VILNIUS UNIVERSITY
FACULTY OF MEDICINE

Medicine study program

Institute of Clinical Medicine, Clinic of Chest Diseases, Immunology and Allergology

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INTEGRATED STUDY MASTER'S THESIS

Cystic Fibrosis. Literature Analysis

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Vilnius, 2026

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1. ABBREVIATIONS

ASL – Airway surface liquid

ATP – Adenosine triphosphate

BMI – Body mass index

cAMP – Cyclic adenosine monophosphate

CF – Cystic fibrosis

cffDNA – Cell-free fetal DNA

CFRD – Cystic fibrosis-related diabetes

CFTR – Cystic fibrosis transmembrane conductance regulator

CFTR2 – Clinical and functional translation of CFTR

CRMS/CFSPID – Cystic fibrosis transmembrane conductance regulator related metabolic syndrome/CF screen positive, inconclusive diagnosis

DIOS – Distal intestinal obstruction syndrome

DNA – Deoxyribonucleic acid

ENaC – Epithelial sodium channel

ETI – Elexacaftor, Tezacaftor, Ivacaftor

FEV1 – Forced expiratory volume in one second

IBMX – 3-Isobutyl-1-methylxanthine

ICM – Intestinal current measurement

IRT – Immunoreactive trypsinogen

IRT-DNA – Immunoreactive trypsinogen/DNA analysis protocol

IRT-PAP – Immunoreactive trypsinogen/Pancreatitis-associated protein protocol

MeSH – Medical subject headings

NBD – Nucleotide-binding domain

NIPD – Non-invasive prenatal diagnosis

NPD – Nasal potential difference

PAP – Pancreatitis-associated protein

PCR – Polymerase chain reaction

PEP – Positive expiratory pressure

PERT – Pancreatic enzyme replacement therapy

PRISMA – Preferred reporting items for systematic reviews and meta-analyses

2. SUMMARY

This thesis is a narrative literature review of cystic fibrosis, focusing on the effects of modern CFTR modulators. Cystic fibrosis is a genetic disorder caused by mutations in the CFTR gene, leading to impaired chloride and bicarbonate transport, excessive mucus production, and progressive organ damage, particularly in the lungs. Progressive airway obstruction, chronic inflammation, and recurrent infections are the primary causes of morbidity and mortality.

Treatment was purely symptomatic and did not address the underlying cause. The introduction of CFTR modulators has fundamentally changed this approach by directly targeting the defective CFTR protein. The active ingredients are divided into potentiators, which enhance channel opening, and correctors, which improve protein folding and transport.

Clinically, these therapies have been shown to significantly improve long-term function, nutritional status, and quality of life. Furthermore, pulmonary exacerbations are reduced. In particular, the triple combination therapy consisting of Elexacaftor, Tezacaftor, and Ivacaftor represents a breakthrough and offers an effective treatment for many patients.

But problems remain, including limited long-term data, varying response rates by mutation type, and unanswered questions about long-term outcomes. In summary, CFTR modulators have the potential to redefine cystic fibrosis as a manageable chronic condition rather than a life-threatening one. Emerging strategies, for example, gene-based therapies, hold promise for further improving long-term outcomes and may ultimately be the way toward a definitive cure.

Aim and objectives: This thesis presents a comprehensive review of the literature on cystic fibrosis, with a specific emphasis on the role and clinical impact of CFTR modulators. It examines how CFTR modulator therapy has influenced the disease's pathophysiology, clinical results, and treatment strategies. Additionally, the review evaluates whether this approach provides meaningful advances over traditional therapies. The thesis also offers insights into the future prospects for managing the disease.

Materials and methods: A systematic literature search was conducted using databases such as the Cochrane Library, PubMed, Google Scholar, and Amboss, as well as a web search, to identify relevant studies on cystic fibrosis and CFTR modulators. The language was limited to German and English.

Results: The treatment enhances long-term function, nutritional health, and quality of life, while decreasing pulmonary exacerbations. The combination of Elexacaftor, Tezacaftor, and Ivacaftor represents a breakthrough, offering effective relief for many patients.

Conclusion: CFTR modulators are a major therapeutic advance in cystic fibrosis treatment. They address the defect itself and offer a great chance for future treatment for people with cystic fibrosis.

Keywords: Cystic fibrosis, F508del mutation, Lung function, CFTR modulators, Triple combination therapy.

SANTRAUKA

Šis darbas yra aprašomojo pobūdžio literatūros apžvalga apie cistinę fibrozę, kurioje daugiausia dėmesio skiriama šiuolaikinių CFTR moduliatorių poveikiui. Cistinė fibrozė yra genetinis sutrikimas, kurį sukelia CFTR geno mutacijos, dėl kurių sutrinka chlorido ir bikarbonato transportas, susidaro per didelis gleivių kiekis ir progresuoja organų, ypač plaučių, pažeidimai. Progresuojanti kvėpavimo takų obstrukcija, lėtinis uždegimas ir pasikartojančios infekcijos yra pagrindinės sergamumo ir mirtingumo priežastys.

Anksčiau gydymas buvo tik simptominis ir nepašalindavo pagrindinės priežasties. CFTR moduliatorių įvedimas iš esmės pakeitė šį požiūrį, nes jie tiesiogiai veikia defektinį CFTR baltymą. Veikliosios medžiagos skirstomos į potenciatorius, kurie stiprina kanalų atidarymą, ir korektorius, kurie gerina baltymų susidarymą ir transportavimą.

Klinikiniais tyrimais įrodyta, kad šios terapijos žymiai pagerina ilgalaikę funkciją, mitybos būklę ir gyvenimo kokybę. Be to, sumažėja plaučių ligų paūmėjimų skaičius. Visų pirma, trijų vaistų kombinacija, sudaryta iš eleksakaftoro, tezakaftoro ir ivakaftoro, yra proveržis ir daugeliui pacientų siūlo veiksmingą gydymą. Tačiau problemos išlieka, įskaitant ribotus ilgalaikius duomenis, skirtingus atsako rodiklius pagal mutacijų tipą ir neatsakytus klausimus apie ilgalaikius rezultatus. Apibendrinant, CFTR moduliatoriai turi potencialą pakeisti cistinės fibrozės supratimą, kaip valdomos lėtinės ligos, o ne gyvybei pavojingos. Naujos strategijos, pavyzdžiui, genų terapijos, teikia vilčių toliau gerinti ilgalaikius rezultatus ir galiausiai gali būti kelias link ligos išgydymo.

Tikslas ir uždaviniai: Šiame darbe pateikiama išsami cistinės fibrozės literatūros apžvalga, ypatingą dėmesį skiriant CFTR moduliatorių vaidmeniui ir klinikiniam poveikiui. Jame nagrinėjama, kaip CFTR moduliatorių terapija paveikė ligos patofiziologiją, klinikinius rezultatus ir gydymo strategijas. Be to, apžvalgoje vertinama, ar šis metodas suteikia reikšmingų pranašumų, palyginti su tradiciniais gydymo būdais. Darbe taip pat pateikiamos įžvalgos apie ligos valdymo perspektyvas ateityje.

Medžiagos ir metodai: Siekiant nustatyti atitinkamus tyrimus apie cistinę fibrozę ir CFTR moduliatorius, buvo atlikta sisteminė literatūros paieška naudojant tokias duomenų bazes kaip Cochrane Library, PubMed, Google Scholar ir Amboss, taip pat atlikta paieška internete. Kalba buvo apribota vokiečių ir anglų kalbomis.

Rezultatai: Gydymas pagerina ilgalaikę funkciją, mitybos būklę ir gyvenimo kokybę, tuo pačiu sumažindamas plaučių ligų paūmėjimus. Elexacaftoro, Tezacaftoro ir Ivacaftoro derinys yra proveržis, suteikiantis veiksmingą palengvėjimą daugeliui pacientų.

Išvada: CFTR modulatoriai yra didelis terapinis laimėjimas cistinės fibrozės gydyme. Jie veikia patį defektą ir suteikia puikią galimybę ateities gydymui žmonėms, sergantiems cistine fibroze.

Raktažodžiai: Cistinė fibrozė, F508del mutacija, Plaučių funkcija, CFTR modulatoriai, Trigubas kombinuotas gydymas.

3. INTRODUCTION

Cystic fibrosis is a hereditary metabolic disorder characterized by the production of thick mucus in the cells, which gradually blocks essential organs. The term cystic fibrosis comes from the fact that, when the disease was first identified, individuals with cystic fibrosis were found to have a buildup of connective tissue (fibrosis) with cysts in the pancreas (103).

Cystic fibrosis remains the most common genetic disorder in terms of mortality among the white population. Mortality is primarily linked to chronic airway mucous obstruction, inflammation, and infections (1). In addition to the respiratory tract, it also affects the gastrointestinal, glandular, and reproductive systems. Despite this, the leading cause of death is respiratory failure due to persistent airway obstruction. Infections and inflammation cause destruction of epithelial cells, leading to tissue remodeling and, eventually, end-stage lung disease (3). The development of the latest drugs for cystic fibrosis began with the discovery of the CFTR gene in August 1989. It was identified that cystic fibrosis results from mutations in the CFTR gene. The CFTR gene encodes a cAMP-dependent anion channel that is essential for proper transport of chloride and bicarbonate across epithelial surfaces (1). The lack of CFTR activity leads to a decrease in chloride secretion and impaired fluid transport, resulting in thick, viscous secretions. These secretions occur in many epithelial tissues, such as the pancreatic ducts, lungs, airways, and intestines (2).

By 2022, the life expectancy of people with cystic fibrosis had already increased by three years, from 57 to 60 years. This improvement is due to modern treatment options, which began with the approval of Ivacaftor in 2012, the first CFTR modulator. Previously, symptoms were treated solely with mucolytics, bronchodilators, cortisone, antibiotics, and physical therapy. Because of the effects of triple combination therapy approved in 2020—consisting of Elexacaftor, Tezacaftor, and Ivacaftor—the frequency of exacerbations was halved by 2022. In 2015, 7-8 out of 10 adults were still treated with antibiotics, but by 2022, this figure had fallen to less than 3 out of 10. Three days after starting treatment with the triple combination, which also significantly reduces infections, the airway secretions - the main issue for patients - disappeared. This directly improves lung function (4). Significant improvements in FEV1 have already been observed through CFTR modulators in various patient studies (2). This progress could transform cystic fibrosis from a fatal disease with a poor prognosis into a treatable condition. Since many patients previously did not even reach adulthood, this appears increasingly achievable.

Currently, about 3,000 mutations in the CFTR gene are known, with approximately 300 causing cystic fibrosis (4). The most common mutation is the F508del mutation (1).

Aim: This thesis provides a comprehensive narrative literature review of cystic fibrosis. A particular focus will be on the role and clinical effects of CFTR modulators. This review will explore how the therapy with CFTR modulators has affected the disease's pathophysiology, clinical outcomes, and overall treatment approaches. It will also assess whether this treatment offers a significant improvement over conventional standard therapy. Also, the thesis will present an outlook on the future of the disease.

Objectives:

- Description of the genetic background, epidemiology, and pathophysiology of cystic fibrosis and its systemic effects.
- Review conventional treatment strategies prior to the introduction of CFTR modulators and highlight their limitations in addressing the underlying disease mechanism.
- Explain the pharmacological principles and mechanisms of action of CFTR modulators.
- Analysis of the influence of CFTR modulators on the overall therapeutic approach of cystic fibrosis and their clinical efficacy.

4. LITERATURE SEARCH STRATEGY

4.1 DATABASES AND SEARCH TOOLS

For this literature review, a thorough electronic search was conducted to identify relevant studies on the retrograde root basis of cystic fibrosis and modern CFTR modulators. The following databases were used:

- Cochrane Library (https://www.cochrane.de/cochrane-library)
- Medline/PubMed including MeSH and advanced search (https://pubmed.ncbi.nlm.nih.gov)
- Google Scholar (https://scholar.google.com)
- Amboss (https://next.amboss.com/us)

4.2 SEARCH TERMS AND STRATEGY

The search was performed using a combination of medical subject headings and free text keywords relevant to the topic. Boolean operators AND and OR were used to refine the results. The main search terms included:

- Cystic fibrosis AND genetics AND etiology
- Cystic fibrosis AND epidemiology
- Cystic fibrosis AND clinical features (AND Pulmonary manifestations OR Sinus disease OR Digestive System OR Reproductive system OR Skeletal system)
- Cystic fibrosis AND pathophysiology (AND respiratory tract OR Liver OR Pancreas OR Intestines OR nutrition)
- Cystic fibrosis AND diagnosis (AND Prenatal screening OR Neonatal screening OR Sweat chloride test OR Electrophysiology)
- CFTR-Modulators AND Cystic fibrosis
- Cystic fibrosis AND Treatment

4.3 INCLUSION CRITERIA

- Studies written in English or German language
- Comparative studies, randomized controlled trials, observational studies, systematic reviews, narrative reviews
- Studies with a focus on cystic fibrosis
- Studies with a focus on CFTR modulator therapy
- Studies and publications investigating the clinical outcome of cystic fibrosis
- Studies published from 2018 until today with emphasis on literature in the age of CFTR modulators
- Studies about pediatric and/or adult patients with confirmed cystic fibrosis
- Studies that evaluate different CFTR modulators
- Articles relevant for cystic fibrosis

4.4 EXCLUSION CRITERIA

- Studies not related to cystic fibrosis or CFTR-Modulators
- Publications in other languages than German or English
- Studies prior to 2018 regarding CFTR modulators
- Studies with a limited approach, methodological quality, or unclear measures
- Studies without clinical data

4.5 STUDY SELECTION AND DATA EXTRACTION

The study selection process followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. After removing duplicate records, the remaining articles were evaluated based on their titles and abstracts. Full-text versions of the selected papers were then reviewed against the predetermined inclusion and exclusion criteria. Additionally, the reference lists of relevant publications were manually checked to find more studies that met the eligibility criteria.

The following information was collected from each study included in the review:

- Authors and year of publication of each included study
- Study type and design
- Material investigated and type of material
- Sample size and characteristics of the study population
- Duration of observation or follow-up period
- Clinical parameters assessed and outcome parameters
- Pharmacological drugs used
- Main findings and conclusion

5. BASICS OF CYSTIC FIBROSIS

5.1 GENETICS AND ETIOLOGY

Cystic fibrosis is a life-shortening genetic disorder. It is inherited in an autosomal recessive pattern and affects approximately 70.000 people worldwide (2). It is a multisystem disorder caused by deletions of genetic variants. The CFTR protein is located on chromosome 7q31.2 (3). The cystic fibrosis gene compromises 250.000 base pairs and encodes a protein with 1480 amino acids that produces CFTR (1).

Defects in the CFTR protein can lead to the absence or malfunction of chloride channels on the apical surface of the lungs or glandular epithelium (3). Furthermore, abnormal viscous secretions in the lungs or pancreatic ducts cause blockages. These blockages result in inflammation and tissue destruction in both organs. Other organ systems with epithelium, such as sweat glands, the biliary duct of the liver, the male reproductive system, and the intestines, are also affected (2).

The ongoing destruction of lung tissue caused by inflammation and infection plays a crucial role in the prognosis of cystic fibrosis. Many studies from the US have identified mutations in the transforming growth factor-ß1 gene as the most important modifier genes influencing pulmonary progression (1). Children with both parents as heterozygous carriers of cystic fibrosis have a 25% chance of inheriting the disease (4).

Depending on the literature, CFTR mutations are classified into five or six classes (3). These are shown in the following image.

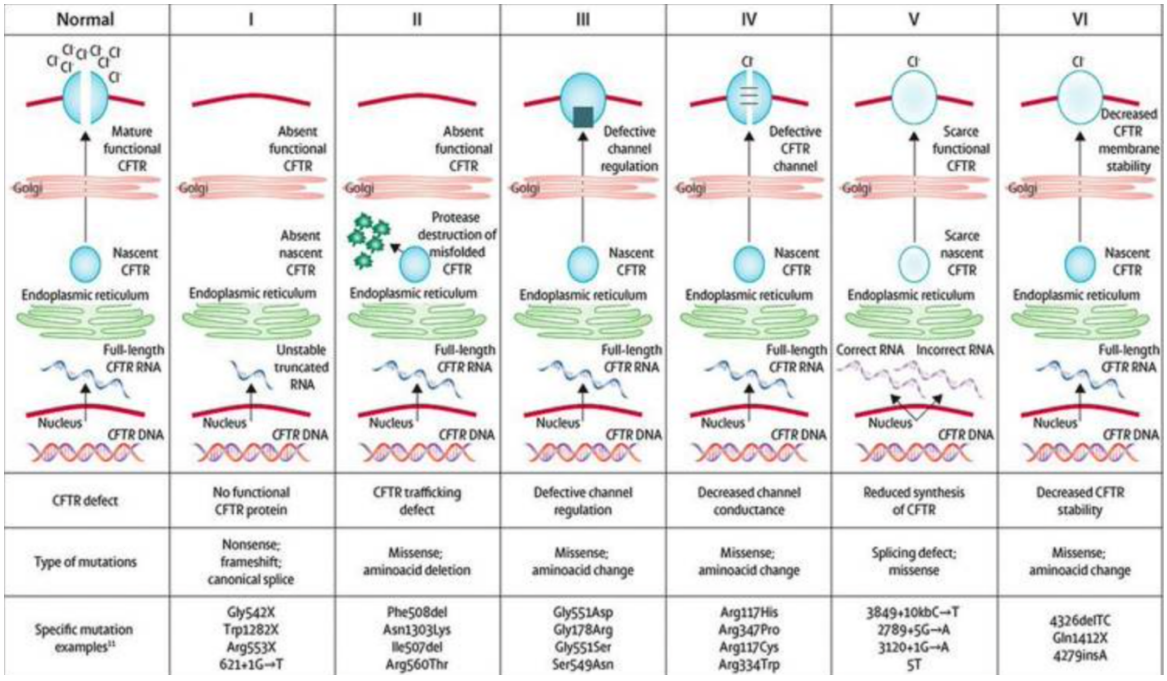


Fig. 1: Classification of CFTR Mutations (104).

Class 1: CFTR is not synthesized at all.

Class 2: Due to faulty folding in the endoplasmic reticulum, no processing of functional CFTR protein takes place.

Class 3: Impaired activation and regulation of the CFTR protein.

Class 4: Impaired flow of Ions, due to the decreased transmission of channels.

Class 5: Reduced amount of intact protein.

Class 6: The stability of CFTR is decreased.

In total, there are more than 2.000 different CFTR variants. Overall, 44,2% of individuals with cystic fibrosis are heterozygous for F508del class 2. An additional 40,5% have one copy of F508del and another variant, while 15,8% carry two non-F508del variants. The specific CFTR variants a person carries determine the amount of functional CFTR protein present. This partly correlates with the severity of the phenotype and organ involvement (3).

5.2 EPIDEMIOLOGY

In recent decades, there have been many advances in the treatment of cystic fibrosis. These advances have greatly changed the epidemiology of the disease. As a result, cystic fibrosis is no longer solely a pediatric disease (9).

The introduction of CFTR modulators alone has dramatically increased life expectancy. In Germany, the average life span for people with cystic fibrosis rose from 57 years in 2021, it increased to 60 years in 2022 (4). In short, the incidence of cystic fibrosis is decreasing, and the survival rate has improved substantially in recent years (9).

When cystic fibrosis was first described by Dorothy H. Anderson in 1938, children with the disease often died within their first year of life (9). Therefore, there has been a significant improvement in this regard.

Approximately 70.000 people worldwide are currently affected by the disease. The incidence rate is 1/3,000 live births. The highest prevalence is observed in North America, Europe, and Australia. In the US, about 1,000 new cases of cystic fibrosis are diagnosed each year, affecting males and

females equally. Since 2010, neonatal screening for CF has been in place in the US. This accounts for 60% of initial diagnoses each year (7).

5.3 PATHOPHYSIOLOGY

Cystic fibrosis is caused by a defect in the CFTR chloride channel (13). The CFTR gene encodes an anion channel of 1480 amino acids, with a structure comprising 12 transmembrane domains, 2 nucleotide-binding domains (NBD1 and NBD2), and 1 regulatory domain (20). Regulation occurs via cAMP-dependent protein kinase A at the regulatory domain. When intracellular cAMP concentration increases, the channel opens, allowing passive transport of chloride and bicarbonate ions across the apical cell membrane (20). The resulting electrochemical gradient drives passive water influx into the lumen of exocrine glands and contributes significantly to the hydration of epithelial surfaces (20-22).

In healthy individuals, the CFTR channel is located apically in epithelial cells of various duct systems, including the bronchi, intestine, pancreas, and vas deferens (13). Its absence or dysfunction results in decreased or absent transepithelial secretion of chloride and, consequently, water into these lumens (13). This causes dehydration of the surface liquid, the formation of thick, viscous secretions, disruption of secretion transport, and inflammatory changes that ultimately lead to the long-term destruction of the affected duct systems (20-22).

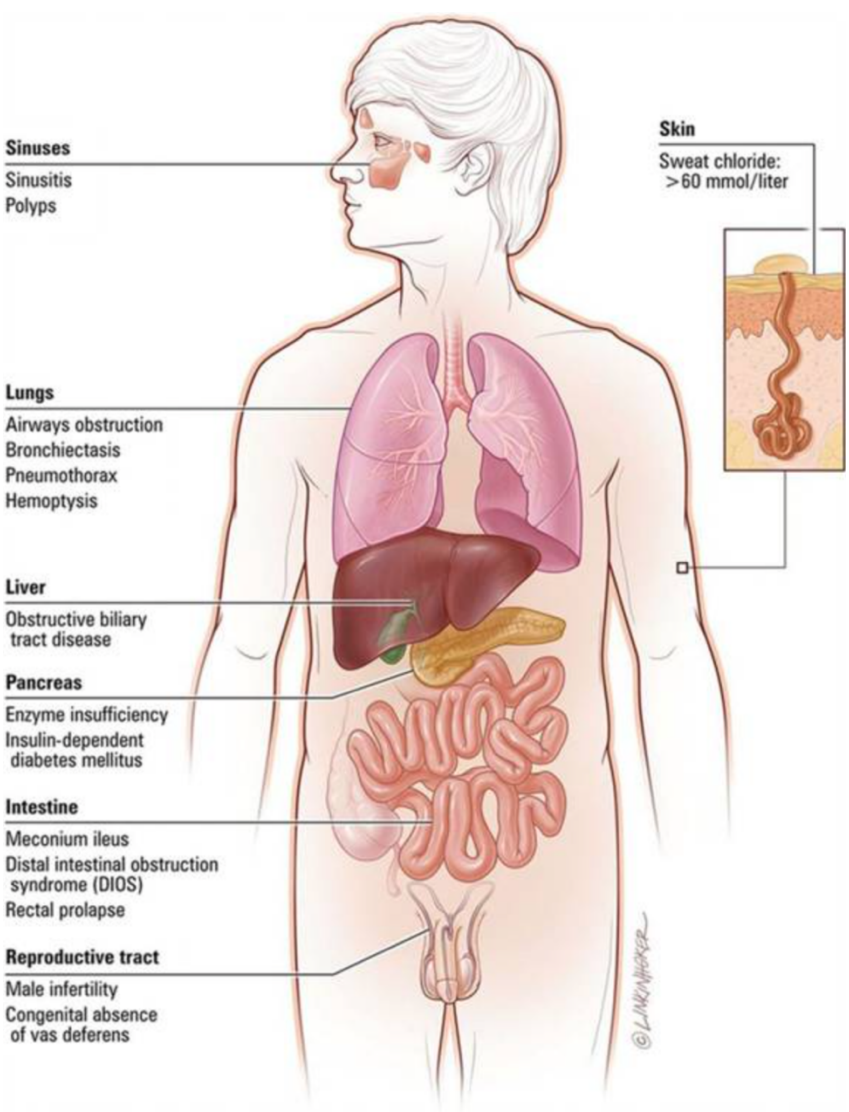
The loss of CFTR function is most severe in the pulmonary epithelium (14). Under normal conditions, sodium is absorbed at the apical surface of the airways primarily through the epithelial sodium channel (ENaC) and is transported basolaterally out of the cell by NaCl ATPase. Chloride, however, is absorbed basolaterally via the sodium-potassium-chloride transporter and secreted apically via CFTR (15). Water passively follows chloride into the airway's periciliary layer. Together with the overlying mucus layer, this forms the airway surface liquid, which supports effective mucociliary clearance through coordinated ciliary movement (16,17).

In patients with cystic fibrosis, CFTR mutations lead to reduced or absent chloride secretion (19). At the same time, ENaC is overexpressed, resulting in increased sodium resorption into the cell (18). Due to osmosis, water follows intracellularly, causing the airway surface liquid to become insufficiently hydrated and impairing mucociliary clearance (16). The highly viscous mucus accumulates, obstructs small airways, and creates an environment that promotes bacterial persistence. Consequently, recurrent bacterial exacerbations, chronic inflammation, bronchiectasis, and progressive decline in lung function develop (14).

The pathophysiology of sweat glands differs from that of the airways (17). In the secretory portion, an isotonic primary solution is formed. As the solution passes through the excretory duct, sodium and chloride are reabsorbed, producing hypotonic sweat. When CFTR function is impaired or absent, chloride reabsorption, in particular, is reduced, leaving more sodium chloride in the duct's lumen. This increases the electrolyte content of sweat and forms the basis of the diagnostic sweat test, which shows increased chloride concentration (13).

The loss of CFTR function impairs chloride and bicarbonate secretion, leading to dehydration of epithelial surfaces. This increase in secretion viscosity results in obstructions, chronic inflammation, and ultimately structural damage to organs, with progressive loss of function. Pulmonary manifestations are the most important prognostic factor (14, 20).

5.4 CLINICAL FEATURES



Cystic fibrosis is a multisystem disease that primarily impacts the epithelial tissue of the respiratory tract, exocrine pancreas, gastrointestinal tract, hepatobiliary system, and sweat glands. Progressive lung disease remains the leading cause of morbidity and mortality in patients with cystic fibrosis (10).

The disease typically presents with a triangular pattern of recurrent sinus and lung infections, steatorrhea, and malnutrition (7). However, the disease course can vary significantly. Cystic fibrosis can be diagnosed immediately after birth, even in utero, or later in life.

Fig. 2: Classical manifestations of Cystic fibrosis (105).

Most patients exhibit mild or atypical symptoms. Therefore, a differential diagnosis is crucial (11). In countries with newborn screening programs, CF is often diagnosed during screening. In contrast, in countries without newborn screening, the typical signs include failure to gain weight, extreme hunger, and steatorrhea, followed by lower respiratory symptoms caused by recurrent airway inflammation, obstruction, and infection (10).

5.4.1 PULMONARY MANIFESTATIONS

In the lungs, accumulated dehydrated secretions cause inflammation, chronic infections, increased airway obstruction, and the development of bronchiectasis. This condition impairs secretion clearance, increasing the risk of infection (7), and also leads to abnormal airway dilation (10).

Regular pulmonary exacerbations include severe cough, rapid breathing, shortness of breath, increased sputum, malaise, loss of appetite, and weight loss. These episodes often cause permanent lung damage (10). As a result, pulmonary exacerbations are a key prognostic indicator in cystic fibrosis.

Typical pulmonary features include a productive cough, lung hyperinflation on computed tomography scans, and obstructive patterns on pulmonary function tests. As the condition progresses, recurrent infections from inflammation and cellular buildup release cellular contents, damaging the bronchial walls. This damage leads to loss of bronchial cartilage support and can develop into bronchiectasis. Disease progression often presents with acute episodes of cough, rapid breathing, shortness of breath, increased sputum, malaise, loss of appetite, and weight loss. In early childhood, patients with cystic fibrosis frequently experience transient respiratory infections caused by pathogenic bacteria.

As the disease progresses, patients often develop persistent respiratory tract infections, commonly caused by Staphylococcus aureus or Pseudomonas aeruginosa. In addition, the respiratory systems of patients with cystic fibrosis can be colonized or infected by other microbes, including Stenotrophomonas maltophilia, Achromobacter xylosoxidans, members of the Burkholderia cepacia complex, non-tuberculous mycobacteria—including Mycobacterium avium complex and Mycobacterium abscessus—and the filamentous fungus Aspergillus fumigatus.

Chronic airway colonization and infection, particularly by Pseudomonas aeruginosa, heighten the inflammatory immune response. This occurs as neutrophil granulocytes release large amounts of DNA and extracellular matrix proteins into the airway lumen. These activities increase mucus

viscosity in the respiratory tract and significantly impair mucociliary clearance. Recent research focuses on identifying other bacterial species within the respiratory microbiome of cystic fibrosis patients, including obligate anaerobic microorganisms, which can now be detected using advanced next-generation sequencing technologies (11).

5.4.2 SINUS DISEASE

Most patients with cystic fibrosis develop sinus disease as they age, especially in older children, teenagers, and adults (11, 7).

Chronic rhinosinusitis is a frequent extrapulmonary feature of cystic fibrosis and contributes significantly to the disease's overall impact. It typically presents with persistent nasal obstruction, ongoing nasal discharge, and cough due to postnasal drip. Many patients also experience sleep disturbances from difficulty breathing through the nose (11). Additional common symptoms include recurrent or persistent sinus headaches and the development of nasal polyps (10).

Additionally, beyond local symptoms, chronic sinusitis affects the course of pulmonary disease. In some patients, it can trigger exacerbations of the lower respiratory tract. However, microbial studies show that pathogens detected in the paranasal sinuses do not necessarily match those isolated from the lower respiratory tract. This suggests a complex interaction between the upper and lower respiratory tracts that is not exclusively mediated by direct bacterial colonization. In addition, some patients with isolated chronic rhinosinusitis show signs of CFTR dysfunction without fully meeting the diagnostic criteria for cystic fibrosis. This observation underscores the importance of partial or mild CFTR dysfunction in the spectrum of chronic inflammatory diseases of the upper respiratory tract. In this context, a case-control study found that the prevalence of individual CFTR mutations in a cohort of patients with chronic rhinosinusitis was significantly higher than in the general population (7% vs. 2%). These data suggest that heterozygous, functionally relevant CFTR variants could act as a genetic risk factor for the development of chronic rhinosinusitis, even in the absence of classic cystic fibrosis (11).

5.4.3 DIGESTIVE SYSTEM

Involvement of the pancreas and gastrointestinal tract is a key clinical feature of cystic fibrosis and is largely responsible for morbidity and disease progression. Approximately 80-85% of patients with cystic fibrosis develop exocrine pancreatic insufficiency (10). An additional 20-25% show

progressive impairment of pancreatic function during the first years of life, and the majority already show clinical signs of fat malabsorption by age 1 (11).

Cystic fibrosis-associated pancreatic diseases typically progress over time. Many affected individuals have normal or only mildly impaired pancreatic function at birth and develop signs of exocrine insufficiency in childhood or adulthood (11). Pathophysiologically, viscous secretions obstruct the pancreatic ducts, impairing enzyme secretion and leading to progressive destruction of pancreatic tissue (10).

Clinically, exocrine pancreatic insufficiency primarily manifests as steatorrhea, characterized by frequent, voluminous, foul-smelling, and sometimes oily stools. In addition, there is failure to thrive and insufficient weight gain due to malabsorption of fats and proteins. Infants with severe exocrine pancreatic insufficiency often develop edema, hypoproteinemia, electrolyte loss, and anemia due to insufficient absorption of macro- and micronutrients. There are also clinical manifestations of fat-soluble vitamin deficiencies, such as coagulation disorders from vitamin K deficiency and rickets from vitamin D deficiency (11).

Persistent dysfunction of ductal and acinar secretion can lead to progressive structural damage to the pancreas and increase the risk of acute or chronic pancreatitis. In addition to exocrine involvement, many patients develop endocrine dysfunction over time. Destruction of islet cells leads to insulin deficiency, which initially results in glucose intolerance and, over time, in cystic fibrosis-associated diabetes (CFRD) (11). The incidence increases significantly with age: approximately 20% of adolescents and up to 50% of adults with cystic fibrosis are affected. Early diagnosis of CFRD is prognostically significant, as adequate therapy can significantly improve clinical outcomes (10).

In summary, both exocrine and endocrine pancreatic insufficiency can occur in cystic fibrosis. Endocrine insufficiency is primarily characterized by insulin deficiency and the development of CFRD, whereas exocrine insufficiency leads to malabsorption of fats, carbohydrates, and proteins, resulting in malnutrition (7).

Moreover, hepatobiliary involvement reflects a manifestation of the disease. Viscous bile may cause focal biliary cirrhosis, which can further develop into periportal fibrosis, cirrhosis, portal hypertension, and variceal bleeding (10). Prolonged jaundice is typically observed during the neonatal period, often resulting from biliary stasis or bile duct obstruction (7).

The gastrointestinal tract plays a particularly important role in the pathogenesis of cystic fibrosis in newborns and infants. Intestinal complications can manifest as early as the neonatal period and are often the first clinical indication of cystic fibrosis. Approximately 10-20% of newborns with cystic

fibrosis develop meconium ileus, which is also associated with a poorer prognosis (11). Prenatal sonographic abnormalities may also indicate intestinal obstruction. Hyperechoic or dilated intestinal loops are suggestive of intrauterine obstruction. In 50-78% of these cases, cystic fibrosis is the underlying cause postnatally (7).

Viscous secretions in the gastrointestinal tract lead to delayed meconium passage or the development of meconium ileus in 11.9% of cases (7). Pathophysiologically, impaired CFTR function reduces chloride and water secretion into the intestinal lumen, resulting in thickened intestinal contents and obstruction (12).

In addition to meconium ileus, rectal prolapse is a relevant gastrointestinal manifestation in early childhood. In recent years, it has been observed more frequently (11). If left untreated, it occurs in about 20% of children between 6 months and 3 years of age (7). The underlying mechanisms include malabsorption leading to malnutrition and chronic constipation, both of which increase intra-abdominal pressure (7). In older children, distal intestinal obstruction syndrome (DIOS) may also develop. DIOS is characterized by complete obstruction of the ileocecal region (10). In this condition, thickened intestinal contents resulting from impaired fluid secretion play a central pathophysiological role. DIOS is a clinically relevant complication that is often accompanied by abdominal pain, vomiting, and meteorism and requires rapid diagnostic and therapeutic intervention (12).

5.4.4 REPRODUCTIVE SYSTEM

In addition to pulmonary and gastrointestinal manifestations, cystic fibrosis is associated with marked impairment of fertility. More than 95% of men with cystic fibrosis are infertile, usually due to congenital bilateral aplasia of the vas deferens (10). Despite largely preserved spermatogenesis, the absence of the efferent ducts leads to obstructive azoospermia and clinical infertility (7). Notably, nearly half of men born with isolated congenital absence of the vas deferens and otherwise normal lung function have 2 CFTR mutations. This underscores the pathogenic significance of CFTR variants even in monochromatic or atypical forms of the disease (11).

In contrast, fertility in women with cystic fibrosis is generally preserved, though it is lower than in the general population. The underlying factors are thought to be malnutrition and the production of abnormally viscous cervical mucus, which can impede sperm migration. In addition, chronic disease severity and metabolic stress can contribute to menstrual cycle disorders (10). In principle, pregnancy is possible for women with cystic fibrosis. However, family planning requires careful interdisciplinary consultation. As part of an individual risk assessment of the mother's health,

comprehensive genetic counseling is essential to evaluate the risk of passing on CFTR mutations and to discuss reproductive medicine options (11).

5.4.5 SKELETAL SYSTEM

Cystic fibrosis is also associated with significant metabolic and musculoskeletal complications that contribute substantially to the burden of disease. A clinically significant phenomenon is salt depletion syndrome, which has been described in association with hypoproteinemia resulting from severe malabsorption (7). Reduced absorption of essential nutrients and increased electrolyte loss through sweat and the gastrointestinal tract disrupt fluid and electrolyte balance, which can be clinically relevant, especially in infants and young children.

Another significant problem is impaired bone health. Across all age groups, patients with cystic fibrosis have clinically significant reductions in bone density. Reduced bone mineral content is associated with an increased fracture rate and the development of spinal deformities. Up to 75% of adults have a clinically significant reduction in bone density. The pathogenesis is multifactorial and includes chronic inflammation, reduced physical activity, endocrine dysfunction, and malabsorption of vitamin D and calcium (11).

Patients may also develop characteristic changes in skeletal and soft tissues. These include digital clubbing of the fingers and toes and hypertrophic osteoarthropathy (11). Drumstick fingers occur particularly in patients with a long history of the disease and are interpreted as an expression of chronic hypoxia and systemic inflammatory processes (7). These extrapulmonary manifestations illustrate that cystic fibrosis is a multisystemic disease whose effects extend far beyond the primary pulmonary pathology and require continuous interdisciplinary care.

5.5 DIAGNOSIS

5.5.1 CLINICAL DIAGNOSIS

Cystic fibrosis is a multisystem disease with a broad clinical spectrum, ranging from asymptomatic newborns to patients with exocrine pancreatic insufficiency and chronic, progressive lung disease. In individual cases, the sweat chloride value allows only limited conclusions about disease severity and course. The classification into typical and atypical cystic fibrosis, recommended by the European Cystic Fibrosis Society Diagnostic Network Working Group and also reflected in ICD 11, is of limited relevance for clinical management (40).

The diagnosis therefore remains fundamentally based on the presence of a suitable clinical constellation - consisting of symptoms, clinical signs, and/or a positive family history - in combination with evidence of CFTR dysfunction (sweat test, CFTR genotyping, nasal potential difference measurement, or intestinal current measurement). The diagnosis of cystic fibrosis is justified (40,41). Although newborn screening represents a significant advance in early detection, it does not replace clinical diagnosis in individuals who have not been screened or who have not been identified through screening. With the increasing identification of different CFTR variants, our understanding of the clinical picture is expanding, so that milder forms of the disease and CFTR-associated manifestations in the pulmonary, gastrointestinal, or reproductive systems must also be considered. The aim is to continuously refine the diagnostic criteria to enable patients to access specialized care and modern treatment options at an early stage (41).

Some of those affected, including adults, remain undiagnosed despite having the disease, for example, due to non-participation in newborn screening for CFTR mutations or atypical clinical manifestations. In primary care, complications such as malnutrition, liver disease, infertility, or reduced bone density may provide initial indications of previously undiagnosed cystic fibrosis. However, pulmonary involvement remains the primary determinant of prognosis. Forced expiratory volume in one second (FEV1) is considered a key parameter of lung function and an important predictor of life expectancy in people with cystic fibrosis. Optimizing lung function is therefore a key therapeutic goal. Physical activity is recommended to slow the decline in respiratory function, support the effectiveness of respiratory physiotherapy, improve bone mineral density, and maintain muscle strength, flexibility, and posture (42).

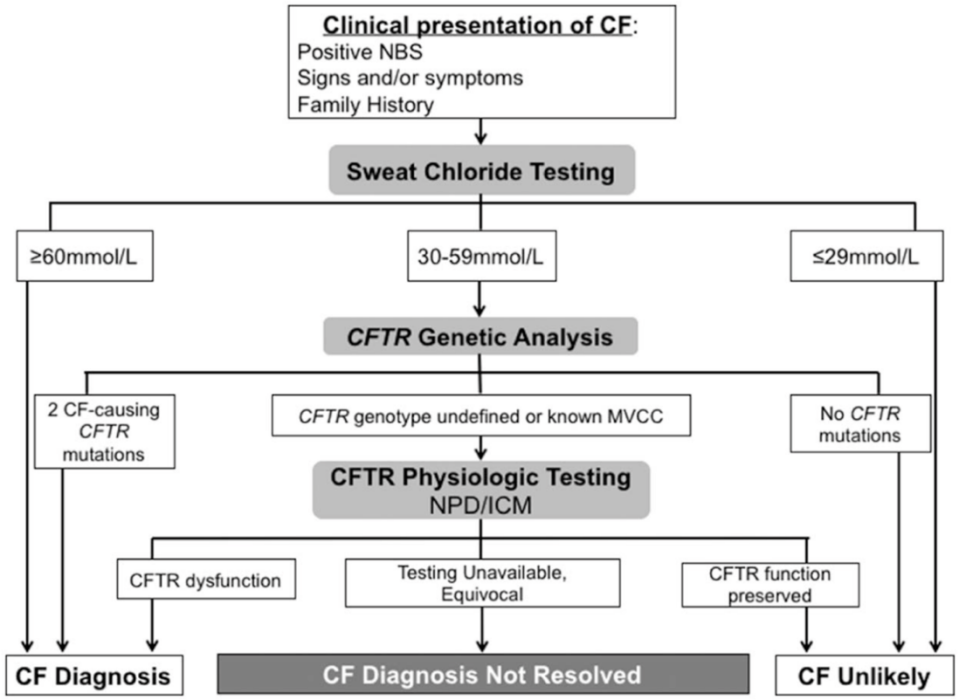


Fig. 3: Diagnosis pattern of Cystic fibrosis (106).

5.5.2 PRENATAL SCREENING

Cystic fibrosis is an autosomal recessive disease, meaning there is a risk of having an affected child if both parents are carriers of a disease-causing mutation in the CFTR gene (43). In such cases, prenatal diagnostics can be performed to determine the presence of the disease in the fetus at an early stage (50). Traditionally, this diagnosis is made using invasive procedures such as chorionic villus sampling or amniocentesis, in which fetal genetic material is obtained and examined using molecular genetic methods (43, 47, 50). These procedures enable reliable analysis of the CFTR gene but are associated with a small risk of miscarriage (43).

Indications for prenatal diagnosis include cases of known heterozygosity in both parents, homozygosity in one parent, a positive family history, or prenatal abnormalities such as an echogenic intestine on ultrasound (47,48). If disease-causing mutations are known in both parents, targeted molecular genetic testing can be performed on the fetus. If one or both mutations have not been identified in the parents of a clinically confirmed CF patient, linkage analysis can be used for indirect genetic testing. In cases where the fetal and maternal genotypes are identical, testing for maternal cell contamination must also be performed (48).

In addition to established invasive procedures, noninvasive prenatal testing (NIPD) is becoming increasingly important. These procedures are based on the analysis of cell-free fetal placental DNA (cffDNA) in maternal blood (43,51). Fetal DNA can be detected in maternal blood as early as the 5th to 7th week of pregnancy, with diagnostic reliability increasing significantly from the 10th week of pregnancy onwards as the proportion of fetal DNA rises with advancing pregnancy (51). The analysis is usually performed using next-generation sequencing or digital PCR, which also allows specific CFTR mutations to be identified (43). One advantage of this method is that it enables early diagnosis in the first trimester and can be used in particular to identify mutations inherited from the father (43). However, methodological challenges remain in distinguishing between maternal and fetal DNA (43). In the future, such tests could enable early diagnosis by analyzing fetal genetic material from maternal blood, similar to what is already practiced in noninvasive tests for the diagnosis of trisomy 21 (49).

Another innovative method is cell-based prenatal diagnostics, in which fetal trophoblast cells are isolated from maternal blood (45). These cells contain pure fetal DNA, which reduces the analytical challenges associated with cffDNA and enables direct examination of the fetal CFTR gene (45). Studies show that such procedures have high diagnostic accuracy and specificity and could be an alternative to invasive diagnostic procedures (45).

In addition to these methods, there are invasive procedures for particularly early diagnosis, such as coelocentesis, in which coelomic fluid is removed from the early amniotic cavity. This method can be performed as early as between the 7th and 9th week of pregnancy, allowing very early genetic analysis for couples with known CFTR mutations. The advantage is early diagnosis, which gives parents more time to make informed decisions, but the procedure requires a high level of technical expertise (46).

Prenatal testing is often used by carrier couples to make reproductive decisions. Many parents prefer non-invasive testing, provided it offers comparable diagnostic accuracy, because the reliability of the test is a decisive factor in their decision-making. In addition, the timing of the diagnosis plays an important role, as earlier results open up more options for action and allow for early preparation for a potentially affected child (44). In this context, comprehensive genetic counseling before and after prenatal testing is essential for correctly interpreting the results and supporting informed decisions (44, 47).

Prenatal CF tests ultimately serve to confirm or rule out the presence of cystic fibrosis in the fetus (47). After birth, infants with positive or unclear results from a terminal or prenatal screening usually undergo a sweat chloride measurement to confirm the diagnosis (50). Overall, it is evident that, in addition to invasive methods, non-invasive and cell-based diagnostic procedures are increasingly being developed that could enable earlier and lower-risk prenatal diagnosis of cystic fibrosis in the future (43, 45, 49, 51).

5.5.3 NEONATAL SCREENING

Before the introduction of comprehensive newborn screening, there was a significant delay in diagnosing cystic fibrosis. In 2015, only 55% of affected children were diagnosed in their first year of life. At the time of diagnosis, 40% of children had pulmonary or gastrointestinal symptoms, while 20% already had both manifestations. By then, many patients had already developed prognostically unfavorable conditions, such as underweight or structural lung damage, which could potentially have been avoided with earlier diagnosis (23).

Newborn screening for cystic fibrosis has been established in numerous countries for years and has shown positive effects on the physical development, lung function, and survival of affected children. In Germany, for example, screening was introduced nationwide on 01.09.2016 (23).

General newborn screening occurs in the first week of life and includes testing for congenital metabolic disorders, including CF. If the screening result is abnormal, a sweat test is performed to

confirm the diagnosis. Early diagnosis enables early initiation of therapy, prevents worsening of the disease course, and supports better physical development in children (25, 27).

The introduction of CFN newborn screening is justified by several criteria: CF is the most common autosomal recessive inherited metabolic disease, with a carrier frequency of approximately 1:25. The disease has a highly variable clinical presentation and places a considerable burden on those affected and their families. In addition, numerous therapeutic measures are available that can positively influence the course of the disease, whereas without treatment, death in childhood is often a threat (26,28).

The screening used in Germany is based on the determination of immunoreactive trypsinogen (IRT), with a sensitivity of 85.7% and a specificity of 99.8%; the measurement of pancreatitis-associated protein (PAP); and genetic testing for the 31 most common CFTR mutations. The test is performed on a single blood sample. Approximately 5 out of 5000 screening tests are abnormal and require further investigation. Approximately 1 in 5000 newborns tested is ultimately diagnosed with CF (23).

Despite its high diagnostic accuracy, screening has limitations. Meconium ileus can lead to false-negative results, so additional diagnostics, such as sweat tests or genetic testing, are necessary in these cases, regardless of the screening result (31). In principle, a negative screening result makes CF unlikely but does not completely rule it out. If there is clinical suspicion, further diagnostics are therefore always indicated. Data from London and southern England show that 7% of children diagnosed later had previously had a false-negative screening result (23).

Families with positive screening results should also be informed about the goals and progress of CF research and about opportunities to participate in clinical trials (24).

The IRT test is the classic screening method. It was first described in 1979 and introduced in 1981 in New Zealand and parts of Australia (33). Pathophysiologically, it is based on detecting elevated trypsinogen levels in cases of pancreatic duct obstruction. Trypsinogen enters the bloodstream when the pancreas is still functioning properly. The test is meaningful only in the first two months of life. It is a two-stage procedure: the first blood sample is taken on the 3rd to 6th day of life, and if the level is elevated, a second test is performed in the 4th to 6th week of life (26, 30). An IRT value below the 99th percentile is considered negative. If the value is above this, a follow-up examination is performed after 21 days. The sensitivity of the two-stage IRT test is 89 to 95% (29). Regardless of the IRT result, meconium ileus always requires additional diagnostics by means of a sweat test or genetic testing (31). Disadvantages of the IRT-IRT protocol include a high rate of false-positive results, the need for two blood samples, and a final result only after four to six weeks (26, 34).

The IRT-PAP protocol represents a further development. PAP is a stress protein in the diseased pancreas. A positive screening result is obtained with IRT >50 ng/ml in combination with PAP >1,8 ng/ml, or with IRT >100 ng/ml and PAP >1,0 ng/ml (35,36). One advantage of this method is that it avoids identifying healthy heterozygous carriers; however, a disadvantage is that the positive predictive value is comparatively low (32).

The IRT-DNA protocol combines IRT determination with direct mutation analysis from the Guthrie card. This method shortens the time to the final result and has a high sensitivity of 98-100%. However, healthy heterozygous carriers are also identified in this process (26).

The benefits of newborn screening are well documented. The lungs of newborns with CF are usually structurally healthy at birth, but signs of inflammation can be detected early, even in clinically unremarkable children (37). Studies show that screening can lead to less deterioration in lung function, better clinical scores, a higher survival rate (38), and improved growth in the first years of life (39). Overall, neonatal screening for sick fibrosis is an essential measure for early diagnosis, enabling a significant improvement in the prognosis and quality of life of affected children.

5.5.4 SWEAT CHLORIDE TEST

The sweat chloride test remains a central component of cystic fibrosis diagnostics. Current guidelines recommend that the diagnosis of diseases in the spectrum of CFTR-associated diseases be made primarily by assessing CFTR function, with the sweat chloride test playing the most important role in this process. Clear and standardized diagnostic criteria are required, particularly given the introduction of newborn screening and the increasing number and complexity of identified CFTR variants. Despite advances in genetic diagnostics, the sweat chloride test remains the core component of diagnostic confirmation. Current mutation classifications, for example, from the CFTR2 project, should be used to interpret genetic findings (52).

The test should be performed according to established, standardized protocols to ensure high diagnostic reliability. Chloride determination should be performed within a few hours after a sweat collection, and the result, including interpretation, should be communicated to the treating physicians and parents or patients on the same day. To increase the likelihood of obtaining enough sweat, bilateral testing is recommended. In infants, the test can be performed as soon as they reach a body weight of over two kilograms and a corrected gestational age of at least 36 weeks. Ideally, the test should be performed as soon as possible after a positive newborn screening, at the earliest from the 10th day of life and, if possible, within the first four weeks of life. In cases of suspected cystic

fibrosis after a positive screening, treatment should not be delayed while diagnostic confirmation is being obtained. In children with positive screening, clinical symptoms, or a positive family history, cystic fibrosis can be diagnosed if the sweat value is >60 mmol/l. Values between 30 and 59 mmol/l are considered intermediate and require further assessment of CFTR function. Even if two disease-causing mutations are detected, a sweat test is still necessary to confirm the diagnosis. Conversely, the absence of two CF-causing mutations does not rule out cystic fibrosis, so the sweat test remains a crucial part of the diagnosis. Patients with positive screening and diagnostic sweat test results should also undergo genetic testing if the screening does not include complete genotyping (53).

Despite modern genetic diagnostics, the sweat chloride test remains the most important functional test for assessing CFTR function and is used in cases of positive newborn screening, clinical suspicion of cystic fibrosis, unclear genetic findings, and CFTR-associated diseases. Historical observations from the 1940s first showed that patients with fibrosis have elevated chloride concentrations in their sweat. Since 1959, the test has been performed clinically using the method developed by Gibson-Cooke. The pathophysiological basis is impaired CFTR-dependent chloride absorption in the sweat glands. In healthy individuals, isotonic primary sweat is first formed, from which sodium and chloride are reabsorbed in the sweat duct, resulting in hypertonic terminal sweat. In patients with cystic fibrosis, the function of the CFTR channel and the sweat duct is impaired, so that chloride cannot be sufficiently reabsorbed. Sodium passively follows this concentration gradient, increasing the salt concentration in sweat and forming the basis of the diagnostic test. The test is performed in several steps: First, sweat production is stimulated using pilocarpine iontophoresis, in which pilocarpine is introduced into the skin via a weak electrical current (typically 1.5 to 4 mA for about 5 minutes). The sweat produced is then collected for about 30 minutes using filter paper or a macro duct system, and the chloride concentration is subsequently determined. Various methods, such as coulometric titration, ion-selective electrodes, or conductivity measurements, can be used for analysis, with quantitative chloride determination considered the diagnostic gold standard. Diagnostic thresholds are >60 mmol/l as an indication of cystic fibrosis, 30-59 mmol/l as an intermediate range, and <30 mmol/l as normal. Intermediate results require additional tests, such as CFTR gene analysis, nasal potential difference measurement, or intestinal current measurement. A sufficient amount of sweat is necessary for a valid test, approximately 75 mg for filter paper or approximately 15 µl for macro duct systems. Various factors, such as dehydration, skin diseases, incorrect electrode placement, insufficient sweat quantities, or contamination of the sample, can influence the measurement results. In the diagnostic process, a positive newborn screening is usually followed by confirmation via the sweat chloride test, while additional genetic or functional tests are performed in the case of unclear results. In addition to the classic method, new technologies are increasingly being investigated,

including conductivity measurements that determine the total ion concentration in sweat, and the Nanoduct system, which requires particularly small amounts of sweat and is therefore suitable for newborns. Portable sensors are also being developed that will enable continuous measurement of sweat electrolytes. None of these approaches yet represents a replacement for the sweat chloride test (54).

Despite its high diagnostic significance, an elevated sweat chloride level does not necessarily indicate cystic fibrosis. The sweat test remains the gold standard in CF diagnostics and is used in symptomatic patients, after positive newborn screening, and for monitoring patients undergoing CFTR modulator therapy. Other diseases can also lead to elevated chloride levels in sweat. Possible causes of false-positive results include metabolic or endocrine disorders, genetic syndromes, electrolyte regulation disorders, or certain medications. Therefore, an elevated sweat chloride level should always be interpreted in a clinical context and correlated with genetic and clinical findings. In case of unclear or conflicting results, additional diagnostic measures, such as extended CFTR gene analysis or repetition of the sweat test are necessary (55).

5.5.5 ELECTROPHYSIOLOGY

In addition to the sweat chloride test, electrophysiological methods are available for the functional assessment of CFTR activity. The most important procedures include intestinal current measurement (ICM) and nasal potential difference (NPD). These methods enable direct functional assessment of ion transport in epithelial tissues and are used particularly in cases with unclear diagnostic findings.

ICM examines ion transport in the intestinal epithelium by measuring the transepithelial short-circuit current. Various pharmacological agents are used to stimulate CFTR-dependent ion transport. These include Forskolin/IBMX, which activates cAMP-dependent, CFTR-mediated chloride secretion; Carbachol, which stimulates cholinergic chloride secretion; and Bumetanide, which inhibits chloride transport via the Na-k-2Cl cotransporter. These stimuli can be used to quantify CFTR-dependent currents. Studies have shown significant differences between CF patients and control subjects, with chloride currents measured after stimulation being significantly higher in individuals without cystic fibrosis than in CF patients. This makes ICM from rectal biopsies a reliable method for multicenter studies and suitable as a biomarker for assessing CFTR activity, for example for diagnosis or for evaluating new CFTR therapies (56).

The diagnosis of cystic fibrosis can be difficult in certain cases, especially in patients with positive newborn screening but unclear diagnostic classification. These patients are often classified as

CRMS/CFSPID (Cystic Fibrosis Transmembrane Conductance Regulator-Related Metabolic Syndrome/CF Screen Positive, Inconclusive Diagnosis). Studies show that ICM results reveal significant differences between patients with cystic fibrosis and both CRMS/CFSPID patients and healthy controls. However, no significant differences were found between CRMS/CFSPID patients and healthy controls. These results underscore that ICM can be a valuable diagnostic adjunct, particularly in cases of intermediate sweat test results, CFTR variants with unclear clinical significance, and patients with CRMS/CFSPID. The method enables a direct functional assessment of CFTR activity in the intestinal epithelium and can thus help to confirm or rule out cystic fibrosis (57).

Another important electrophysiological procedure is the nasal potential difference (NPD). This test examines ion transport in the respiratory epithelium and provides a functional assessment of CFTR activity in cystic fibrosis. It is particularly useful when genetic testing or sweat chloride measurements do not yield a clear diagnosis, as it directly assesses the electrophysiological properties of epithelial ion transport mechanisms. NPD measures the voltage difference across the nasal epithelium generated by transepithelial ion transport. An electrode is placed on the nasal epithelium, while a reference electrode is positioned subcutaneously in the forearm. The measured voltage difference primarily reflects the activity of the CFTR chloride channel and the epithelial sodium channel (ENaC). These channels play a central role in regulating salt and water transport at the airway surface and thus influence the hydration of the airway surface liquid (ASL) (58).

NPD thus enables a direct functional assessment of CFTR activity in vivo. The most important applications include diagnosing atypical or unclear CF cases, confirming CFTR dysfunction when sweat test results are inconclusive, and serving as a biomarker in clinical studies, for example, to evaluate CFTR modulators or other therapies that influence CFTR or ENaC activity. Standardized measurement protocols ensure that the method can be applied reliably (58).

6. TREATMENT OF CYSTIC FIBROSIS

6.1 TREATMENT OF CYSTIC FIBROSIS BEFORE THE INTRODUCTION OF CFTR-MODULATORS

The treatment of cystic fibrosis has made significant progress in recent decades. For many years, therapeutic strategies focused on managing the clinical symptoms of the disease without directly targeting the underlying molecular defect. Traditional treatment methods include respiratory physiotherapy and techniques to clear secretions, mucolytic inhalation therapies, antibiotics for

respiratory infections, nutritional support, and pancreatic enzyme replacement. These interventions have led to notable improvements in prognosis and life expectancy for patients with cystic fibrosis, but they have not fixed the fundamental problem with the CFTR protein.

A major breakthrough in cystic fibrosis treatment was the development of CFTR modulators, which directly target the dysfunction of the CFTR protein. The first drug in this class, Ivacaftor, was approved in 2012 and can improve the function of certain CFTR mutations, especially gating mutations. In subsequent years, additional combination therapies were developed, including Lumacaftor-Ivacaftor and Tezacaftor-Ivacaftor, as well as the highly effective triple therapy consisting of Elexacaftor-Tezacaftor-Ivacaftor. This triple therapy has notably expanded treatment options and now offers causal treatment for most patients. Clinical studies demonstrate that CFTR modulators are associated with improved lung function, fewer pulmonary exacerbations, better nutritional status and body mass index, and enhanced quality of life. The introduction of highly effective CFTR modulators marks a paradigm shift in cystic fibrosis treatment, as they are the first therapies available that directly target the root cause of the disease.

CFTR modulators can at least partially restore the function of the defective CFTR protein and thereby affect the pulmonary microenvironment. This includes improved hydration of the airway surface, increased mucociliary clearance, and enhanced local immune defenses. These changes can influence the development of chronic respiratory infections or help resolve existing ones. Despite these positive effects, questions remain about their long-term impact on airway microbiology, the complete elimination of chronic infections, and potential long-term shifts in infection patterns in cystic fibrosis (60).

Because of the disease's multisystem nature, cystic fibrosis treatment has traditionally relied on multidisciplinary care. Various professionals, including doctors, nurses, nutritionists, physical therapists, and psychologists, work closely together to provide comprehensive patient care. Over time, specialized cystic fibrosis centers and care networks have been established to enable standardized treatment strategies, regular follow-up visits, and the integration of multiple medical disciplines. However, the introduction of highly effective CFTR modulators has significantly changed care, as clinical outcomes and disease progression have markedly improved in many patients. These advancements necessitate adaptations to existing care models, especially given the increasing life expectancy and evolving therapeutic needs of patients. Along with improvements in medication, digital and patient-centered care approaches are becoming more prominent. These include telemedicine, home monitoring, and greater patient involvement in therapeutic decision-making, all aimed at improving care efficiency and enhancing the quality of life for those affected (61).

6.2 RESPIRATION THERAPY

Pulmonary therapy is a key component of cystic fibrosis treatment. The defect in the CFTR protein impairs chloride and water secretion in the airway epithelium, leading to thick, viscous secretions. These secretions hinder mucociliary clearance and cause airway obstruction, chronic infections, and inflammation, which can result in long-term decline in lung function. Therefore, respiratory therapy focuses on improving secretion mobilization, reducing mucus viscosity, and clearing airway secretions (62, 63).

An essential part of therapy involves respiratory physiotherapy, typically performed daily. Techniques for airway clearance include conventional chest physiotherapy, positive expiratory pressure, high-pressure PEP, active cycle of breathing techniques, autogenic drainage, oscillating airway systems, external high-frequency chest compression, physical activity, and exercise therapy. An evaluation of several Cochrane reviews found that no method is clearly superior to the others. For example, after six months, no significant difference in lung function was observed between PEP therapy and oscillating airway systems. Because some studies have small sample sizes and methodological limitations, the evidence remains limited. Therefore, it is recommended that patients choose the airway clearance technique that best fits their individual needs and preferences (62).

In addition to physiotherapy, mucolytic inhalation therapies are used to reduce mucus viscosity and enhance mucociliary clearance. In clinical practice, these therapies typically involve inhaling Dornase alfa, hypertonic saline solution, or mannitol, usually combined with physiotherapy. Hypertonic sodium chloride acts primarily through osmotic mechanisms, drawing water into the airway mucus layer and rehydrating secretions. This helps mobilize and remove mucus and can improve mucociliary clearance. Clinical studies show that inhaling hypotonic saline solution can provide short-term improvements in lung function and reduce the frequency of pulmonary exacerbations. It is also a cost-effective and readily available treatment option (63).

Another well-known mucolytic drug is dornase alpha, a recombinant human deoxyribonuclease that degrades extracellular DNA in sputum, thereby reducing mucus viscosity and helping clear airway secretions. Studies indicate that dornase alpha likely improves lung function, especially forced expiratory volume in one second (FEV1), and may reduce the frequency of pulmonary exacerbations. Dornase alpha is thus an important part of inhaled mucolytic therapy for cystic fibrosis (64).

In addition to mucolytic therapies, bronchodilators are used to support respiratory treatment. These drugs relax the smooth muscles of the bronchi, causing the airways to dilate, which improves

airflow and helps clear secretions. Commonly used medications include β-2 agonists such as salbutamol and anticholinergic agents such as ipratropium bromide. Short-acting bronchodilators are often used to reduce airway obstruction, alleviate dyspnea, and enhance the effectiveness of physiotherapy (65,67). Studies indicate that β-2 agonists can provide short-term improvements in lung function (65).

Long-acting inhaled bronchodilators like salmeterol or formoterol are used to extend bronchodilation and reduce respiratory symptoms. Some studies indicate a modest short-term improvement in lung function, particularly in FEV1 values, after using these drugs. However, the evidence is limited due to small and brief studies, so routine use cannot be definitively recommended at this time (66). The effectiveness of bronchodilators in cystic fibrosis varies, and not all patients experience equal benefits. Those with bronchial hyperreactivity or mild to moderate disease may find this treatment helpful, which is why personalized therapy is recommended (67).

6.3 ANTIBIOTIC THERAPY

Chronic bacterial respiratory tract infections are a key pathogenic factor in the pulmonary manifestations of cystic fibrosis. Infections with Pseudomonas aeruginosa, in particular, play a significant role in the progression of lung disease and are associated with increased inflammation, structural lung damage, and progressive loss of lung function. Antibiotic therapy therefore plays a central role in the overall therapeutic concept for fibrosis and pursues various goals, including the eradication of early bacterial colonization, the control of chronic infections, and the treatment of acute pulmonary exacerbations (68).

An important therapeutic goal is the early eradication of a newly detected Pseudomonas aeruginosa infection, as chronic colonization with this pathogen is considered an unfavorable prognostic factor and is associated with more rapid deterioration of lung function and increased morbidity. Studies show that early antibiotic intervention can achieve high eradication rates and is therefore an important strategy for preventing chronic infections. In a multicenter study, patients received either inhaled tobramycin in combination with oral ciprofloxacin or inhaled colistin combined with oral ciprofloxacin over 28 days. Both treatment regimens showed high eradication rates, underscoring the importance of early antibiotic therapy after the initial detection of Pseudomonas aeruginosa (70).

In patients with established chronic Pseudomonas infection, long-term inhaled antibiotic therapy is an important part of treatment. The aim of this therapy is to reduce the bacterial load in the airways, slow the progression of lung disease, and reduce the frequency of pulmonary exacerbations.

Systematic reviews show that long-term inhaled antibiotic therapy is likely to improve lung function while reducing the rate of pulmonary exacerbations. The best available evidence is for inhaled tobramycin, which has established itself as an effective therapy for controlling chronic Pseudomonas infections (68).

Randomized clinical trials also confirm the efficacy of inhaled antibiotics. In a double-blind, placebo-controlled study, treatment with inhaled tobramycin powder led to a significant improvement in lung function compared with placebo. In addition, a reduction in Pseudomonas aeruginosa density and sputum volume was observed. Patients receiving tobramycin also required additional antipseudomonal antibiotics less frequently and had a lower rate of respiratory-related hospitalizations. The therapy was well tolerated overall and was characterized by a shorter inhalation duration (71).

In addition to controlling chronic infections, antibiotic therapy plays a central role in treating pulmonary exacerbations, which are characterized by an acute worsening of respiratory symptoms. These episodes are often accompanied by increased bacterial load in the airways and deterioration in lung function. Antibiotics are therefore a key therapeutic measure for such episodes. However, various studies show that different antibiotic regimens do not show clear differences in clinical outcomes. Both intravenous and oral or inhaled antibiotics can be part of therapy. The optimal choice of antibiotic, route of administration, and duration of therapy continues to be the subject of current research (69).

In addition to antipseudomonal therapy, many patients receive long-term treatment with macrolide antibiotics, especially azithromycin. Macrolides not only have antimicrobial effects but also possess anti-inflammatory and immunomodulatory properties that can help control chronic respiratory tract infections. Randomized controlled trials show that long-term azithromycin therapy is associated with a slight but consistent improvement in lung function, a reduction in pulmonary exacerbations, and a prolongation of the time to the occurrence of a new exacerbation. Overall, the therapy is considered well tolerated, although gastrointestinal side effects may occasionally occur. At the same time, there are concerns about the possible development of antibiotic resistance, which is why long-term use should be carefully considered (72).

Overall, antibiotic therapy is crucial in managing cystic fibrosis. Implementing early strategies to eradicate bacterial infections, maintaining long-term control of chronic colonization, and applying targeted treatments for pulmonary exacerbations can decelerate lung disease progression and enhance patients' clinical outcomes (68-72).

6.4 THERAPY OF EXTRAPULMONARY MANIFESTATIONS

Besides affecting the lungs, cystic fibrosis is a systemic condition that impacts many other organ systems outside the lungs. Effectively managing these extra-pulmonary symptoms is crucial for a comprehensive treatment approach, focusing on preventing complications, maintaining nutritional health, and enhancing patients' quality of life over time.

One of the most common extrapulmonary manifestations of cystic fibrosis is exocrine pancreatic insufficiency, which occurs in approximately 80 to 90% of patients. Reduced secretion of pancreatic digestive enzymes leads to maldigestion and malabsorption of nutrients, frequently resulting in malnutrition and growth disorders (73,74). The standard treatment is pancreatic enzyme replacement therapy (PERT), in which pancreatic enzyme preparations are taken orally with every meal. The dosage is adjusted individually based on the fat content of the diet and the patient's body weight (73). Studies show that this therapy improves fat absorption, reduces symptoms of malabsorption, and can thus help stabilize nutritional status and improve body mass index (73,75). Fecal elastase measurement is frequently used to diagnose exocrine pancreatic insufficiency, although this marker is only of limited use for monitoring treatment success. Therefore, clinical assessment of nutritional status remains an important component of therapeutic management (74). Furthermore, it is debated whether modern CFTR modulators may influence pancreatic function in the future, although exocrine pancreatic insufficiency remains a relevant clinical problem (74).

Another important extrapulmonary complication is cystic fibrosis-associated diabetes mellitus (CFRD). This metabolic disorder frequently occurs during the course of the disease and is associated with deterioration in lung function, reduced nutritional status, and increased morbidity and mortality. Pathophysiologically, insulin deficiency resulting from pancreatic damage is the primary factor. Therefore, insulin therapy is the standard treatment. Treatment goals include improving glycemic control, stabilizing nutritional status, and reducing pulmonary exacerbations. At the same time, patients with cystic fibrosis continue to require a high-calorie diet to meet their increased energy needs and prevent weight loss (76).

Hepatobiliary complications also represent a significant extrapulmonary manifestation of cystic fibrosis. These arise, among other factors, from impaired biliary secretion, which can lead to thickening of the bile and bile duct obstructions. Over the long term, this can progress to chronic liver disease. Ursodeoxycholic acid is frequently used for treatment, typically at approximately 10 to 20 mg/kg/day over several months. However, randomized controlled trials indicate that the current evidence is limited and that a clear benefit regarding clinically relevant endpoints has not

been conclusively demonstrated. Despite this limited evidence, ursodeoxycholic acid continues to be frequently used in clinical practice due to its good tolerability (77).

As life expectancy increases among patients with cystic fibrosis, bone disorders are becoming increasingly significant. CF-associated bone disease is characterized by reduced bone mineral density and an increased risk of fractures. Treatment includes both preventive and pharmacological measures. Basic measures include ensuring adequate intake of vitamin D and calcium, optimizing nutritional status, and engaging in regular physical activity. In patients with severe osteopenia or osteoporosis, bisphosphonates may also be used. Bisphosphonates are currently considered the most important pharmacological therapy and can improve bone mineral density. In addition, new therapeutic approaches, such as monoclonal antibodies or anabolic therapies, are being investigated. However, their use in CF-associated bone disease requires further research. Modern CFTR modulators could also have long-term positive effects on bone health, although only limited long-term data are available to date (78).

The management of extrapulmonary manifestations of cystic fibrosis necessitates a multidisciplinary approach, considering nutritional, endocrinological, and hepatological factors. Early diagnosis and specific treatments can decrease complications and improve long-term outcomes for patients.

6.5 INTRODUCTION OF CFTR-MODULATORS

Cystic fibrosis is an autosomal recessive multisystem disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR). The CFTR protein functions as a chloride and bicarbonate channel in epithelial cells and plays a central role in regulating fluid and iron transport in various organs, particularly in the respiratory tract. Impaired CFTR function leads to reduced hydration of the surface fluid, resulting in viscous mucus that impairs mucociliary clearance and promotes chronic infections and inflammatory processes in the Airways (79). The discovery of the CFTR gene enabled the development of targeted therapeutic strategies, known as CFTR modulators, which directly address the underlying protein dysfunction and thus represent a fundamental advance in the treatment of the disease (79, 81). In contrast to earlier therapeutic approaches, which were primarily symptomatic, CFTR modulators can partially restore the function of the defective protein and thus directly address the disease's molecular cause (79).

CFTR modulators are classified into different classes based on their mechanism of action (80). Potentiators increase the probability of CFTR channel opening at the cell membrane, thereby improving ion transport, while correctors improve CFTR protein folding and promote its transport

to the cell surface (80, 81). Correctors include Lumacaftor, Tezacaftor, and Elexacaftor, while Ivacaftor, as a potentiator, increases CFTR channel activity at the cell surface, thereby improving chloride transport across the cell membrane (81). In addition, other therapeutic approaches are in development, including stabilizers, amplifiers, and so-called read-through agents, which also aim to improve CFTR function (80). Molecular studies show that potentiators such as Ivacaftor increase the activity of the CFTR channel by stabilizing the open state of the channel, thereby increasing the channel's open probability. This effect is based on allosteric modulation of channel gating and results in increased chloride conductance (83).

In recent years, several CFTR modulator therapies have been developed and introduced clinically. Ivacaftor was the first approved CFTR potentiator and initially demonstrated efficacy primarily in patients with so-called gating mutations, such as the G551D mutation (79,82). Real-world data and clinical trials have demonstrated that treatment with Ivacaftor leads to sustained improvements in lung function, particularly a significant increase in FEV1 values compared to baseline levels prior to the start of therapy. Furthermore, a significant reduction in pulmonary exacerbations was observed, accompanied by fewer hospitalizations and a reduced need for intravenous antibiotic therapy. Additionally, an improvement in traditional status was noted, with increases in BMI and body weight, indicating improved overall health and potentially improved nutrient absorption. Long-term observations also suggest that Ivacaftor may slow disease progression and improve long-term clinical outcomes, including a reduced disease burden and potentially improved survival rates. Overall, the therapy demonstrated a favorable safety profile with no new safety-related adverse effects (82).

The most common mutation in CF patients is the F508del mutation in the CFTR gene, which primarily leads to misfolding of the CFTR protein and impaired transport to the cell membrane. Previous CFTR modulators improved CFTR function only to a limited extent in patients with this mutation (84). Consequently, combination therapies have been developed that simultaneously address various pathophysiological mechanisms. Of particular significance here is the triple therapy consisting of Elexacaftor, Tezacaftor, and Ivacaftor, which combines two correctors with a potentiator (79, 84). While Elexacaftor and Tezacaftor improve the folding of the CFTR protein and promote its transport to the cell membrane, Ivacaftor increases the activity of the channel at the cell surface. In a randomized, double-blind phase III study, this combination therapy led to a significant improvement in lung function, as measured by the percentage of predicted FEV1, compared to the placebo group. Furthermore, a significant reduction in pulmonary exacerbations was observed, along with improvements in respiratory symptoms and quality of life, as measured by the CFQ-R score. Also, there was a significant reduction in sweat chloride concentration, a biomarker for

improved CFTR function. The triple therapy also demonstrated an overall favorable safety profile with rare serious adverse effects (84).

In addition to pulmonary effects, CFTR modulators affect other organ systems because the CFTR protein is expressed in numerous tissues. Clinical trials and real-world data demonstrate significant improvements in clinical parameters, including improved lung function, fewer pulmonary exacerbations, higher BMI, and better quality of life (59). Positive effects on the gastrointestinal system have also been reported, including improved mucus hydration, improved intestinal motility, and reduced intestinal inflammation. Improvements in gastrointestinal symptoms, such as abdominal pain, reflux, and bowel irregularities, as well as changes in the gut microbiota, including an increase in beneficial bacteria, have also been observed. These effects may contribute to improved digestion and nutrient absorption. During therapy, particularly with the triple combination, changes in nutritional status have also been described, including weight gain, increased BMI, elevated levels of fat-soluble vitamins, and increased lean body mass. These changes may have a positive impact on lung function and overall health, but they also require careful clinical monitoring, as weight gain can occur in some cases (81).

Furthermore, potential effects on bone metabolism have been noted, as patients with CF often show reduced bone mineral density. CFTR modulators might improve bone formation and help maintain bone structure, potentially through improved nutrition and reduced systemic inflammation. Meanwhile, the impact of the therapy on liver function is not yet fully understood. Although some cases have shown improvements in liver parameters, there have also been reports of occasional increases in liver enzymes and changes in bile acid metabolism, which is why regular monitoring of liver function is advised (81).

Despite notable therapeutic progress with CFTR modulators, several issues persist. These include limited effectiveness in certain mutation classes, a scarcity of long-term safety and efficacy data, potential drug interactions, and uncertain effects on patients with advanced lung disease or post-lung transplant (79). Future research should focus on long-term impacts of early therapy initiation and personalized treatment approaches (79). Overall, CFTR modulators have revolutionized cystic fibrosis treatment by targeting the disease's molecular basis, providing systemic benefits beyond lung function improvement (81).

6.6 CFTR-MODULATOR THERAPY

6.6.1 POTENTIATORS

CFTR potentiators are a key class of drugs within the CFTR modulator family and are designed to enhance the function of CFTR channels that are already localized at the cell surface but have reduced activity (85). Unlike correctors, which influence the processing and transport of the protein, potentiators act directly on channel gating to increase the activity of the CFTR protein at the cell membrane (83, 85).

The main drug in this class is ivacaftor, the CFTR potentiator that improves the function of the CFTR protein by increasing the channel's open probability (82). The prerequisite for efficacy is that the CFTR protein reaches the cell surface but exhibits impaired gating function. By increasing the open probability, the activity of the chloride channel is enhanced, enabling a partial restoration of CFTR function (82).

Molecular studies show that CFTR potentiators exert their effect by modulating channel gating. They promote channel opening while simultaneously reducing the channel-closure rate, thereby increasing the overall activity of the CFTR channel. This effect occurs in both ATP-dependent and ATP-independent gating and is largely independent of ATP hydrolysis as well as the dimerization of the nucleotide-binding domains, which normally regulate channel opening. Furthermore, the data suggest that potentiators preferentially bind to the open state of the CFTR channel and allosterically stabilize it, which represents a central mechanism of drug action. A comparison of various potentiators, such as ivacaftor and GLPG 1837, reveals a common molecular mechanism of action despite differing chemical structures, with the absence of additive effects in combination therapies suggesting a shared binding site on the CFTR protein (83).

Ivacaftor was initially approved for patients with at least one G551D mutation, a typical gating mutation in which the CFTR protein is correctly transported to the cell membrane but exhibits reduced activity (82, 85). Clinical studies and real-world data showed that treatment with ivacaftor leads to sustained improvement in lung function over several years. Furthermore, a significant reduction in pulmonary exacerbations was observed, particularly those requiring antibiotic therapy. Additionally, a decrease in the detection of Pseudomonas aeruginosa was noted, and pulmonary effects and systemic improvements are also evident, including improvements in growth and nutritional parameters as well as quality of life. Positive effects on gastrointestinal function and insulin secretion have also been described. Notably, these effects persist over the long term and have been demonstrated over a period of up to five years, indicating a disease-modifying effect of the therapy (82).

In summary, CFTR potentiators enable functional improvement of the CFTR protein in specific mutations by targeted modulation of channel gating and thus represent an essential component of causal therapy for cystic fibrosis (82, 83, 85).

6.6.2 CORRECTORS

CFTR correctors are designed to correct the underlying misfolding and impaired processing of the CFTR protein (92). In particular, the most common mutation, F508del, leads to structural instability of the CFTR protein, causing it to be recognized by cellular quality control mechanisms as early as in the endoplasmic reticulum and prematurely degraded, so that it does not reach the cell membrane and functional CFTR is absent from the cell surface (87, 90).

Correctors such as Lumacaftor, Tezacaftor, and Elexacaftor specifically target this pathophysiological process by stabilizing protein folding, promoting the maturation of the CFTR protein, and improving its intracellular transport to the cell membrane (86, 88, 92). This results in increased expression of functional CFTR at the cell surface, thereby partially restoring chloride transport (88, 92). At the molecular level, correctors stabilize key structural domains of the CFTR protein, particularly the transmembrane domains, and enhance intramolecular interactions between functional protein regions. They also promote correct folding in the endoplasmic reticulum and reduce the premature degradation of misfolded proteins, which together increase the amount of stable and functional CFTR protein at the cell membrane (91).

An important aspect is that different characters bind to distinct sites on the CFTR protein, thereby stabilizing different steps of protein folding (90). While Lumacaftor and Tezacaftor primarily influence early folding processes, Elexacaftor acts on a different structural region of the protein, resulting in a complementary mechanism of action (90). The combination of multiple characters therefore leads to additive or synergistic effects, enabling significantly stronger stabilization of the CFTR protein and increased functional expression at the cell membrane (91).

Correctors functionally lead to a partial rescue of the CFTR protein, as more correctly folded protein reaches the cell surface and is active there (89). These effects manifest systematically across various organs and lead to improved CFTR-dependent chloride secretion in vivo (89). This results in improved symptoms, including reduced dyspnea, fewer pulmonary exacerbations, and overall improvement in clinical parameters (88). Moreover, extrathoracic effects have also been described, including improvements in nutritional status and body composition, particularly in pediatric patients receiving combination therapies (86).

The efficiency of correctors as monotherapy is limited because only partial restoration of CFTR function is achieved (88, 89). This explains why correctors are not used in isolation in clinical practice but are usually administered in combination with other CFTR modulators to achieve greater functional restoration of the CFTR protein (92). The limited effectiveness of individual correctors was a key factor in the development of modern combination therapies, particularly triple therapy, which addresses multiple pathophysiological defects simultaneously (88).

CFTR correctors represent the central causal therapeutic approach because they address the fundamental protein misfolding caused by F508del mutations and create the prerequisite for functional CFTR to be available at the cell membrane in the first place (87, 89). In combination with other modulators, they enable a significantly more effective restoration of CFTR function and thus form the basis of modern therapeutic strategies for cystic fibrosis (92).

6.6.3 COMBINATION THERAPY

The discovery of combination therapies represents a major advance in the causal treatment of cystic fibrosis. Following the introduction of the CFTR potentiator ivacaftor, combinations of CFTR correctors and potentiators were subsequently developed, in particular Lumacaftor/Ivacaftor and Tezacaftor/Ivacaftor, which were specifically developed for patients with the F508del mutation. These dual therapies address both impaired protein processing and reduced channel activity of the CFTR protein and enabled causal therapy for a large patient group (96).

Despite substantial clinical improvements, the efficacy of these approaches remained limited because only partial restoration of CFTR function could be achieved and the underlying molecular dysfunction was not fully corrected. These limitations highlighted the need for further development of therapeutic strategies aimed at a more comprehensive functional restoration of the CFTR protein (96).

A decisive advance in this context is the introduction of triple therapy consisting of Elexacaftor, Tezacaftor, and Ivacaftor. This first approved combination of two CFTR modulators and one potentiator enables the simultaneous modulation of multiple pathophysiological effects of the CFTR protein (93). When the modulators improve the folding and transport of the protein to the cell membrane, the potentiator increases the activity of the channel, thereby effectively increasing both the quantity and function of the CFTR protein (93, 94). This results in a significantly improved restoration of CFTR function and end-of-transepithelial chloride and bicarbonate transport (94).

The clinical relevance of this therapy is reflected in an expansion of the treatable population. Earlier modulators addressed only about 50% of patients, whereas triple therapy allows treatment of up to 90% of patients with at least one F508del mutation. Clinical studies show improvements in lung function, a reduction in sweat chloride concentration as a marker of CFTR activity, a marked decrease in pulmonary exacerbations, and an improvement in health-related quality of life (93). Furthermore, relevant positive effects on traditional status and body weight have been observed, demonstrating the therapy's multisystemic efficacy (94).

These results are supported by data demonstrating an improvement in key clinical parameters and a significant reduction in disease burden in clinical practice (94, 97). It is important to note that triple therapy can lead to clinical stabilization even in patients with advanced disease, thereby significantly improving prognosis (97).

Marked efficacy is also evident in pediatric populations. In a phase three study involving children aged 6 to 11 years, triple therapy led to a significant improvement in lung function within a short period of time, with an increase in FEV1 of approximately 10.2% (95). Improvements in the lung clearance index and a reduction in sweat chloride concentration were also observed, indicating effective restoration of CFTR function. Improvements in quality of life and nutritional status were noted, showing the systemic effects of the therapy. Overall, the treatment was well tolerated, with observed side effects predominantly mild to moderate. These results underscore the importance of early initiation of therapy, as this can slow disease progression and may prevent long-term organ damage (95).

Alyftrek is the second triple therapy available for the treatment of cystic fibrosis and belongs to the class of CFTR modulators. The combination consists of two correctors, Vanzacaftor and Tezacaftor, as well as the potentiator Deutivacaftor. It is designed to improve the processing and function of the CFTR protein. Unlike previous triple therapies, it needs to be taken only once daily. In Germany, for example, Alfytrek is approved for patients aged six years and older, but patients must have at least one non-class 1 mutation. Alfytrek therefore covers the same patient group as ETI. The advantage of Alfytrek is that it does not have to be taken with a high-fat meal, for example, or with complex time-based dosing. Clinical studies show that Alfytrek leads to an improvement in CFTR function, which is reflected, among other signs, by a reduction in sweat chloride concentration. A decrease of 8.4 or 2.8 mmol/l was observed, depending on the respective study. This tends to be slightly higher compared to ETI therapy (99).

Despite these significant advances, limitations remain. About 10% of patients do not benefit from CFTR modulators because their underlying mutations cannot be addressed by available therapies.

Long-term safety and efficacy data remain the subject of ongoing investigations (93). Pharmacokinetic considerations also pose challenges, particularly regarding optimal dosing and specific patient groups, such as children, patients with severe liver dysfunction, and those during pregnancy and breastfeeding. Future studies are needed to fill these knowledge gaps and enable further optimization of therapy (98).

Combination therapies, mainly triple therapy, have transformed the treatment of cystic fibrosis. By modulating multiple pathophysiological mechanisms, they enable a significantly more effective restoration of CFTR function and lead to substantial improvements in clinical parameters as well as in patients' long-term prognosis (93, 94, 97).

7. OUTLOOK FOR FUTURE THERAPY: GENE THERAPY

Gene therapy is an approach aimed at correcting the genetic mutation that causes cystic fibrosis. A defective CFTR gene would be replaced by a functional one in all affected cells, thereby enabling a lifelong cure. Despite numerous studies, no clinical breakthrough has been achieved to date. The development of gene therapy for cystic fibrosis is associated with challenges. For successful therapy, the correct target cells must be reached, the therapeutic molecules must enter the cells and be transported to the cell nucleus so the defective gene can be replaced. The target cells, particularly in the respiratory tract epithelium, are difficult to access, and long-term effects can be achieved only if progenitor cells are also reached. Due to the high genetic heterogeneity, with over 2000 known CFTR mutations, current research approaches often follow a “one fits all” strategy. In addition to DNA-based approaches, therapies at the mRNA level are also being investigated. However, this leads only to temporary effects, as the mRNA introduced into the cell is rapidly degraded. Inhalation therapy is considered a potential route of administration to directly reach the target cells in the lungs, but it is unclear how other affected organs can be efficiently targeted (100).

A central challenge is the delivery of gene therapy agents. To address this, viral vectors have been developed as so-called gene ferries that exploit the natural ability of viruses to infect specific cells. For therapeutic use, these viruses are genetically modified to function exclusively as transport vehicles and to be unable to replicate. Adenoviruses can efficiently infect lung cells but trigger a strong immune response, which limits their efficacy, especially with repeated use. Adeno-associated viruses are less immunogenic and better suited for repeated applications, but they have a limited payload capacity, meaning the complete CFTR gene cannot be transported. Lentiviral vectors offer greater cargo capacity, lower immunogenicity, and the potential for integration into

the host genome, thereby enabling long-term gene expression. The effectiveness of herpes simplex viruses in lung cells has not been sufficiently clarified (100).

Additionally to viral systems, non-viral transport mechanisms are increasingly being developed. These include liposomal nanoparticles that can encapsulate therapeutic molecules such as DNA or mRNA and deliver them into cells. Lipid and extracellular vesicles are also being investigated. These can transport various molecules such as DNA, mRNA, or proteins and are modeled after natural cellular transport mechanisms. One of the greatest challenges remains the precise targeting of the vectors. If the target cell is not reached, therapy remains ineffective. But if the wrong cell types are targeted, this can be potentially harmful. Much of the current research therefore focuses on optimizing the vectors (100, 101).

Despite these limitations, gene therapy is considered a key therapeutic approach for the future. Modern developments such as prime editing open the possibility of correcting CFTR mutations directly at the DNA level. At the same time, future therapies are expected to be increasingly tailored to individual genetic profiles, in line with precision medicine. But there are not only scientific challenges; there are also economic considerations, mainly the high costs of modern therapies, which may limit global access to treatment (102).

8. SUMMARY OF THE RESULTS

This paper highlights the changes that cystic fibrosis treatment has undergone in recent years. While the disease was considered for decades to be a fatal pediatric condition characterized by progressive pulmonary deterioration, recurrent infections, and significant multisystem involvement, this picture has changed significantly. With the introduction of CFTR modulators, cystic fibrosis has increasingly become a disease associated with improved life expectancy and enhanced quality of life.

Despite these therapeutic advances, cystic fibrosis remains a complex autosomal recessive disorder caused by mutations in the CFTR gene. These mutations disrupt chloride and bicarbonate transport across epithelial cells, leading to dehydrated, viscous secretions. As a result, multiple organ systems are affected, mainly the lungs, pancreas, and gastrointestinal tract. In the respiratory tract, chronic obstruction, persistent inflammation, and recurrent infections lead to structural lung damage and remain the primary determinants of morbidity and mortality. For many years, therapeutic approaches were limited to symptomatic treatment with mucolytics, antibiotics, and physical

therapy. Although these measures improved survival, the underlying molecular defect remained untreated, thereby limiting long-term treatment outcomes.

The introduction of CFTR modulators represents the most significant therapeutic breakthrough since the discovery of the CFTR gene. Unlike conventional therapies, these agents directly target the molecular defect by improving the function of the CFTR protein. Clinical trials and real-world data consistently show that highly effective triple therapy leads to significant improvements in lung function, a reduction in pulmonary exacerbations, improved traditional status, and an enhanced quality of life. CFTR modulators offer clinically relevant advantages over previous standard therapy.

The positive effects of CFTR modulators are not limited to the lungs, which is very important. Improvements in gastrointestinal function, body mass index, and possibly endocrine and bone-related parameters indicate a systemic therapeutic effect. This reflects the expression of the CFTR protein in epithelial tissues and underscores the concept of cystic fibrosis as a multisystem disease requiring comprehensive and interdisciplinary treatment. It has been shown that early initiation of modulator therapy, mainly following newborn screening, has the potential to prevent irreversible organ damage. This marks a decisive shift from a primarily reactive to a preventive therapeutic strategy.

Despite these remarkable advances, significant limitations remain. Not all CFTR mutations respond to modulator therapy, so causal therapy is still unavailable for some patients. Long-term data on safety, the durability of the therapeutic response, and effects in advanced lung disease are limited at this time. It also remains unclear to what extent chronic infections can be completely eradicated or controlled under therapy, and how microbial colonization of the airway changes over the long term. These unresolved questions highlight the need for further research as well as for individualized therapeutic approaches.

But the outlook for patients with cystic fibrosis appears promising. Further development of next-generation CFTR modulators could enable virtually all patients, regardless of the underlying mutation type, to benefit from causal therapy. Parallel advances in gene therapy and genome editing are emerging as potential curative approaches aimed at directly correcting the genetic defect. While these methods are still in the experimental phase, initial studies suggest that long-term restoration of CFTR function may be possible.

In addition to pharmacological innovations, personalized medicine is expected to play a central role in the future care of CF patients. Mutation-specific therapies, biomarker-based treatment strategies, and functional testing methods could enable individually tailored therapy. Right now, the

demographic profile of patients is changing. With rising life expectancy, systemic fibrosis increasingly becomes a chronic disease of adulthood. That's why new issues such as fertility, pregnancy, age-related comorbidities, and long-term complications are coming into focus in clinical care.

All in all, the era of CFTR modulators has fundamentally changed the clinical reality of cystic fibrosis. While the disease remains complex, it is no longer necessarily a life-shortening condition in young adulthood and is increasingly evolving into a treatable chronic condition with an improved prognosis. Ongoing research, broad access to modern therapies, and advances in gene-based treatment strategies have the potential to improve care and could pave the way for a curative therapy in the long term.

9. CONCLUSION

The thesis shows that the treatment of CF has been fundamentally transformed by the introduction of CFTR modulators. For the first time, a treatment strategy is available that targets the underlying defect rather than relying solely on symptomatic therapy.

The literature analyzed shows that CFTC modulators lead to significant improvements in clinical parameters. These systemic effects indicate that the treatment not only addresses individual symptoms but also positively influences the disease.

Despite the progress made, limitations remain. Efficacy is strongly dependent on the underlying mutation type. Moreover, long-term data on the durability of the therapeutic effect are limited, partly because CFTR modulators - in particular the triple therapy - have been on the market for only a few years. This makes it clear that while current therapies represent an enormous step forward, they do not yet offer a definitive solution.

The results of this literature analysis confirm that CFTR modulators are superior to the previous standard therapy. The disease is increasingly evolving from a life-shortening condition to a chronic, manageable one, with a significantly improved prognosis.

The question for the future is to what extent it will be possible to address all mutations, including those that are currently untreatable. Advances in gene therapy could be decisive and play a central role. For patients with CF, the latest developments offer hope that they can lead a carefree life with a family of their own.

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