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Review Article

Comprehensive diagnosis and management of cystic fibrosis: A narrative review

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ABSTRACT

Cystic fibrosis (CF) is a genetic disorder caused by mutations in the CFTR gene, leading to the malfunction of the CFTR protein, a chloride channel present on various epithelial surfaces. This narrative review examines the current state of CF diagnosis and treatment. CF results in a range of complications, including chronic lung infections, pancreatic insufficiency, liver disease, and gastrointestinal issues. Recent advancements in CFTR modulators like ivacaftor, lumacaftor, and tezacaftor have significantly improved the management of CF, expanding treatment eligibility to around 90% of patients. These therapies correct the defective protein function, enhancing chloride ion transport and improving clinical outcomes. Gene therapy has also shown potential, though it faces challenges such as transient gene expression and immunogenicity. Surgical interventions, including lung and liver transplantation, remain crucial for patients with advanced disease. Pulmonary rehabilitation, combining exercise training, airway clearance techniques, and psychological support, is essential for maintaining lung function and quality of life. Despite these advancements, CF continues to be a complex, multisystem disease requiring comprehensive and individualized care strategies. This paper aims to address the current diagnostic methods and treatment approaches in CF management to further improve patient outcomes and extend survival.

1. Introduction

Cystic fibrosis (CF) results from a mutation in the gene that encodes the cystic fibrosis transmembrane conductance regulator (CFTR), a chloride channel present on various epithelial surfaces. These surfaces include the airway, paranasal sinuses, pancreas, gut, biliary tree, vas deferens, and sweat ducts, all of which express CFTR. The dysfunction of this protein causes several issues, including lung infections and bronchiectasis, pancreatic insufficiency leading to malabsorption, episodic intestinal obstruction, liver disease, and male infertility. The failure of CFTR-mediated chloride transport in sweat ducts results in a significantly elevated chloride concentration in sweat, forming the basis for the definitive diagnostic test for CF. Although the incidence of cystic fibrosis in North America and Western Europe remains stable at about 1 in 3500 live births, its prevalence is rising due to early diagnosis through newborn screening and increased patient survival, with the median survival age now estimated to be around 50 years. Additionally, there is a growing recognition of cystic fibrosis in countries and ethnic groups where it was previously considered rare. [1]

Numerous animal models for CF have been developed based on specific human CFTR mutations, but their effectiveness in replicating human CF characteristics varies. For instance, the mouse model exhibits significant differences from human CF at the pathological level. Conversely, although the CFTR genes of pigs and humans are highly homologous at the molecular level, their CFTR protein structures and functions differ substantially.

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Currently, ferret and rabbit CF models show promise as models for human CF, but it is also important to evaluate additional models based on other species. Introducing human CFTR genes with CFTR mutations into animal genomes holds potential for creating more accurate models of human CF. Despite this, each existing animal model has unique features that are valuable for studying specific aspects of human CF, as detailed below.[2]

In this review, we will discuss the pathophysiology, clinical features, and management of cystic fibrosis, beginning with its diagnosis. We will explore various diagnostic methods, followed by a detailed discussion of treatment approaches. These include enhancing mucociliary clearance, anti-inflammatory therapies, anti-infectives, restoring CFTR function, pulmonary rehabilitation, oxygen support and non-invasive ventilation, and surgical options. We will conclude with future directions and emerging therapies that hold promise for improving the prognosis and quality of life for CF patients.

2. Materials and Methods

This narrative review was conducted by searching the PubMed, Scopus, and Cochrane Library databases for articles published from January 2010 to June 2024. Keywords included “cystic fibrosis,” “diagnosis,” “treatment,” “CFTR modulators,” “gene therapy,” “mucociliary clearance,” “anti-inflammatory drugs,” “anti-infectives,” “pulmonary rehabilitation,” “oxygen support,” “non-invasive ventilation,” and “surgery.” Only articles in English were included. We also reviewed guidelines from major CF foundations and organizations. Grey literature has also been included. Articles were selected based on relevance and contributions to understanding the current status and advancements in CF treatment.

3. Discussion

3.1. Pathogenesis of cystic fibrosis

Cystic fibrosis arises from pathogenic mutations in a large gene on human chromosome 7 that encodes the CFTR protein. This protein forms a chloride channel that spans the cell membrane, regulated by phosphorylation through cAMP-dependent phosphokinases. When phosphorylated in the presence of ATP, the CFTR channel opens, allowing about 10 chloride ions to exit the cell every minute. Certain mutations in the CFTR gene produce defective proteins that the endoplasmic reticulum cannot properly process and transport to the cell membrane. The few mutant CFTR proteins that reach the membrane are dysfunctional, unable to transport chloride ions, leading to chloride ion accumulation and water retention in epithelial cells, and resulting in dehydrated extracellular mucus and secretions.

CFTR mutations are classified based on their impact on protein function, including translation, cellular processing, and channel gating. Missense mutations (single amino acid substitutions) constitute 38.74% of CFTR mutations, frameshift mutations (insertions or deletions) make up 16.25%, splicing mutations (incorrect intron splicing) account for 10.93%, and nonsense mutations (premature stop codons) comprise 8.41% of known CFTR mutations worldwide.

CFTR gene mutations are divided into six classes corresponding to specific types of dysfunctions. They are,

1. Class I Mutations: Defective Protein Production - Typically caused by nonsense, frameshift, or splice-site mutations, leading to premature termination of mRNA and absence of CFTR protein.
2. Class II Mutations: Defective Protein Processing - Result in abnormal post-translational processing, preventing the CFTR protein from reaching the correct cellular location. The F508del mutation, found in a homozygous state in about 50% of CF patients and heterozygous in 90%, exemplifies this class.
3. Class III Mutations: Defective Regulation **-** Lead to reduced channel activity despite adequate ATP levels. The G551D mutation, which prevents ATP binding, is the most common class III mutation in Caucasians.
4. Class IV Mutations: Defective Conduction - CFTR protein is correctly produced and transported but has reduced ion flow and channel opening duration compared to normal CFTR. The R117H mutation is the most common class IV mutation in Caucasians.
5. Class V Mutations: Reduced Functional CFTR Protein - This class, sometimes not included in classification schemes, includes mutations affecting mRNA stability and mature CFTR protein stability.
6. Class VI Mutations: Decreased CFTR Stability - Cause substantial plasma membrane instability, including Phe508del when rescued by most correctors.

Mutations in classes I to III generally result in more severe disease than those in classes IV to VI. Specific mutations should not determine assumptions about CF severity; clinical decisions should be based on patient growth, lung function, and nutritional status metrics. Nevertheless, identifying mutations can guide initial therapy, as new treatments targeting specific CFTR mutation classes have been developed.[2]

3.2. Clinical presentation of cystic fibrosis

Over the past two decades, significant advancements in our understanding of CF have greatly influenced its management. Historically known as a digestive and lung disease affecting young children, CF has evolved into a complex, multisystem condition that now extends into adulthood, with projections indicating that adults with CF will soon outnumber children. For babies born in the 21st century, the predicted median survival is now over 50 years.

While CF affects various organs, it primarily impacts the upper and lower airways, pancreas, bowel, and reproductive tracts. For most patients, lung disease poses the greatest challenge in terms of symptoms, required treatments, and is the most common cause of death.[3]

Let us go through the age wise presentation of cystic fibrosis. Antenatally, they may present with an echogenic bowel on ultrasound. In neonates, meconium ileus affects 10% of CF patients leading to bowel obstruction, potentially with perforation and peritonitis. Less commonly, it can also cause gut atresia, obstructive jaundice and fat-soluble vitamin deficiencies. In infants and young children, failure to thrive is the most common presentation. They also present with recurrent respiratory symptoms (cough, wheeze, pneumonia). Rectal prolapse, dehydration and electrolyte disturbances (pseudo-Bartter's syndrome), anemia, edema, and hypoproteinemia are some other less common presentations in this age group. In older children and adults, recurrent respiratory symptoms are the most common presentations. Males can present with infertility due to congenital bilateral absence of the vas deferens. Acute pancreatitis, liver disease and malabsorption could be the GI presentations.[3]

3.3. Screening

Newborn screening (NBS) for cystic fibrosis began in the 1980s and involves measuring immunoreactive trypsinogen (IRT) levels in neonatal blood spots. In infants with CF, mucus plugs partially obstruct pancreatic ducts, preventing trypsinogen from converting to trypsin in the intestine. A positive screening is indicated if the IRT level remains high between 7 and 14 days of life or if at least one harmful CFTR variant is detected through genetic testing. A positive NBS result prompts notification of either a neonatal intensive care provider or primary care provider, and the infant should be referred to a CFF-accredited centre for definitive evaluation and sweat testing within 72 hours of a positive result.

Diagnosing asymptomatic infants with CF offers benefits such as early attention to lung health to slow disease progression, optimization of nutritional status with early enzyme replacement and nutritional counselling, and psychosocial support for families to prevent or delay serious complications. However, NBS also carries risks, including increased medical interventions, exposure to respiratory pathogens at CF clinics, financial burdens due to CF-related therapies, potential side effects from early therapy exposure, and caregiver anxiety or guilt from false-positive results caused by perinatal asphyxia or other issues. False-positive rates may be higher in African-American children due to naturally higher IRT levels compared to Caucasians, despite a lower CF risk. NBS can also yield false negatives, particularly in neonates with meconium ileus or those tested with IRT/DNA, which may be less sensitive to mutations in minority populations. Current NBS practices might identify CFTR variants that do not meet clinical criteria for CF diagnosis in individuals with normal or intermediate sweat chloride tests, known as CFTR-Related Metabolic Syndrome (CRMS)/Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID).[4]

3.4. Diagnosis of cystic fibrosis

The Cystic Fibrosis Foundation (CFF) published consensus guidelines in 2017 that outline the criteria for diagnosing CF. A diagnosis can be made if an individual exhibits a clinical presentation consistent with the disease, such as a positive newborn screening, clinical features of CF (chronic, recurrent sinus and pulmonary disease, nutritional and gastrointestinal issues, urogenital abnormalities in males, or salt depletion syndromes), or a positive family history of CF combined with evidence of CFTR dysfunction (e.g., sweat chloride concentration ≥60mmol/L).[5]

Although prenatal screening and NBS enable early detection of CF in asymptomatic individuals, the quantitative pilocarpine iontophoresis sweat test remains the gold standard for CF diagnosis. This test, developed by Lewis Gibson and Robert Cooke in 1959, measures chloride levels in sweat. It should be conducted as soon as possible after a positive NBS result, ideally after 10 days of age and no later than 4 weeks, with the infant weighing more than 2 kg or corrected to 36 weeks gestation to ensure sufficient sweat collection. Infants with meconium ileus and those with symptoms indicative of CF, such as recurrent bacterial respiratory infections or failure to thrive, should undergo sweat chloride testing regardless of age or NBS results. Abnormal sweat test results should be repeated on a separate date or confirmed with genetic testing.[4]

Sweat chloride test results can be categorized as diagnostic, intermediate, or unlikely. Diagnostic values (≥60 mmol/L) require a confirmatory second sweat test or the identification of CF-causing genetic variants for a definitive diagnosis. Intermediate values (30-59 mmol/L) necessitate periodic repeat testing and further evaluation at a CF centre. A CF diagnosis can be made in individuals with intermediate values if they have CF-causing genetic variants. Individuals with sweat chloride values <30 are unlikely to have CF but should be diagnosed if CF-causing genetic variants are identified.[6]

Genetic testing, widely available, complements sweat testing to confirm CF diagnoses, especially in cases with intermediate sweat chloride values. Identifying specific CF-causing variants is crucial for prescribing CFTR modulator therapies approved for particular variants. A genotype-based diagnosis can be made by identifying two pathogenic variants on separate chromosomes. Most CF diagnoses are made through commercial laboratories testing common CFTR variants, but complete CFTR gene sequencing may be necessary for atypical presentations.[4]

The advent of genetic testing has deepened our understanding of CFTR dysfunction but also introduced complexity in diagnosing CF. Some individuals exhibit CF phenotypes without known CF-causing mutations, while others with detected mutations remain asymptomatic. Limitations in sweat chloride and genetic testing may necessitate both tests for a conclusive diagnosis in certain patients with strong clinical suspicion of CF.[4]

Another type of testing is Nasal Potential Difference (NPD) Testing. In healthy individuals, sodium absorption and chloride transport maintain airway surface liquid volume and ionic content, crucial for mucociliary clearance. NPD measures voltage differences across airway epithelia using electrodes: an exploring electrode on the nasal epithelium and a reference electrode, typically in the forearm. In CF, the ion transport profile is abnormal, and NPD measurements reveal distinct characteristics. Initially, the basal NPD in CF patients is significantly more negative due to heightened ENaC activity, attributed to the lack of CFTR regulation. The most consistent abnormality is the absence of hyperpolarization after perfusion with chloride-free solution and isoproterenol. Overall, these differences in sodium and chloride transport effectively distinguish CF patients from non-CF individuals.[7]

3.5. Treatment of cystic fibrosis

Management of CF now involves a multifaceted approach, encompassing early diagnosis through newborn screening, proactive infection control, nutritional support, and the use of CFTR modulators to correct the dysfunctional protein. This comprehensive care model not only aims to prolong life but also to improve the quality of life for individuals with CF. Recent developments in treatment strategies include enhancing mucociliary clearance, employing anti-inflammatory and anti-infective agents, and innovative approaches like gene therapy. Additionally, supportive therapies such as pulmonary rehabilitation, oxygen supplementation, and surgical options like lung transplantation are essential components of CF care, particularly in advanced stages of the disease. Let us look at them one by one.

3.5.1. Improvement of mucociliary clearance

Effective mucociliary clearance is crucial in cystic fibrosis CF to prevent the buildup of thick mucus that can obstruct airways and lead to chronic infections. Several therapeutic strategies have been developed to enhance mucus clearance and improve respiratory function in CF patients.

3.5.1.1. ENaC inhibitors. In healthy airways, a balance between CFTR-mediated chloride secretion and ENaC-mediated sodium absorption ensures proper hydration of airway surfaces, crucial for effective mucociliary clearance. In cystic fibrosis, the lack of CFTR-mediated chloride and fluid secretion combined with increased ENaC-mediated sodium and fluid absorption results in airway surface dehydration, reduced periciliary layer (PCL), hyper concentrated mucus, flattened cilia, impaired mucociliary clearance, bacterial colonization, and neutrophilic inflammation. Several new compounds targeting ENaC inhibition are in active preclinical development. Among these, BI 1265162, a new small-molecule ENaC inhibitor, is in Phase II development. Preclinical studies show it is significantly more potent than amiloride (30–70 times lower IC50) and does not affect serum potassium or plasma electrolytes. Additionally, BI 1265162 has demonstrated safety in Phase I volunteer studies.[8]

3.5.1.2. Chloride channel antagonists. In addition to CFTR, two major chloride channels in humans are SLC26A9 and TMEM16A. Once inserted into the apical membrane of airway epithelial cells, SLC26A9 is spontaneously active and likely provides the basal chloride conductance in airways. In CF patients with the F508del-CFTR mutation, the absence of basal chloride secretion is due to the lack of SLC26A9 expression in the apical membrane. SLC26A9 forms a complex with CFTR. The complex remains intracellular and degrades. Identifying small molecules to interfere with the F508del-CFTR/SLC26A9 complex formation could be a potential therapeutic approach.[9]

TMEM16A, a Ca2+-activated chloride channel (CaCC), is part of a family of 10 proteins (TMEM16A-K). During inflammatory lung diseases such as CF, TMEM16A is significantly upregulated, correlating with goblet cell metaplasia and mucus hypersecretion. TMEM16A expression is predominant in mucus-producing cells and less so in ciliated epithelial cells. Though its expression in normal adult airways is minimal, airway inflammation can induce TMEM16A upregulation in mucus-producing club/goblet cells. Future drugs can target this as well.[9]

3.5.1.3. Mucolytics. Mucolytic agents break down mucus, reducing its viscosity and improving clearance. Dornase alfa is an inhaled medication used to thin mucus in cystic fibrosis patients, particularly effective for those with a forced vital capacity (FVC) over 40% of predicted. In cases of moderate to severe lung disease, dornase alfa is highly recommended due to its substantial benefits. In healthy individuals, cilia in the respiratory tract help expel mucus that traps invaders and particles through coughing. However, in CF patients, thick mucus impairs this mucociliary clearance, leading to bacterial colonization, especially by Pseudomonas, inflammation, and neutrophil accumulation. The death of neutrophils releases highly polymerized DNA into the mucus, further thickening it and increasing the risk of airway blockage and infection. Repeated infections and damage from neutrophil oxidants cause irreversible lung damage and can lead to respiratory failure, the leading cause

of death in CF patients. Dornase alfa is a recombinant human deoxyribonuclease I (rhDNase) that breaks down extracellular long-chain DNA in sputum, reducing mucus viscosity. This action prevents airway infections and lung damage, improving lung function and quality of life for CF patients. [10]

Hypertonic saline solution is another option. It is an affordable and easily reproducible treatment, and complements respiratory physiotherapy for CF patients both long-term and during respiratory exacerbations. Studies have shown that 3% hypertonic saline significantly improves mucus clearance, by breaking ionic bonds to reduce mucus viscosity, increasing ionic concentration for better mucociliary clearance, and promoting osmotic flow to rehydrate secretions. Long-term use enhances mucociliary function, reducing bacterial load and chronic airway inflammation. [11] However, a study by Mayer-Hamblett et al., 2023 [12] showed that in individuals with cystic fibrosis who have relatively well-preserved pulmonary function and are on ETI (Elexacaftor/Tezacaftor/Ivacaftor) therapy, stopping daily hypertonic saline or dornase alfa for six weeks did not lead to significant changes in pulmonary function compared to those who continued the treatment. More studies are needed to prove the benefit of these drugs.

3.5.1.4. Bronchodilators. Short and long-acting bronchodilators are prescribed for most people with cystic fibrosis to widen the airways and improve symptoms. Short-acting bronchodilators provide rapid relief from sudden breathlessness, acting within minutes and lasting four to six hours for beta-2 agonists like albuterol and six to eight hours for muscarinic antagonists like ipratropium. In contrast, long-acting bronchodilators like salmeterol offer extended effects for maintenance, with maximum bronchodilation occurring after several hours and lasting at least 12 hours. [13]

3.5.2. Anti-inflammatory drugs

Inflammation plays a significant role in the progression of lung damage in cystic fibrosis. Anti-inflammatory drugs aim to reduce this inflammation, thereby preserving lung function and improving overall respiratory health in CF patients. Steroids aren't indicated unless there is another underlying inflammatory pulmonary pathology like asthma.

Neutrophil elastase (NE) is a key inflammatory protease released by neutrophils found in the airways of patients with cystic fibrosis, chronic obstructive pulmonary disease (COPD), non-CF bronchiectasis, and bronchopulmonary dysplasia. While NE aids leukocyte migration to infection sites and helps clear Gram-negative bacteria, it also triggers inflammation in chronic airway diseases. Effective mucociliary clearance requires normal mucin levels, proper airway surface liquid hydration, and a healthy ciliated epithelium. NE disrupts these by increasing mucin production, degrading CFTR, activating ENaC, impairing airway hydration, reducing ciliary motility, and damaging ciliary structures. These disruptions lead to mucus obstruction, a hallmark of chronic inflammatory airway diseases. Some examples of neutrophil elastase inhibitors are elafin and SLP1. [14]

3.5.3. Anti-infective drugs

Chronic and recurrent respiratory infections are a hallmark of cystic fibrosis, significantly contributing to disease progression and morbidity. This management includes regular respiratory cultures (oropharyngeal or sputum) to monitor for pathogens like Staphylococcus aureus (especially MRSA) and Pseudomonas aeruginosa. Microbiology labs should be informed of the patient's CF diagnosis to detect common CF-related pathogens. Initial P. aeruginosa infections are typically treated with anti-pseudomonal antibiotics, such as nebulized tobramycin or oral azithromycin, aiming for eradication. Nebulized antibiotics like tobramycin or aztreonam are also used as suppressive therapy for chronic P. aeruginosa infections or colonization, administered every other month to reduce antibiotic resistance. Other monitored organisms include Burkholderia cepacia complex, nontuberculous mycobacteria, and fungal pathogens like Aspergillus fumigatus, which can significantly impact CF lung disease. Notably, CF patients may develop allergic bronchopulmonary aspergillosis (ABPA) due to Aspergillus, requiring corticosteroid treatment to manage lung function. [15]

3.5.4. Restoring CFTR Function

Significant advancements in CFTR modulating therapies have been made over the past decade. With the development of the CFTR "potentiator" ivacaftor and the "correctors" lumacaftor and tezacaftor, around 50% of CF patients became eligible for these treatments. Ivacaftor acts as a potentiator for common gating mutations, enhancing chloride ion flow. Tezacaftor, a corrector, aids in the proper folding and cell surface presentation of the mature CFTR protein, improving function for the F508del mutation. Elexacaftor, another corrector, binds to a different site on the CFTR protein than tezacaftor, further enhancing CFTR function at the cell surface. Combined, elexacaftor, tezacaftor, and ivacaftor increase the functionality of the F508del CFTR protein, resulting in improved chloride ion transport. Recently, a new combination therapy containing elexacaftor, tezacaftor, and ivacaftor (Trikafta, Vertex Pharmaceuticals) has been approved for CF patients aged 12 and older with at least one F508del mutation, regardless of their second mutation type. This approval expands the eligibility for CFTR modulating therapy to about 90% of CF patients. The clinical benefits of elexacaftor-tezacaftor-ivacaftor combination therapy surpass those of other available options, significantly altering the course of

CF.[16]

3.5.5. Gene therapy

Since CF was first described in 1938 and the CFTR gene was discovered in 1989, numerous efforts have been made to develop gene therapy as a cure for CF lung disease. Initial attempts in the 1990s using recombinant adenoviral (rAd) vectors showed proof-of-concept but were hindered by transient gene expression and strong immunogenicity. Recombinant adeno-associated virus (rAAV) vectors emerged as more promising, with several approved for clinical use. From 1998 to 2007, rAAV-2 vectors were evaluated in clinical trials, showing safety and some functional restoration in CF patients, though they did not achieve the primary efficacy endpoint of improved lung function.

Non-viral vectors, which are less immunogenic, were also explored. The UK Cystic Fibrosis Gene Therapy Consortium conducted the largest phase IIb trial with 116 CF patients using a cationic liposome (GL67A)-formulated CFTR plasmid. This trial showed a modest 3.7% increase in FEV1 after 12 months, insufficient to fully restore lung function.[17]

Despite almost three decades of research and 36 clinical trials involving approximately 600 CF patients, a definitive cure through gene therapy remains elusive. However, these efforts have established proof-of-concept and provided valuable insights for future developments in CF gene therapy.

3.5.6. Surgery

Surgical interventions in cystic fibrosis are considered for advanced disease complications and include procedures such as lung transplantation, liver transplantation, and bowel surgeries. These surgeries can significantly improve quality of life and survival in selected CF patients with severe organ involvement.

3.5.6.1. Lung transplantation. The landscape of lung transplantation for CF is changing. Advances in CFTR modulator therapies and improved patient care have increased the age of transplant recipients and improved survival rates. The median survival for CF patients after lung transplantation is 8.3 years, compared to 5.7 years for all indications. While lung transplantation is the standard care for CF patients with end-stage lung disease, predicting post-transplant mortality remains challenging. A systematic review identified pre-existing Burkholderia cepacia complex infection as a significant risk factor for increased mortality post-transplant. Other factors associated with waitlist mortality, such as low FEV1 and pulmonary hypertension, did not affect post-transplant survival. Low BMI, once considered a contraindication for lung transplantation, has been reconsidered. Recent data indicate that low BMI may not significantly impact post-transplant outcomes, with muscle mass being a more critical factor. Re-transplantation, though sometimes necessary, often results in worse outcomes compared to initial transplants. Chronic lung allograft dysfunction (CLAD) occurs in about 50% of recipients five years post-transplant. Risk factors for CLAD are not well-defined, but early identification and intervention are crucial. Further research is needed to refine transplantation indications and contraindications, optimize pre- and post-transplant care, and better understand CLAD and re-transplantation outcomes. Continued advancements in CF care and transplantation practices are expected to improve longevity and quality of life for CF patients.[18]

3.5.6.2. Liver transplantation. Liver disease is the third leading cause of mortality in cystic fibrosis patients. Initially considered a childhood issue, CF-associated liver disease (CFLD) is now a significant concern in adults due to increased life expectancy. The development of severe liver involvement in certain patients is not well understood, and no specific CFTR mutation has been clearly linked to CFLD. The definition of CFLD is debated, but commonly used criteria require at least two of the following: evidence of hepatomegaly or splenomegaly (confirmed by ultrasound), elevated AST, ALT, or GGT levels on three occasions over 12 months, or ultrasonic evidence of liver involvement, portal hypertension, or biliary involvement.

CFLD is not limited to the liver parenchyma, as MRCP can reveal periportal fibrosis and large duct anomalies such as strictures and calculi, resembling sclerosing cholangitis in up to 70% of patients. The only recognized treatment for CFLD is ursodeoxycholic acid (UDCA), which stimulates bile flow. Liver transplantation is considered when medical treatments fail to address CFLD complications, with liver failure and hepatocellular carcinoma being the primary indications.

There are no established guidelines for liver transplantation in CFLD, and decisions are made case-by-case. Some centres opt for early or pre-emptive liver transplantation based on nutritional status or respiratory function. Although it has been suggested that liver transplantation is contraindicated when FEV1 is below 50%, successful transplants have been performed in these cases without adverse events. Thus, while liver transplantation can be a crucial intervention for CF patients with severe liver disease, careful assessment and individualized decision-making are essential to optimize outcomes and improve patient survival.[19]

3.5.6.3. Gastrointestinal complications. Cystic fibrosis involves various gastrointestinal (GI) complications due to the malfunction of the CFTR protein. Key GI issues include meconium ileus, distal intestinal obstruction syndrome (DIOS), and gastroesophageal reflux disease (GERD). Meconium ileus, occurring in newborns, is a blockage of the intestine by thick meconium. It often requires surgical

intervention. DIOS, common in older children and adults, is characterized by bowel obstruction due to thickened faecal matter and is managed through hydration, laxatives, and sometimes surgery. GERD, prevalent in CF patients, leads to acid reflux and requires both medical and surgical management, such as fundoplication. CF also increases the risk of colorectal cancer, necessitating regular screenings and potential surgeries to remove polyps or cancerous sections. Pancreatic complications, including pancreatitis and pancreatic insufficiency, arise from blocked ducts leading to enzyme replacement therapy and occasionally surgical procedures. Hepatobiliary issues, such as liver cirrhosis and gallstones, also occur frequently, requiring monitoring and sometimes liver transplantation. Overall, managing these complications involves a combination of medical treatments and various surgical interventions to ensure patient health and quality of life.[20]

3.5.7. Pulmonary rehabilitation

Pulmonary rehabilitation is a comprehensive, individualized intervention essential for managing cystic fibrosis. It combines exercise training, airway clearance techniques, education, and behaviour modification to enhance the physical and psychological well-being of patients with chronic respiratory diseases, promoting long-term health improvements.

Exercise training is a core component, targeting both aerobic and anaerobic systems to improve exercise capacity, muscle strength, and overall lung health. Aerobic exercises, such as walking or cycling, are recommended to enhance aerobic capacity, which is often compromised in CF due to multifactorial pathology. Anaerobic training, like resistance exercises, helps in building muscle strength and endurance.

Airway clearance techniques (ACTs) are crucial for managing the thick bronchial secretions characteristic of CF. These techniques, including positive expiratory pressure (PEP) therapy, autogenic drainage, and high-frequency chest compression, aim to mobilize and clear mucus, thus improving airway patency and reducing infection risk. Regular application of ACTs is recommended across the lifespan of CF patients.

In addition to traditional rehabilitation methods, new technologies such as video games, social media, and web-based platforms are being integrated into pulmonary rehabilitation programs. These technologies can enhance patient engagement and adherence to exercise regimens, making rehabilitation more enjoyable and effective.

Moreover, pulmonary rehabilitation programs address psychological and nutritional needs, as CF patients often experience depression, anxiety, and malnutrition. Comprehensive care plans include psychological support and nutritional interventions to optimize overall health and quality of life. Overall, pulmonary rehabilitation is a multidimensional approach that significantly benefits CF patients, improving their exercise capacity, lung function, and quality of life.[21]

4. 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.

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None.

6. Conflict of Interest

None.

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