WDOWIAK, Natalia, CHOINKA, Martyna, KONOPKA, Agata, SZCZEPANIAK, Zuzanna, ADAMSKA, Kinga and KACZMAREK, Aleksandra. Cystic Fibrosis: A Review of Current Knowledge, Treatment Methods and Diagnostics. Quality in Sport. 2024;23:55065. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.23.55065
https://apcz.umk.pl/QS/article/view/55065

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 10.09.2024. Revised: 19.09.2024. Accepted: 28.09.2024. Published: 30.09.2024.

Cystic Fibrosis: A Review of Current Knowledge, Treatment Methods and Diagnostics

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Abstract

Introduction: Cystic fibrosis (CF) is an autosomal recessive genetic disease caused by a mutation in the CFTR gene. Characteristic symptoms include persistent lung infection, pancreatic insufficiency, and elevated sweat chloride, although many patients have mild or atypical symptoms. Diagnosis of CF is based primarily on the detection of genetic and/or functional abnormalities in the CFTR gene. Treatment includes pancreatic enzyme replacement therapy, mucolytic drugs, respiratory physiotherapy, and antibiotic therapy.

Purpose of the work: This study aims to review and characterize the clinical and pathophysiological aspects of cystic fibrosis.

Materials and methods: A comprehensive analysis of research papers available on PubMed, Google Scholar, Web of Science, Embase and Scopus was undertaken using the searchterms encompassing the following keywords: Cystic fibrosis, CFTR, Chloride Channels, Lung Inflammation, Diagnosis, Gene therapy, Cystic fibrosis Treatment.

Results: Cystic fibrosis is the most common, multisystem, life-threatening recessive disease in the white race. Although many organs are affected, the leading cause of morbidity and mortality is lung disease. Treatment requires pharmacotherapy, extensive physiotherapy, and nutritional support. In recent years, there has been significant progress in the diagnosis and treatment of cystic fibrosis, and the average survival has increased from a few to almost 50 years.

Keywords: Cystic fibrosis, CFTR, Chloride Channels, Lung Inflammation, Diagnosis, Gene therapy, Cystic fibrosis Treatment.

Introduction

Cystic fibrosis (CF) is a multi-organ, monogenic genetic disease, inherited in an autosomal recessive manner, caused by mutations in the CFTR gene, encoding the cystic fibrosis transmembrane conductance regulator, located on chromosome 7. It was first officially described in 1949. The lack of CFTR protein or its impaired function causes malabsorption of fat and chronic lung infections. Symptoms mainly concern the lungs and pancreas, but also the upper respiratory tract, liver, intestines, kidneys and male reproductive organs. Treatment of cystic fibrosis mainly consists of taking pancreatic enzyme replacement therapy, using mucolytic drugs, respiratory physiotherapy, antibiotic therapy, and some patients with severe symptoms still require lung transplantation. Thanks to early diagnosis, based mainly on the detection of abnormalities in the CFTR gene, the life expectancy of patients with CF has been extended to an average of 50 years. Previously, this disease was considered fatal in infancy and childhood. Today, thanks to newborn screening, this is a thing of the past [1-3].

Epidemiology

Cystic fibrosis (CF) is the most common life-shortening genetic disease among whites in the United States, affecting over 30,000 people in the U.S. and 80,000 worldwide. It primarily impacts the pulmonary system, leading to significant morbidity and mortality. The prevalence of CF varies by geography and ethnicity, being most common in whites and northern Europeans, with the highest incidence in Ireland and rare cases in Finland and non-Caucasian populations. The F508del mutation is the most prevalent CF-causing mutation among Caucasians. Due to advances in specialized care, survival rates have improved significantly, with the median life expectancy in the U.S. reaching 37 years by 2008. [4-6]

Pathophysiology

The pathophysiology of cystic fibrosis begins at the genetic level, where mutations in the CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) gene lead to various defects in the CFTR protein that functions as a chloride channel on the cell membrane [7]. The CFTR gene is located on the long arm of chromosome 7 (7q31.2). The protein it encodes primarily acts as a chloride channel regulated by cyclic adenosine monophosphate (cAMP) in various types of polarized epithelial cells. Serving as a transepithelial anion channel, CFTR facilitates the transport of chloride, gluconate, and bicarbonate [5]. Normally, the CFTR protein is involved in the regulation of salt and water transport across epithelial cells, especially in the lungs, pancreas, and other organs. When CFTR function is compromised due to mutations, it leads to the hallmark features of CF, including thickened mucus secretions, chronic respiratory infections, and pancreatic insufficiency [8].

Over 2,000 mutations have been identified, and these are broadly categorized into six classes based on their impact on the CFTR protein's function and structure [9]:

- Class I mutations include frameshift, splicing, or nonsense mutations that introduce premature termination codons (PTCs), leading to significantly reduced or absent CFTR protein expression.
- Class II mutations cause the CFTR protein to misfold, leading to its premature degradation by the endoplasmic reticulum's (ER) quality-control system, which severely limits the number of CFTR proteins that reach the cell surface.
- Class III mutations disrupt the regulation of the CFTR channel, resulting in abnormal gating with a reduced probability of the channel being open.
- Class IV mutations affect the channel's conductance by obstructing the ion conduction pore, leading to decreased unitary conductance.
- Class V mutations do not alter the protein's conformation but affect its abundance by causing promoter or splicing defects.
- Class VI mutations destabilize the CFTR channel in post-ER compartments and/or at the plasma membrane (PM), reducing its conformational stability and/or introducing additional internalization signals, which accelerates PM turnover and reduces expression at the apical PM [10].

For many identified mutations, the impact on disease severity is not yet fully understood, but ongoing research aims to evaluate their functional and clinical consequences.

These mutations disrupt the normal function of the CFTR protein, leading to an imbalance in chloride and sodium ion transport across epithelial cells. This imbalance causes the production of thick, sticky mucus that obstructs airways in the lungs and ducts in the pancreas

and other organs [11]. In the lungs, the mucus build-up promotes chronic bacterial infections and inflammation, leading to progressive lung damage, a primary cause of morbidity and mortality in CF patients [5].

Some individuals with CFTR mutations that allow for about 10% of the normal level of CFTR mRNA may have normal sweat chloride levels, lung function, and pancreatic function, and therefore might not exhibit clinical symptoms of CF, though males may experience congenital bilateral absence of the vas deferens. Around 50% of American CF patients are homozygous for the ΔF508 mutation. However, even among these patients with identical CFTR genes, disease severity can vary widely. This suggests that environmental factors, therapeutic interventions, and other genetic factors may influence the course of the disease. Studies have shown that exposure to tobacco smoke and lower socioeconomic status negatively affect outcomes, highlighting the importance of clinical guidance and social policy. While aggressive treatment regimens are crucial, the optimal approach is still being determined. Even when controlling for these factors, inherent differences in the CF disease process remain, prompting ongoing research into modifier genes [12].

Understanding these molecular mechanisms has been crucial in developing targeted therapies aimed at correcting specific defects in the CFTR protein, offering hope for more effective treatments and improved outcomes for individuals with CF [9].

Clinical Manifestations

Cystic fibrosis is the result of a dysfunction of the CFTR protein, which acts as a chloride channel in exocrine glands. This defect leads to the formation of thick, sticky secretions in the lungs, pancreas, liver, intestines, and reproductive tract, as well as increased salt content in sweat gland secretions. Ultimately, the progressive lung disease becomes the primary cause of complications and mortality in CF patients. The course of the disease can be highly variable, starting from a few months after birth to several decades later, with many patients exhibiting mild or atypical symptoms. For this reason, doctors should be cautious not to exclude CF as a potential diagnosis, even if patients only show a few typical symptoms of the disease [1,3].

- **Respiratory tract involvement:** Typical respiratory symptoms in cystic fibrosis include a persistent, productive cough, hyperinflation of the lung fields visible on chest radiographs, and pulmonary function tests indicating obstructive airway disease. As the disease progresses, recurrent infections due to the accumulation and release of inflammatory cells cause damage to the bronchial walls, leading to the loss of bronchial support from cartilage and muscle tension, and ultimately resulting in bronchiectasis. Disease progression is characterized by acute exacerbations of cough, tachypnea, dyspnea, increased sputum production, malaise, anorexia, and weight loss. These acute episodes are associated with a transient loss of lung function, which improves with treatment but often results in permanent loss of lung function over time [9]. After many years of CF, chronic respiratory infection with Staphylococcus aureus or Pseudomonas aeruginosa is often detected based on radiological evidence of bronchiectasis. The airways of CF patients can also be colonized or infected by other microorganisms, including Stenotrophomonas maltophilia, Achromobacter xylosoxidans, the Burkholderia cepacia complex, atypical mycobacteria, and the mold Aspergillus fumigatus. Persistent airway colonization and bacterial infections (especially by P. aeruginosa) can exacerbate the inflammatory response, leading to the release of large amounts of DNA and matrix proteins by neutrophils. These substances,

combined with impaired airway clearance and chronic inflammation, increase mucus viscosity in the airways [13,14].

- **Sinus disease:** Most patients with cystic fibrosis develop sinusitis. Symptoms of sinusitis may include chronic nasal congestion, headaches, cough due to persistent post-nasal drip, and sleep disturbances. Sinus infections can lead to exacerbations in the lower respiratory tract in some patients, although the microorganisms found in the sinuses are not always the same as those found in the lungs. Interestingly, some patients with isolated chronic sinusitis may display symptoms suggesting CFTR dysfunction, even though they do not meet the diagnostic criteria for CF. In such cases, specialists classify this condition as a CFTR-related disorder [15].

- **Digestive system diseases:** Approximately 85% of individuals with cystic fibrosis (CF) eventually develop clinically significant pancreatic insufficiency. Common signs and symptoms of pancreatic insufficiency include steatorrhea, characterized by frequent, bulky, foul-smelling stools that may be oily, as well as insufficient or poor weight gain due to malabsorption of fats and proteins. Infants with severe, untreated pancreatic insufficiency may present with signs such as edema, hypoproteinemia, electrolyte loss, and anemia resulting from inadequate absorption of macro- and micronutrients. Some patients may also exhibit symptoms related to deficiencies in fat-soluble vitamins, such as vitamins A, D, E, and K. Vitamin K deficiency can lead to coagulopathy, while a lack of vitamin D can cause rickets. Moreover, individuals with exocrine pancreatic insufficiency often develop endocrine pancreatic dysfunction, which can result in glucose intolerance and CF-related diabetes [16]. Approximately 10% to 20% of newborns with CF experience meconium ileus, a condition characterized by bowel obstruction due to meconium, which is associated with a poor prognosis for CF. Rectal prolapse, previously rarely observed in children with CF, is now seen more frequently and appears to be associated with constipation and/or malnutrition. Additionally, many patients with CF suffer from focal biliary cirrhosis due to thickened bile, which can lead to elevated levels of alkaline phosphatase in the blood and liver enlargement [17].

- **Reproductive system diseases:** Approximately 95% of men with cystic fibrosis are infertile due to issues with sperm transport, although spermatogenesis itself is not impaired. Women with CF have lower fertility compared to healthy women, primarily due to malnutrition and the production of abnormally thick cervical mucus. However, women with CF can still conceive and should receive proper counseling on contraception and decisions related to parenthood [18].

- **Nutrition and growth disorders:** Patients with cystic fibrosis (CF) have reduced bone mineral content and an increased incidence of fractures and kyphoscoliosis. Clubbing of the fingers is commonly seen in patients with long-term disease, whereas hypertrophic osteoarthropathy is rarely observed [3].

Comorbidities

Cystic fibrosis-related diabetes (CFRD)

The most common endocrine complication of CF is diabetes, caused by progressive fibrosis of the pancreas and damage to the pancreatic islets, and is associated with increased mortality. Early diagnosis and treatment are important because they improve survival in patients with

CFRD. The prevalence is about 20% in children and increases after the age of 10, reaching 40% to 50% in adults. CFRD is caused by reduced insulin secretion and, in part, insulin resistance. It is hypothesized that high blood sugar levels with the resulting high levels of fluid glucose on the airway surfaces create an environment that favors bacterial growth and inflammation. The development of CFRD is associated with a more rapid decline in FEV1, worsening respiratory disease, and an increased frequency of pulmonary exacerbations. On the other hand, good control of hyperglycemia reduces the number of respiratory exacerbations and slows the progression of lung disease. In patients with cystic fibrosis, annual screening with oral glucose tolerance tests from the age of 10 is recommended for diabetes, and since it is caused by insulin deficiency, the only treatment is insulin therapy [2,12,19]

Male infertility

90% of men with CF have congenital bilateral absence of the vas deferens (CBAVD), which can also occur as an isolated clinical feature in CFTR-related disorders. Although spermatogenesis is normal in men, 98% of them are infertile. However, some CFTR mutations may be associated with preserved fertility, so semen analysis is necessary to determine fertility. The most common genotype in single-organ disorders is the in trans combination of the CF mutation and the IVS8-5T polymorphism [2,19].

Bone disease

People with CF often have osteopenia and osteoporosis, and low bone mineral density on dual-energy X-ray absorptiometry (DEXA), with prevalences of 38% and 23%, respectively, in adults, and appear to decline over time. The risk of bone disease is associated with many factors, including malnutrition, low BMI, poor mobility, calcium, vitamin D and K deficiency, hypogonadism, corticosteroid use, pancreatic insufficiency, CF-related diabetes, recurrent pulmonary exacerbations, low peak bone mass, and circulating inflammatory cytokines. The test of choice for determining bone mineral density and bone mineral content in people with CF is dual-energy X-ray absorptiometry (DEXA). Strategies to prevent and treat low bone mineral density include ensuring adequate nutrition of patients, supplementing calcium, vitamin D and K, encouraging weight-bearing exercise, limiting corticosteroid therapy, and considering bisphosphonate therapy in those undergoing long-term treatment [2,19]

Pneumothorax and Pulmonary Hypertension

About 3% of patients with cystic fibrosis develop spontaneous pneumothorax during their lifetime. In addition, patients also develop pulmonary hypertension, which is correlated with hypoxemia and reduced lung function. This mainly affects older people, in the advanced stage of the disease, which is associated with a worse prognosis and higher mortality, and treatment of pulmonary hypertension does not bring benefits to these patients. The best treatment to limit pulmonary hypertension is to delay the progression of the disease. Furthermore, the presence of subclinical pulmonary hypertension is associated with increased mortality in cystic fibrosis and is an absolute contraindication to pregnancy [2,19].

Anxiety and depression

The prevalence of depression ranges from 8% to 29% in children with CF and from 13% to 33% in adults with CF, which is higher than that observed in the general population [19]. In

addition, rates of depression in caregivers of people with CF are 20–35%, which translates into a higher prevalence of anxiety/depression in sick children. Factors that influence the occurrence of psychological symptoms also include reduced lung function, poorer treatment adherence, poorer quality of life, and more frequent hospitalizations. It is recommended that all patients with CF over the age of 7 years be screened for anxiety and depression annually. Preventive, supportive, psychological, and pharmacological treatment is recommended, appropriate to the severity of symptoms.

Diagnostics

In 2017, the Cystic Fibrosis Foundation published consensus guidelines that established the criteria for diagnosing cystic fibrosis. According to these guidelines, a diagnosis of cystic fibrosis can be made if a patient exhibits clinical features consistent with the disease, such as a positive newborn screening result, characteristic clinical features (e.g., chronic and recurrent sinus and lung disease, nutritional and gastrointestinal abnormalities, male reproductive system anomalies such as the absence of the vas deferens, and/or salt-loss syndromes), or a positive family history of cystic fibrosis. Additionally, the diagnosis must be supported by evidence of CFTR dysfunction, such as a sweat chloride concentration ≥60 mmol/L.These guidelines form the foundation of modern cystic fibrosis diagnostics, emphasizing the importance of a comprehensive approach that combines screening results, family history, and specific clinical features to ensure an accurate diagnosis and optimal treatment for patients.Early diagnosis of cystic fibrosis is crucial, as it allows for the timely introduction of appropriate treatment and improves the quality of life for patients [20].

Prenatal diagnosis of cystic fibrosis is a critical aspect of managing the risk for couples with a known probability of having a child affected by the disease. For couples where the risk of having a child with cystic fibrosis is 1/4 or 1/2, the molecular strategy used in prenatal diagnosis is relatively straightforward. It involves detecting known CF-causing variants that were previously identified either in a proband or in the parents. Significant advancements have been made in the field of preimplantation genetic diagnosis and non-invasive prenatal testing (NIPT). For several years, early detection of paternal CF variants in maternal blood has been routinely available, and it is expected that in the near future, non-invasive procedures based on NGS haplotyping approaches will be accessible to all at-risk couples.

Prenatal diagnosis of cystic fibrosis can also be pursued in the absence of a family history of the disease if digestive abnormalities are observed during pregnancy via ultrasound. Such abnormalities include echogenic fetal bowel, fetal bowel loop dilation, and non-visualization of the fetal gallbladder. Depending on national regulations, gestational age, and ultrasound findings, the strategy and scope of testing may mirror those used in diagnosis. Ensuring coverage of population-specific variants in this context is crucial [21].

The continuous newborn screening test for cystic fibrosis is a detailed process aimed at the early detection of this genetic disorder. The screening is typically performed within 24–72 hours after birth. During this time, a blood sample is collected from the newborn’s heel.

The blood is drawn using a specialized device called a "heel lance" and placed on screening cards (filter paper). The sample is then sent to a laboratory. The purpose of the test is to measure the level of immunoreactive trypsinogen (IRT), an enzyme whose concentration is typically elevated in cases of cystic fibrosis. If the IRT result is elevated, a sweat test is conducted to confirm the diagnosis of cystic fibrosis [22].

The sweat test with pilocarpine iontophoresis is a critical tool in the diagnosis of cystic fibrosis and is considered the gold standard. Developed in 1959 by Lewis Gibson and Robert Cooke, this test measures the chloride concentration in a patient's sweat. The procedure involves stimulating sweat glands using pilocarpine, followed by the collection and analysis of the sweat sample for chloride content.The sweat test should be performed as soon as possible after a positive newborn screening (NBS) result, but not earlier than 48 hours after birth due to transiently elevated sodium levels in sweat during the first 24 hours of life. It is recommended to perform the test between 10 days and 4 weeks of age. To increase the likelihood of collecting an adequate sweat sample, the infant should weigh over 2 kg or be corrected to 36 weeks of gestational age. The test should also be performed on infants with meconium ileus and on children with symptoms suggestive of CF, such as recurrent respiratory infections or failure to gain weight, regardless of age or NBS results.

The results of the sweat test are classified as diagnostic, intermediate, or unlikely for cystic fibrosis:

- **Diagnostic** results show chloride concentrations ≥60 mmol/L, which requires confirmation with a second sweat test or identification of two CF-causing genetic variants.

- **Intermediate** results fall within the range of 30–59 mmol/L. In such cases, the test should be periodically repeated, and further evaluation at a specialized CF center should be considered. A diagnosis of CF can still be made if the patient with an intermediate result has two identified CF-causing genetic variants.

- **Unlikely** results are chloride concentrations <30 mmol/L, which generally rule out cystic fibrosis. However, if two CF-causing genetic variants are identified in a patient with such a result, the diagnosis of CF should be considered.

Any abnormal sweat test result should be repeated or confirmed with genetic testing to ensure diagnostic accuracy [20].

Molecular genetic tests represent the second stage of confirmatory diagnostic testing for cystic fibrosis. Given that there are over 2,000 known CFTR mutations on the long arm of chromosome 7, the informativeness of these tests varies depending on the mutation spectrum analyzed and the patient’s ethnic background. Of these mutations, 306 have been characterized as disease-causing. The type of mutation can often provide clues about the disease. For instance, the most common mutation, F508del, is found in 70% of German patients but only in 25% of patients of Turkish descent. In Germany, the neonatal screening mutation spectrum (including all mutations with a frequency ≥0.1%) covers 95.5% of all CFTR mutations documented in the German cystic fibrosis registry as of 2012. This spectrum allows for a definitive diagnosis by identifying two disease-causing mutations in 90% of patients. A more comprehensive genetic investigation of the CFTR gene can detect up to 99% of all mutations, making it possible to find two mutations in 98% of all cystic fibrosis patients. Patients with a positive sweat test should undergo molecular genetic testing to confirm the diagnosis, enable genetic counseling for the family, and explore potential mutation-specific treatments. Conversely, patients with a genetically confirmed diagnosis should still undergo a sweat test to ensure that the diagnosis is not the result of a sample mix-up.In specific cases, electrophysiological tests may also be employed. These include measuring the short-circuit current in biopsy samples of rectal mucosa and/or nasal potential difference, which can provide additional diagnostic information [1].

After confirming a diagnosis of cystic fibrosis, a series of tests and evaluations are conducted, which are crucial for effectively managing the disease and optimizing treatment. The process begins with regular visits to a healthcare provider, where clinical symptoms and the overall health of the patient are assessed. The physician conducts a detailed interview and physical examination, paying particular attention to pulmonary, pancreatic, and general symptoms. For pulmonary function assessment, spirometry is performed to measure the volume of air and the speed of airflow during inhalation and exhalation. This helps evaluate the degree of lung damage and monitor disease progression and treatment effectiveness. Pulse oximetry, which measures blood oxygen levels, is also used to monitor respiratory function and detect any potential hypoxia.Imaging studies, such as chest X-rays, allow for the assessment of lung condition and detection of any infections, bronchiectasis, or other pathological changes. In more specific cases, a computed tomography scan of the chest may be performed for more detailed evaluation of lung and bronchial structure.Regarding pancreatic function, stool samples are analyzed to assess digestion and pancreatic function. The presence of fat in the stool can indicate insufficient production of pancreatic enzymes. Monitoring levels of pancreatic enzymes, which may be supplemented in therapy, is also important for evaluating treatment effectiveness [23].

Treatment

Cystic fibrosis is a chronic genetic disease that requires a comprehensive therapeutic approach. In managing the respiratory system, it is crucial to reduce mucus viscosity and facilitate its removal from the lungs. To achieve this, inhaled β-agonists are used in combination with humidified oxygen and a 3–6% hypertonic saline solution and dornase alfa, which help to thin and clear the thick, sticky mucus. Daily care also involves physical therapy and physical activity. The use of positive expiratory pressure (PEP) devices or high-frequency chest wall oscillation (HFCWO) vests supports the process of airway clearance. For the digestive system, to prevent or treat intestinal obstruction, oral hydration and osmotic laxatives are used for partial blockages. In cases of complete obstruction (DIOS), hyperosmolar contrast enemas are recommended. To prevent recurrences, oral polyethylene glycol 3350 may be given for 6 months to a year. For pancreatic insufficiency, pancreatic enzyme replacement therapy (PERT) is administered, which includes a combination of proteases, lipases, and amylases to support digestion and nutrient absorption. To ensure adequate nutrition and prevent dehydration in cystic fibrosis patients, a high-calorie, fat-rich diet is recommended along with supplementation of vitamins ADEK and minerals such as fluoride and zinc. Additionally, sodium chloride supplementation is adjusted based on the patient's age and environmental conditions to maintain proper electrolyte balance and hydration [24].

Gene therapy and CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) modulators represent a significant breakthrough in the treatment of cystic fibrosis. Cystic fibrosis is a genetic disorder caused by mutations in the CFTR gene, which encodes a protein responsible for chloride ion transport across cell membranes. These mutations lead to CFTR protein dysfunction, resulting in the production of thick, sticky mucus in the lungs, pancreas, and other organs.

CFTR Modulators CFTR modulators are drugs that bind to the CFTR protein, increasing its availability and functionality on the cell surface. There are several categories of therapies that can ultimately increase the amount of CFTR protein available at the cell surface, including:

- Potentiators: These drugs increase the activity of the CFTR protein, enhancing chloride and bicarbonate ion transport. They are particularly effective for class III and IV mutations, where the primary protein defect is related to ion channel dysregulation. An example of a potentiator is ivacaftor.

- Correctors: These drugs bind to the immature CFTR protein and assist in its folding, processing, and trafficking to the cell membrane. They have shown effectiveness in treating mutations such as F508del. Correctors include lumacaftor, tezacaftor, and elexacaftor.

- Read-Through Agents: Targeting class I nonsense mutations, these drugs suppress premature stop codons, allowing the production of full-length CFTR protein.

- Amplifiers: These drugs stabilize mRNA, increasing the production of immature CFTR protein, which can be particularly effective for class V mutations.

- Stabilizers: Theoretically, these drugs extend the lifespan of mature CFTR protein on the cell membrane, counteracting the effects of class VI mutations.

One of the most advanced and effective combinations of CFTR modulators is the triple therapy known as Kaftrio (known as Trikafta in the United States). It consists of two correctors (elexacaftor and tezacaftor) and one potentiator (ivacaftor). Ivacaftor was approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2012 as the first clinically available CFTR modulator. Ivacaftor is a potentiator that binds to the CFTR protein and prolongs the time that the ion channel remains open, thereby increasing ion transport across the cell membrane.

Clinical studies have shown that ivacaftor is exceptionally effective in restoring physiological function in patients with class III mutations, such as G551D. Ivacaftor significantly improved lung function, reduced respiratory symptoms, and decreased the frequency of exacerbations. It also had a beneficial impact on patient weight gain [25].

In the treatment of cystic fibrosis, a critical challenge is the vicious cycle of infection, inflammation, and airway obstruction, which leads to lung damage and ultimately respiratory failure. The eradication of microorganisms that are detected for the first time in the respiratory tract is a key aspect of therapy, particularly for dangerous pathogens like *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA). Chronic infections with these bacteria can significantly reduce lung function.

Key Medications Used in Eradication Therapy:

- Amoxicillin-Clavulanate: Administered orally for 2-4 weeks in the case of the first isolation of methicillin-sensitive *Staphylococcus aureus* (MSSA). This combination is effective against bacteria producing beta-lactamase enzymes, which can inactivate other penicillins.

- Cephalexin: An oral first-generation cephalosporin used if MSSA reappears within six months of the initial isolation. It is particularly useful when beta-lactamase production is not a concern.

- Trimethoprim/Sulfamethoxazole (TMP-SMX): Used in combination with other anti-staphylococcal antibiotics for recurrent infections, especially when other treatments have failed or in cases of resistance.

- Amikacin: An aminoglycoside given intravenously, often combined with cefalothin or meropenem in more severe cases. Administering amikacin once daily reduces the risk of nephrotoxicity, which is a common side effect.

- Meropenem: A broad-spectrum carbapenem antibiotic used intravenously in treating complex infections, particularly when resistance to other antibiotics is a concern.

- Teicoplanin: A glycopeptide antibiotic primarily effective against gram-positive bacteria, including MRSA, and is used in prolonged therapies due to its once-daily dosing convenience.

The treatment regimen is tailored based on the patient's clinical condition and the specific pathogen identified. Additionally, preventing cross-infections and adhering to strict hygiene protocols in medical centers are crucial to minimizing the spread of these infections [26].

Respiratory physiotherapy in individuals with cystic fibrosis is a crucial aspect of treatment, aimed at improving lung function, preventing infections, and slowing the progression of the disease. Since cystic fibrosis causes the accumulation of thick, sticky mucus in the airways, physiotherapy focuses on techniques that aid in clearing the lungs and enhancing ventilation.

One of the fundamental methods is postural drainage, where the patient assumes specific body positions that help drain mucus from the lungs. The patient often lies on their side or with their head below the level of the torso, allowing mucus to move towards the main airways, making it easier to cough up. Breathing techniques are also important, such as "huffing," which involves taking a deep breath followed by a forceful, controlled exhalation through an open mouth, helping to move mucus into larger bronchi. Another method is the active cycle of breathing technique, which involves performing short, strong exhalations after a deep breath to help clear the airways of accumulated mucus.

Respiratory physiotherapy often incorporates the use of supportive devices like Positive Expiratory Pressure (PEP), which generates positive pressure in the airways during exhalation, helping to open the airways and move mucus. Other devices, such as high-frequency chest wall oscillation (HFCWO) vests, generate rapid, oscillating vibrations in the chest, loosening mucus and making it easier to clear. Small, portable devices like Flutter or Acapella combine vibrations with positive expiratory pressure, aiding in mucus mobilization.

Inhalations of hypertonic saline or dornase alfa solutions are often used before respiratory physiotherapy to thin the mucus and facilitate its removal. Regular physical activity, such as running, swimming, or cycling, also supports lung ventilation and naturally aids in airway clearance. Exercise helps maintain overall physical fitness and improves quality of life [27].

Conclusions

Respiratory problems are undoubtedly the most important cause of morbidity and mortality in CF, but other significant gastrointestinal, hepatic, pancreatic, and nutritional symptoms are also observed. Over the past 30 years, significant progress has been made in understanding the basis and pathophysiology of the disease, which has led to new treatments and significant

improvements in outcomes for people with CF. The median survival time is now almost 50 years, which is an amazing achievement considering that it used to be a cause of death in childhood and even infancy. As diagnostic and treatment advances, new opportunities and challenges arise, and healthcare providers need to know how to monitor and educate patients to slow the progression of the disease and help them achieve the best quality of life.

Disclosure:

Authors' contribution:

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Project Administration: Natalia Wdowiak, Martyna Choinka, Agata Konopka

All authors have read and agreed with the published version of the manuscript.

Funding statement:
The study did not receive special funding.

Institutional review board statement:
Not applicable.

Informed consent statement:
Not applicable.

Data availability statement:
Not applicable.

Conflict of interest:
The authors declare no conflict of interest

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