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Cystic fibrosis: Genetic basis, symptoms and chronic treatment

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DISCOVERY SCIENTIFIC SOCIETY

ABSTRACT

Cystic fibrosis (CF) is a common genetic condition caused by mutations in the CFTR gene, which leads to thick, sticky mucus that obstructs various organ systems, especially the lungs and gastrointestinal tract. Mutations are categorized into six classes, with Class I–III associated with severe disease. Key symptoms include respiratory infections, pancreatic insufficiency, malabsorption, and male infertility. Chronic treatments focus on airway clearance, nutrition, and infection control. Airway clearance techniques like Specific Cough Technique (SCT), Forced Expiration Technique (FET), Positive Expiratory Pressure (PEP) therapy, and The Active Cycle of Breathing Technique (ACBT) are crucial to managing mucus build-up, complemented by physical activity. Mucolytics such as dornase alfa, hypertonic saline, and mannitol improve mucus clearance and respiratory function. Antibiotics address bacterial infections, particularly Pseudomonas aeruginosa, though antibiotic resistance remains a challenge. CFTR modulators target the specific protein defect. The treatment strategy also includes nutritional supplementation due to fat-soluble vitamin deficiencies and the need for pancreatic enzyme supplementation. Developments in CF management have improved life expectancy and quality of life. Unfortunately, there are still difficulties to overcome. This review examines the genetics, symptoms, and life-long treatment in CF patients.

Keywords: Cystic Fibrosis (CF), CFTR Modulators, Airway Clearance Therapy (ACT), Antibiotic Resistance, Pancreatic Insufficiency

1. INTRODUCTION

Cystic fibrosis (CF) is the most common inherited condition involving cells that produce mucus and sweat, impacting various organs, with the lungs being the most seriously affected (Rafeeq and Murad, 2017). The disease is passed down in a recessive pattern and is the most common recessive genetic disorder among people of European descent (Ratjen and Döring, 2003; Radlović, 2012). A mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene alters a protein that acts as a regulated chloride channel, which influences

the activity of other chloride and sodium channels on the surface of epithelial cells. The CFTR protein allows chloride to move through mucus-producing cells, followed by water, which helps keep the mucus thin. The malfunction of the CFTR protein in individuals with cystic fibrosis leads to thickened mucus in the respiratory, digestive, and reproductive systems, as well as disrupted chloride and sodium absorption in the sweat glands (Radlović, 2012). This dysfunction also contributes to inflammation, infections, and structural damage, which can significantly impact daily activities and reduce overall quality of life (O'Sullivan and Freedman, 2009; Fahy and Dickey, 2010; Royce and Carl, 2011).

2. METHODOLOGY

Keywords such as "Cystic Fibrosis (CF)", "CFTR Modulators", "Airway Clearance Therapy (ACT)", "Antibiotic Resistance" and "Pancreatic Insufficiency" were used to search accessible medical sources, including PubMed and Google Scholar. The review analyzed studies published from 1979 to June 2024, selecting articles deemed relevant to the topic based on evaluating their titles and abstracts. This review includes clinical studies, systematic reviews, and meta-analyses focusing on methods of chronic treatment in patients with cystic fibrosis. Articles in languages other than English were excluded from consideration.

3. RESULTS AND DISCUSSION

Cystic fibrosis (CF) is a multisystem disorder in which CFTR protein dysfunction leads to the accumulation of thick mucus in various organs, primarily the lungs and digestive tract. Symptoms include recurrent respiratory infections, pancreatic insufficiency, malabsorption, and male infertility. Airway clearance therapy plays a crucial role in CF treatment, combining techniques to promote mucus removal, such as the Specific Cough Technique (SCT), Forced Expiration Technique (FET), and Positive Expiratory Pressure (PEP) therapy. Mucolytics like dornase alfa, hypertonic saline, and mannitol help to clear airway secretions and improve lung function (Table 1). Antibiotic therapy is key to properly managing bacterial infection, especially chronic Pseudomonas aeruginosa colonization.

However, due to the progressive development of drug resistance, the treatment requires the careful use of antibiotics. The introduction of CFTR modulators, such as ivacaftor, lumacaftor, tezacaftor, and elexacaftor, has revolutionized CF management by directly targeting the underlying protein defect, improving lung function, and reducing pulmonary exacerbations. Nutritional support is equally important due to pancreatic insufficiency and fat-soluble vitamin deficiencies. Pancreatic enzyme replacement therapy (PERT) provides normal digestion. Vitamin supplementation reduces the negative effects of malnutrition. In spite of the progress in CF management, challenges such as chronic infections, antibiotic resistance, and disease progression highlight the need for continuous research and personalized treatment approaches.

Genetics

The CFTR gene is found at location 7q31.2, and over 2000 mutations have been identified, of which only around 20 mutations occur with a frequency greater than 0.1%. The most common of these is "F508del" (second mutation class), which involves the deletion of three bases that code for phenylalanine at position 508. Various mutations affect the quantity or functionality of the CFTR protein in distinct ways, leading to a range of outcomes, which led to their division into six classes. Class I–III mutations result in a more severe course of the disease (Rogan et al., 2011; Rafeeq and Murad, 2017; Bergeron and Cantin, 2019).

Symptoms

The CFTR gene is active across various organ systems, which accounts for the diverse range of health issues faced by individuals with CF, impacting the lungs, endocrine system, digestive tract, pancreas, bile ducts, and reproductive organs. The respiratory system in cystic fibrosis is affected by conditions such as acute bronchitis, Pseudomonas infections, and respiratory failure. The pancreas shows complications, including intestinal malabsorption, pancreatic steatorrhea, acute pancreatitis, and chronic pancreatitis.

The gastrointestinal tract is impacted by abdominal pain and intestinal obstruction. The endocrine system and nutritional status are disrupted, leading to diabetes, dehydration, and fluid and electrolyte disorders. The hepatobiliary system presents issues such as abnormal liver serum enzyme levels and jaundice. The reproductive system is also affected, with male infertility being a common complicationm (De-Boeck et al., 2017; Polgreen and Comellas, 2022).

Treatment

Airway clearance physiotherapy

Airway Clearance Physiotherapy (ACP), composed of different airway clearance therapies (ACTs, also known as chest physical therapy), plays a vital role in managing CF. Traditionally, they relied on postural drainage, using gravity-assisted positions, along with percussion and vibration, usually performed with the help of a caregiver and combined with forced expirations. In recent years, more user-friendly, self-administered methods have been developed, allowing individuals to perform these techniques comfortably. These therapies increase both mucus clearance and sputum production and improve respiratory function, giving patients relief. However, they can be time-consuming and exhausting. Effective airway clearance is crucial for alleviating symptoms, reducing complications, and improving patients' ability to maintain daily activities and overall quality of life (McIlwaine et al., 2019; Gursli et al., 2022; Wilson et al., 2023).

Techniques for Clearing Mucus

Coughing and forced expirations are considered some of the most effective techniques for helping move mucus and clear sputum from the central airways. While coughing acts as a natural cleaning mechanism and a supportive tool to aid mucociliary clearance, the Forced Expiration Technique (FET) is often used within structured approaches like the active cycle of breathing techniques that, in addition to FET, also include breathing control and thoracic expansion exercises. FET also complements other airway clearance methods, such as positive expiratory pressure (PEP) therapy, making it a valuable part of a comprehensive treatment plan (Gursli et al., 2017; Wilson et al., 2023).

The Specific Cough Technique (SCT) begins with soft, low-intensity coughs aimed at positioning and gathering mucus in the airways. This is followed by two to three stronger, high-intensity coughs to efficiently expel the mucus (Gursli et al., 2017). This approach is particularly successful in clearing the respiratory tract. Another method, the Forced Expiration Technique (FET), is designed to target mucus located in the peripheral regions of the lungs (Wilson et al., 2023). It involves performing one or two huffing breaths (forced expirations), starting at a mid-lung volume and progressing to a lower lung volume. This is accompanied by a phase of calm and controlled diaphragmatic breathing (Pryor et al., 1979).

The Active Cycle of Breathing Technique (ACBT) starts with a breathing control phase that promotes breaths focused on the lower chest while keeping the upper parts relaxed. This provides proper oxygenation and reduced bronchospasm. Later, the thoracic expansion exercises are performed. They involve deep breathing and relaxed exhalations. As a result, the mucus is thinner, and lung ventilation is more efficient. The technique concludes with FET, incorporating one or two huffing breaths combined with controlled breathing to effectively clear mucus from the airways (Lewis et al., 2012; Wilson et al., 2023).

The specific cough technique (SCT) has been found to be equally effective as the forced expiration technique (FET) in terms of sputum production. What sets SCT apart, however, is how much easier it feels to incorporate into daily routines and how naturally it fits into everyday life. Since subjective experiences can play a key role in promoting adherence to treatment plans, thereby enhancing overall therapeutic outcomes, SCT holds potential as a viable and effective alternative for sputum clearance in airway clearance therapy (Gursli et al., 2017).

Devices for Airway Clearance

Positive Expiratory Pressure (PEP) therapy involves a device that creates resistance in the airways during exhalation and enhances airflow to blocked distal lung areas. It is typically used with a mask but can also be adapted for use with a mouthpiece (ensuring proper support for the cheeks) and nose clips. However, there is limited research available on the effectiveness of PEP therapy when using a mouthpiece, as only a few studies have explored this approach (Marks, 2007; McIlwaine et al., 2019). The Positive Expiratory Pressure (PEP) technique begins with the use of a PEP device equipped with a face mask, ensuring the system is sealed to maintain a pressure range of 10 to 20 cm H_2O.

The individual takes 12 to 15 steady breaths through the device. Following this, the mask is removed, and two to three huffing breaths, or forced expirations, are performed to assist in clearing the airways. For High-Pressure PEP (Hi-PEP), the focus shifts to achieving higher expiratory pressures, typically between 40 and 100 cm H_2O. This is accomplished by using the PEP device for strong, controlled exhalations, effectively creating the necessary pressure to aid in mucus clearance and improve lung function (McIlwaine et al., 2019).

Various airway clearance techniques, such as conventional chest physiotherapy, forced expiratory technique (FET), and positive expiratory pressure (PEP) therapy, have been shown to effectively enhance mucus clearance in adults with cystic fibrosis. However, no single method has proven to be significantly more effective than others. Many individuals prefer techniques they can perform independently, like PEP therapy, over those requiring assistance, such as percussion and vibration. PEP is considered safe and may help reduce exacerbations (Dwyer et al., 2019; McIlwaine et al., 2019).

Manual Techniques

Manual therapies (MTs) have been widely studied within conventional healthcare, particularly by chiropractors, osteopaths, and physiotherapists. These therapies have demonstrated positive outcomes across a range of conditions, including musculoskeletal pain, reduced mobility, and respiratory muscle weakness. MTs typically involve a combination of postural drainage and percussion, performed in gravity-assisted positions, often requiring assistance from a caregiver or healthcare professional. This can add to the challenges of treatment by increasing dependence on others, causing inconvenience, or leading to feelings of embarrassment (Zach and Oberwaldner, 1987; Dodd and Prasad, 2005; Main and Rand, 2023). Postural drainage Focuses on positioning the body in specific ways to target different areas of the lungs.

Common positions include head-down, head-up, side-lying, and prone, which all help gravity move mucus toward larger airways. However, this technique has limitations, such as rib fractures or spinal injuries. Chest percussion involves clapping or tapping of the chest wall with hands or a special percussion device. It appears to facilitate the evacuation of mucus trapped in the airways. After percussion, patients are typically encouraged to take deep breaths and cough to clear the mucus, which helps prevent complications like mucus plugs or lung collapse. By combining these approaches, MCP offers an effective way to clear the airways, support respiratory health, and reduce the risks associated with mucus retention (Tripathi and Sankari, 2024).

Physical Activity and Exercise

Although exercise cannot replace traditional airway clearance techniques (ACTs), it is a significant component of managing cystic fibrosis (CF). Regular physical activity helps clear mucus through processes like mechanical vibration, increased airflow, and changes in mucus consistency. This supports the removal of infected secretions, reduces lung inflammation, and helps protect the airways from damage. Research suggests that exercise can lower the frequency of pulmonary exacerbations, reduce hospital stays, and improve physical strength, posture, and mental well-being. Due to better respiratory function and increased life expectancy, exercises should be an essential part of airway clearance routines. Healthcare professionals should encourage individuals with CF to incorporate regular physical activity into their care plans to maximize its benefits (Ding and Zhong, 2020; Heinz et al., 2022).

Mucolytics

Mucolytics, when combined with airway clearance techniques Wark and McDonald, (2023), have become essential in managing cystic fibrosis by helping to break down and remove the thick, persistent mucus that characterizes the condition (Esposito et al., 2023). Integrating mucoactive therapy into active chest physiotherapy (ACP) likely boosts treatment effectiveness and improves airway clearance, as these therapies work synergistically to enhance therapeutic outcomes (Gursli et al., 2022; Wark and McDonald, 2023). Dornase alfa, hypertonic saline, and mannitol are treatments designed to improve airway clearance by using different mechanisms to reduce excess mucus in the respiratory tract.

Dornase alfa works by breaking down mucus and inflammatory substances in the airways, acting somewhat like molecular "scissors". It is administered through inhalation using a nebulizer, typically once or twice daily. Regular use helps to clear mucus, makes it easier to cough up, and lowers the risk of lung exacerbations. This medication is suitable for both children and adults. Hypertonic saline increases salt concentration in the airways, which raises the fluid volume on airway surfaces. The solution is administered once or twice a day via a nebulizer before airway clearance exercises.

Inhalation leads to improved lung function and reduced respiratory symptoms. It is also recommended for children and adults. Mannitol is a hyperosmotic agent with mucus-clearing properties, provided as a dry powder inhaled through a portable inhaler. Mannitol improves mucociliary clearance, helping to clear mucus from the airways. This therapy is primarily intended for adults. These treatments collectively enhance respiratory function, helping to reduce complications and support respiratory health in people with chronic lung conditions (Nevitt et al., 2020; Yang and Montgomery, 2021; Esposito et al., 2023).

Antibiotic therapy

Antibiotic therapy plays a critical role in managing cystic fibrosis (CF), particularly in addressing chronic airway infections and pulmonary exacerbations. Patients with CF often struggle with persistent bacterial infections, which lead to continuous lung damage and decreased respiratory function (Rossi et al., 2021). Proper antibiotic therapy is crucial to prevent the negative effects of these infections, improve lung health, and extend life expectancy (Lund-Palau et al., 2016). Antibiotics not only reduce bacterial load but also address the associated inflammation that exacerbates lung damage (Goss, 2019). Inhaled, oral, or intravenous antibiotics are often employed to target specific pathogens, with treatment tailored to the individual based on microbiological data and clinical response (Zemanick and Bell, 2019).

For early infections, particularly those caused by *Pseudomonas aeruginosa*, eradication strategies using antibiotics have shown promising outcomes, preventing the progression of chronic infection and associated complications (Ng et al., 2020). For chronic infections, long-term suppressive antibiotic therapy can help reduce exacerbations and slow disease progression (Zemanick and Bell, 2019). Despite the challenges of emerging antibiotic resistance and the polymicrobial nature of CF airway infections, the use of antibiotics remains essential (Rossi et al., 2021). When combined with advancements in microbiological testing and personalized treatment regimens, antibiotics provide significant benefits in improving the quality of life and overall outcomes for people with CF (Ng et al., 2020).

Most individuals with CF typically experience chronic bacterial infections in their airways. These infections are often polymicrobial but typically driven by *Pseudomonas aeruginosa* and are rarely fully eliminated with antimicrobial treatments (Goss, 2019). *Pseudomonas aeruginosa*, a common environmental bacterium, frequently infects the airways of CF patients. Although these infections are primarily caused by antibiotic-sensitive strains, they evolve into chronic, life-threatening conditions leading to premature death. It is possible due to bacteria's resistance to antibiotics, which results from the ability to form biofilms in the airways (Rossi et al., 2021). There is a strong connection between chronic *Pseudomonas aeruginosa* infections and a more rapid deterioration of lung function, a higher occurrence of pulmonary exacerbations (PEx), and increased mortality rates.

Notably, despite these severe respiratory complications, the infection rarely spreads beyond the lungs or leads to bacteremia in individuals with CF, as it typically remains confined to the airways (Lund-Palau et al., 2016). The primary goal in treating chronic infections is to suppress bacterial growth, minimize inflammation, and reduce the frequency of exacerbations rather than achieving complete bacterial eradication. Inhaled antibiotics, such as tobramycin, aztreonam, or colistin, are commonly used for long-term maintenance. These medications are often administered in cycles of 28 days on, followed by 28 days off to maintain effectiveness while minimizing side effects and resistance development.

When inhaled therapy alone is insufficient, oral or IV antibiotics may be added to the regimen. Macrolides, particularly azithromycin, are frequently prescribed due to their anti-inflammatory properties. Evidence suggests that azithromycin can decrease the number of exacerbations in patients chronically infected with *P. Aeruginosa* (Zemanick and Bell, 2019). Antibiotic resistance is a critical concern in cystic fibrosis (CF) management. The prolonged exposure to antibiotics eventually fosters the emergence of resistant strains. *Pseudomonas aeruginosa*, a prevalent CF pathogen, is particularly prone to developing multidrug resistance due to repeated exposure and its ability to adapt to long-term colonization (Abbott et al., 2019; Goss, 2019).

CFTR modulators

Cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulators represent a groundbreaking targeted therapy for CF, focusing on enhancing the function of the faulty CFTR protein responsible for the disease (Burgener and Moss, 2018). CFTR modulators are a class of small molecules categorized as potentiators or correctors designed to address the protein abnormalities caused by CFTR mutations. Potentiators work by increasing the likelihood that the CFTR channel will open at the cell surface, improving chloride transport and reducing the thickness of exocrine secretions. Correctors, on the other hand, aim to improve the folding of the CFTR protein, increasing the amount of functional protein available for modulation.

When used together with a potentiator, correctors can lead to significant improvements in lung function for individuals with CF. (Esposito et al., 2023). Ivacaftor, the sole CFTR potentiator currently approved, enhances chloride transport by increasing the likelihood of the CFTR channel remaining open at the cell surface (Van-der-Meer et al., 2021). This treatment resulted in notable enhancements in FEV1, body weight, and quality of life, as well as a reduction in sweat chloride levels among patients possessing at least one G551D

allele (Rafeeq and Murad, 2017). Prolonged administration of this therapy has been linked to a reduced likelihood of requiring lung transplantation and enhanced survival rates.

However, it does not significantly impact the rate of full lung function recovery following a flare-up of symptoms (Lopes-Pacheco, 2020). At present, three CFTR correctors are available on the market. The first, lumacaftor, a first-generation corrector, targets the F508del-CFTR mutation to enhance its cellular processing and trafficking, ultimately boosting the amount of functional CFTR protein at the cell surface. Tezacaftor, a second-generation corrector derived from lumacaftor's design, offers enhanced pharmacokinetic properties and reduced side effects, targeting the first Membrane Spanning Domain (MSD-1) with precision (Lopes-Pacheco, 2020; Van-der-Meer et al., 2021).

Elexacaftor, a next-generation corrector, interacts with distinct sites on the CFTR protein compared to tezacaftor, creating an additive effect that enhances the cellular processing and trafficking of F508del-CFTR, ultimately increasing the quantity of CFTR protein available at the cell surface (Van-der-Meer et al., 2021). Ivacaftor is approved as a standalone treatment for certain gating mutations in the CFTR gene. Additionally, it is available in combination therapies: paired with lumacaftor for individuals who have two copies of the F508del mutation, combined with tezacaftor for those with either two F508del mutations or an F508del mutation alongside certain residual function mutations (Van-der-Meer et al., 2021).

Ivacaftor is also approved as part of triple therapy with elexacaftor and tezacaftor. Initially authorized for individuals with CF who have at least one copy of the F508del mutation, this treatment is now also approved in certain regions for patients with CF who do not carry the F508del mutation (Burgel et al., 2024). The most frequently utilized CFTR modulators include a triple-drug combination and ivacaftor as a standalone treatment. These therapies have shown significant effectiveness in lowering sweat chloride levels, alleviating respiratory symptoms such as cough and sputum production, and reducing pulmonary flare-ups.

Additionally, they have been associated with improved quality of life, increased forced expiratory volume, and higher body mass index in individuals with CF who possess the appropriate CFTR variants (Burgel et al., 2024). Since the introduction of CFTR modulators (CFTRm), a decrease in Pseudomonas aeruginosa infections has been noted in CF registries. However, chronic P. aeruginosa infections often persist, even in those receiving CFTRm. This suggests that lots of patients will not be able to go off inhaled antibiotics (Burgel et al., 2024).

Nutrition

The gastrointestinal (GI) exhibits signs of CF-related complications. In individuals with CF, malabsorption primarily results from pancreatic insufficiency (PI). Blockages in the pancreatic ducts impair the delivery of digestive enzymes and bicarbonate to the intestinal lumen. This disruption leads to exocrine PI, reduced absorption of fat-soluble vitamins (A, D, E, and K), and increased acidity within the intestinal lumen (Mariotti et al., 2023). Vitamins A, D, E, and K play crucial roles in maintaining overall health. Vitamin A supports vision, immune function, tissue repair, and cell differentiation while also aiding in embryonic development and maintaining epithelial barriers. Vitamin D is in charge of calcium and phosphorus levels, promotes bone health, and has an impact on the function of immune, epithelial, and muscle cells.

Vitamin E is an antioxidant which aims to protect cells from damage and supports neurological and muscle health. Last but not least, Vitamin K is necessary for normal bleeding time and bone mineralization, ensuring proper coagulation and maintaining bone strength (Brownell et al., 2019). Pancreatic enzyme replacement therapy (PERT) is necessary for 80–90% of individuals with CF. PERT involves the oral intake of pancreatic enzymes, including lipase, amylase, and protease, to facilitate the digestion of fats and proteins by delivering these enzymes directly to the duodenal lumen (Mariotti et al., 2023). Supplementation of fat-soluble vitamins should commence in patients with pancreatic insufficiency concurrently with the start of pancreatic enzyme replacement therapy (Singh and Schwarzenberg, 2017).

Table 1 Summary of Key Point in Cystic Fibrosis

Key points	Summary
Genetic Basis	Caused by mutations in the CFTR gene.
Symptoms	Affects multiple organ systems, causing respiratory infections, pancreatic insufficiency, malabsorption, liver dysfunction, and male infertility
Airway Clearance Therapy	Includes Specific Cough Technique (SCT), Forced Expiration Technique (FET), Positive Expiratory Pressure (PEP) therapy, and Manual Therapy which help clear mucus and improve breathing.
Physical activity	Regular physical activity supports mucus clearance and improves well-being
Mucolytics	Dornase alfa, hypertonic saline, and mannitol reduce mucus thickness, making it easier to clear from the airways.
Antibiotic Therapy	Treats chronic infections using inhaled, oral, or IV antibiotics. Resistance remains a major challenge.
CFTR Modulators	Ivacaftor, lumacaftor, tezacaftor, and elexacaftor enhance CFTR function, leading to better lung performance and quality of life.
Nutritional Support	Pancreatic enzyme replacement therapy (PERT) supports digestion, while fat-soluble vitamin supplementation (A, D, E, K) prevents deficiencies.

4. CONCLUSIONS

Cystic fibrosis (CF) is a complex, multi-system disease that requires a comprehensive and individualized approach to management. Although improvements in CF management have noticeably improved patient quality of life, difficulties such as chronic infections, antibiotic resistance, and nutrient deficiencies still remain. It shows the need for further research.

Author's Contributions

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Informed consent

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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