Subset analyses demonstrated that adoles cents had the greatest response, although all age groups and disease severity categories showed significant improvement from the therapy. A 24-month open-label follow-up.[21] of these trials demonstrated sustained improvement in FEV1 compared to the group that had initially received placebo.A significant long-term concern in using chronic suppressive therapy of any type is the emergence of antimicrobial resistance. The TOBI trials showed no increase in the prevalence of B cepacia or other resistant organisms in the TOBI-treated group. There was a modest but detectable shift in the minimum inhibitory concentrations of the P aeruginosa strains infecting the TOBI-treated subjects. The sustained improvement in pulmonary function appears to outweigh the risk of tobramycin resistance that may develop over time, but this must be carefully considered for each individual.

Mucolytic Agents: Recombinant human DNase (also known as-dornase or Pulmozyme; Genentech; South San Francisco, CA) decreases the viscosity of CF sputum by catalyzing extracellular DNA into smaller fragments.[22]A large phase IIIrandomized, double-blind, placebo-controlledtrial showed a modest improvement in pulmonary function in the DNase-treated groups (5.8% and 5.6% relative improvement in FEV1 from baseline, respectively, in the groups treated once and twice a day compared to the placebo group), decreased pulmonary exacerbation rate (28% and 37% reductions, respectively, in the age-adjusted risk of pulmonary exacerbations in patients treated once and twice a day compared to the placebo group), and some improvement in CF-related symptoms.[23]

Bronchodilator: The majority of patients with CFdemonstrate bronchial hyperreactivity at least some of the time.[24] Bronchodilators have therefore become a standard component of the therapeutic regimen. Nebulized-adrenergic agonists are the most commonly prescribed agents. They are often used to provide symptomatic relief and, prior to CPT, to facilitate clearance of the airways. Konig and colleagues[25] reported that maintenance albuterol treatment reverses the progressive downhill course in lung function in CF patients. A longer term, placebo-controlled, double blind study.[26]also showed sustained improvement in PFT scores in a group of patients treated with albu www.chestjournal.org www.chestjournal.orgterol, but the difference from the control group was not statistically significant, likely because of an insufficient number of study subjects.

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Anti-inflammatory Therapies: Some patients with CF have asthma or asthma-like symptoms that require more than therapy with bronchodilators alone. The full asthma armamentarium can be used to treat their bronchospasm. Inhaled or oral glucocorticoids seem to be generally more efficacious than cromolyn or nedocromil, but both classes of drugs are widely used in the treatment of CF patients. Other patients with CF require glucocorticoids for the treatment of allergic bronchopulmonary aspergillosis. We will not focus on these issues but rather will address the role of anti-inflammatory agents for the nonasthmatic patient withCF with chronic airways infection and inflammation. Short-term therapy (3 weeks) with daily corticosteroids in stable patients with severe obstruction showed no benefit.[27]A population with less severe disease treated with 2 weeks of daily therapy with corticosteroids (2 mg/kg/d), followed by alternate day steroid therapy for an additional 10 weeks (1 mg/kg every other day), showed improvement in pulmonary function, and a decrease in serum cytokine and IgG levels.[28] A longer study,[29] (4 years) of therapy with alternate-day steroids (2 mg/kg every other day) also suggested a benefit from steroids with respect to pulmonary and nutritional parameters. This promising result led to a larger multicenter randomized trial comparing alternate-day therapy with prednisone at 2 mg/kg and 1 mg/kg to placebo. This trial enrolled only children and adolescents with CF, but the results are of interest to adult care providers.

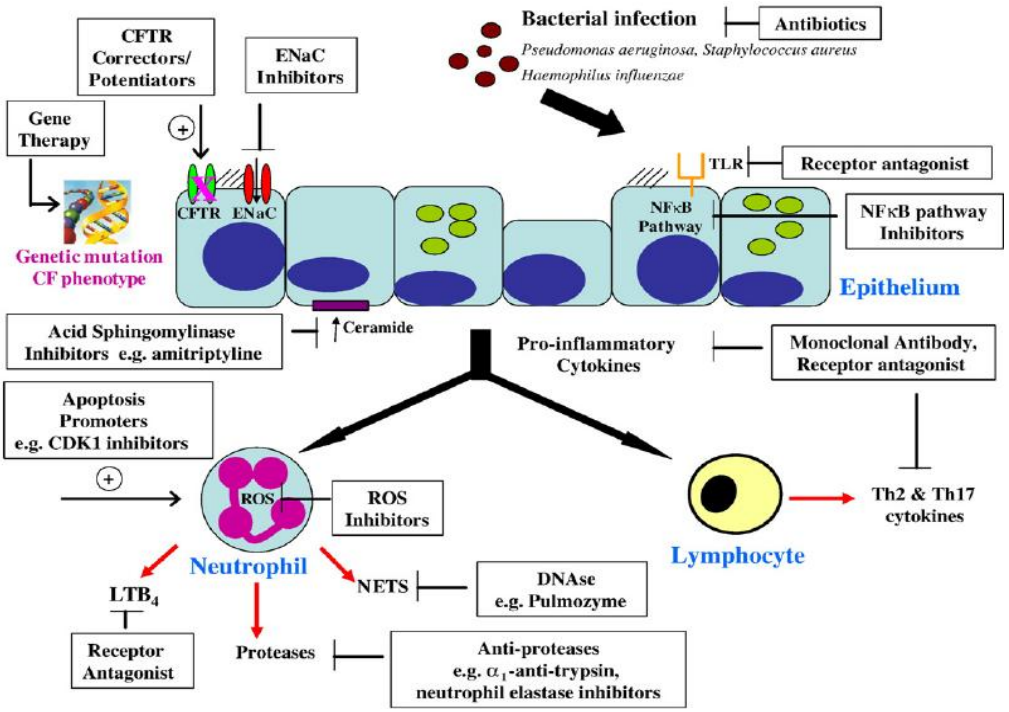

Figure No.7.

(Overview of potential anti-inflametory strategies for the treatment of cystic fibrosis.CF,cystic fibrosis;epithelium sodium channel;TLR,toll-like receptor,NFkB,nuclear factor KappaB;ROS,reactive oxygen species;NETS,neutrophil extracellular traps;)

Anti-inflammatory agents:

Glutathione
Phosphodiesterase-5 inhibitors
Acetylcysteine: HE-3286 (Hollis-Eden Pharmaceuticals)
Simvastatin
Methotrexate Docosahexaenoic acid
Hydroxychloroquine
Pioglitazone
a1-Antitrypsin

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High-dose ibuprofen therapy (20 to 30 mg/kg, up to 1600 mg, bid) slowed the progression of pulmonary disease in mildly affected patients (i.e., FEV1 60% of predicted), particularly in children 5 to 12 years of age.[30] It is important to emphasize that a pharmacokinetic study should be done to verify that therapeutic blood levels of the drug have been achieved. Close monitoring for adverse events is also important, including a semi-annual check on renal function. The potential risks of ibuprofen (GI and renal) should be carefully weighed in deciding whether to treat mildly affected adults. There are no data to support this therapy in patients with moder ate-to-severe obstructive airways disease (ie,FEV1 60% of predicted). Because of concern about an increased risk of haemoptysis, high-dose ibuprofen therapy should be avoided in this subset of patients. The use of leukotriene modifiers in the CF population deserves careful study. These drugs have some attractive features, but, given the scarcity of data in CF patients, they cannot be recommended at this time.

Gene Therapy: The gene defect for CF was discovered in 1989 and since this time there has been a drive to explore the possibility of treatment by replacing the defective CFTR with wild-type CFTR. While clinical trials have achieved delivery of the gene, significant and long-lasting effects on CFTR function haves yet not been achieved.[31] The UK Gene Therapy Consortium(http://www.cfgene therapy.org.uk) was established in 2001 and has developed an impressive research programme. The two options currently being explored as a suitable vector to deliver a functional and long-lasting gene are cationic liposomes, which form complexes with DNA and enter the cell, and lentiviruses, which are retroviruses with the ability to integrate into chromosomal DNA and potentially provide stable and long-lasting expression. The UK Gene Therapy Consortiumis aiming to begin large clinical trials in the near future.[32]

Gene therapy vectors:

Cationic liposomes

Lentiviruses

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

Anti-Infectives: The majority of CF-related morbidity and mortality is a result of chronic pulmonary sepsis. The maor pathogen in CF lung disease is Pseudomonas aeruginosa.

Anti-Pseudomonal Vaccines: A phase III study of a flagella-based P. aeruginosa vaccine failed to demonstrate a reduction in rates of chronic P. aeruginosa infection, although rates were low in both vaccinated and control groups.[33] A recent Cochrane database review concluded that vaccines against P. aeruginosa cannot be recommended.[34] Importantly, the re view discussed a recently completed trial of an octovalent O-polysaccharide toxin A congate vaccine (Aerugen), after which, clinical development was suspended and no data made public.[35]

Inhaled Antibacterials: Inhaled antibacterials are recommended as a component of care for maintenance therapy against chronic P. aeruginosa infection.[36] Neb -ulized colistin has been the main inhaled anti-bacterial used for the past few decades, and there is considerable experience with this treatment, particularly in European CFcentres. In the past decade, preservative-free preparations of tobramycin (TOBI,Bramitob) have been introduced as an alternative nebulized antibacterial specifically for mulated and licensed for inhalation. Large multicentre studies have demonstrated improvements in lung function, and reduced rates of exacerbations and hospitalization.[37]

Inhaled antibacterials:

y-powder tobramycin: tobramycin inhalation powder [TIP] (Novartis)

Dry-powder colistin: Colobreathe (Forest)

Aztreonam lyseine for inhalation (Gilead)

Ciprofloxacin: Bay Q3939 (Bayer Schering), inhaled liposomal ciprofloxacin hydrochloride (Aradigm Corporation)

Levofloxacin: MP-376 (Mpex Pharmaceuticals) Fosfomycin/tobramycin [GS 9310/11] (Gilead)

Liposomal amikacin for inhalation: Arikase (Transave Inc.)

Oral Macrolides :There have been anumberofrandomizedcontrolled trials that have shown benefit from the use of macrolides, particularly azithromycin, in pa -tients with CF, including reductions in hospitalization, and improvements in lung function and quality of life.[19-21] Consequently, azithromycin has now become firmly established as a component of long-term treatment for many patients with CF. Although the true mode of action is un known, anti-

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inflammatory effects are thought to play apart. Unresolved issues include the optimal dose and frequency of administration, and whether the initial benefits are sustained long term.

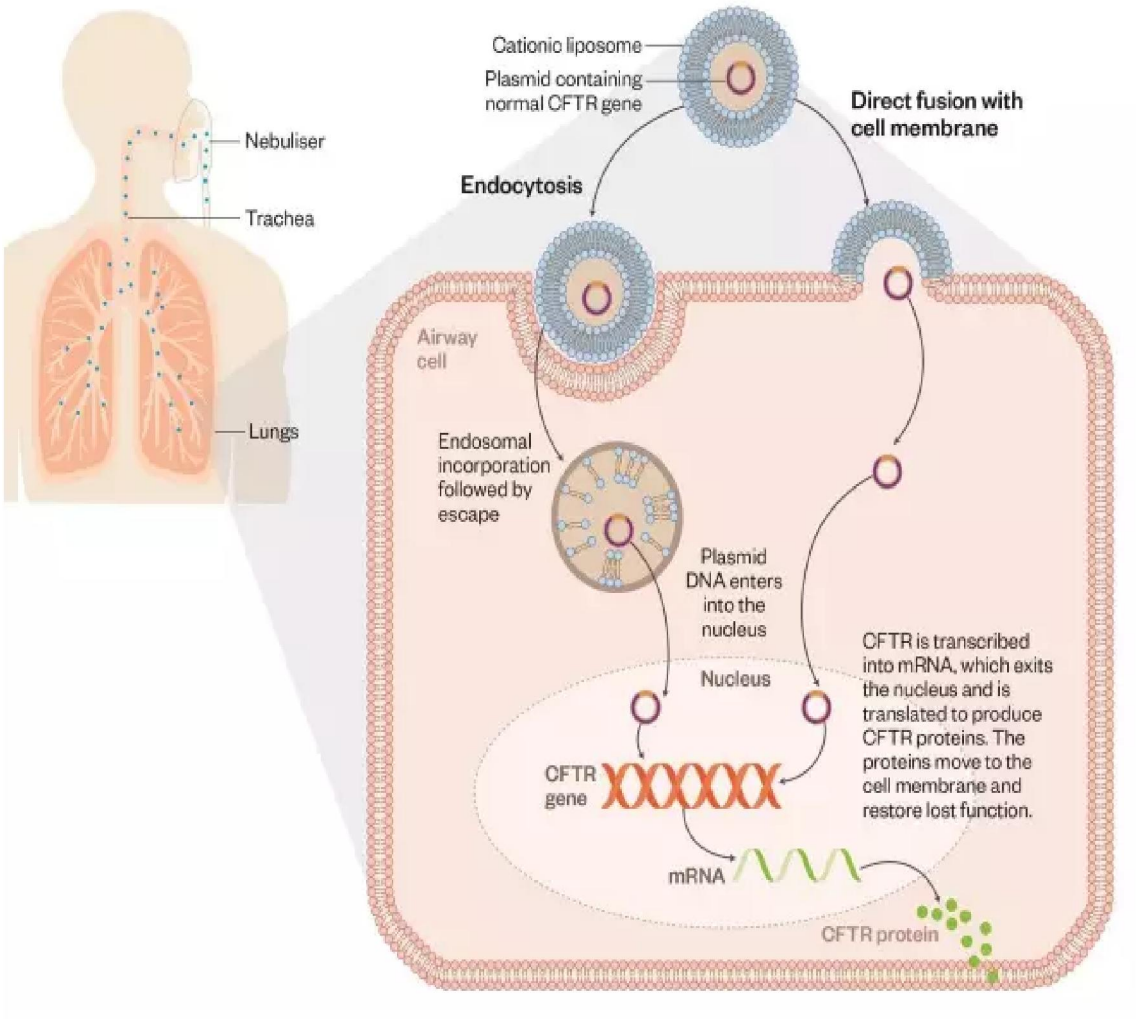

Figure No.8: Gene therapy for cystic fibrosis

II. CONCLUSION

Cystic fibrosis is now recognised as an important genetic disease worldwide. treatment with CFTR modulators is rapidly changing the outlook for people with CF. In the near future, this will lead to effective treatment for at least 85%-90% of patients. In addition, starting these treatments in the first year of life may allow to prevent or reverse complications like pancreatic insufficiency. There is hope that these drugs will also prevent the development of bronchiectasis, diabetes and other complications.

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IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 5, Issue 3, January 2025

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