Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 8 Issue 5 May 2024

Review Article

Deciphering the Intricacies of Cystic Fibrosis: An Advanced Exploration and Comprehensive Analysis

Jyotsana Patel[2], Poonam Bharti[2], Aryan Agrahari[2], Mukul Kumar Yadav[2], Shivendra Shukla[2], Ritik Dixit[2], Surisetti Divya[1]* and Esha Yadav[3]

[1]*Assistant Professor, Department of Pharmacology, Axis Institute of Pharmacy, Rooma, Kanpur, Uttar Pradesh, India*

[2]*Student of B. Pharmacy, Department of Pharmacology, Axis Institute of Pharmacy, Rooma, Kanpur, Uttar Pradesh, India*

[3]*Professor, Department of Pharmacology, Axis Institute of Pharmacy, Rooma, Kanpur, Uttar Pradesh, India*

***Corresponding Author:** Surisetti Divya, Assistant Professor, Department of Pharmacology, Axis Institute of Pharmacy, Rooma, Kanpur, Uttar Pradesh, India.

DOI: 10.31080/ASPS.2024.08.1058

Received: April 08, 2024

Published: April 24, 2024

Abstract

Cystic fibrosis (CF) is a genetic disorder inherited in an autosomal recessive pattern, arising from mutations in the gene responsible for encoding the cystic fibrosis transmembrane conductance regulator (CFTR). While CF primarily manifests with lung disease, it also affects other organs such as the pancreas, intestines, and skin, often utilized for early diagnostic testing. In CF, lung disease represents the primary cause of morbidity and mortality. Despite being largely infectious in nature, the associated inflammation is severe and ineffective in clearing pathogens. This persistent, high-intensity inflammation leads to structural damage in the airways and compromised lung function, ultimately culminating in respiratory failure and death. Autopsy cases of CF reveal multiorgan involvement, with some rarely observed changes. Defective inflammatory responses associated with CFTR deficiency include dysregulation of both innate and acquired immunity, abnormalities in cell membrane lipids, signaling defects in various transcription factors, and altered responses of kinases and toll-like receptors. Recent advancements in understanding the molecular mechanisms underlying CF have facilitated the development of CFTR modulator therapies, marking significant progress in CF treatment. These targeted therapies represent a shift towards precision medicine and are anticipated to further enhance survival rates in the foreseeable future.

Keywords: Cystic Fibrosis; CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) Mutations; Lung Disease; Inflammation; CFTR Therapies; Precision Medicine; Respiratory Failure

Introduction

The ancient adage suggesting that an infant tasting of salt foretells certain demise likely heralds the earliest awareness of cystic fibrosis (CF), a condition marked by aberrant salt transport and historically, infant mortality. Referred to as a cumbersome term, 'cystic fibrosis' (CF) is often simplified by young patients to 'sixty-five roses', an affectionate alias for the distressing ailment, as per the Cystic Fibrosis Foundation. Predominant among the Caucasian populace in the United States, CF stands as the most prevalent inherited fatal malady, afflicting approximately 1 in 2,500 births, with around 30,000 individuals currently grappling with the condition, yet facing an average life expectancy of merely 32 years [1]. CF lung disease is typified by early colonization and infection of the respiratory passages. Despite structural alterations observable at birth in both human and CF pig airways, minimal inflammation is initially noted [2,3]. However, the onset of infection is swift, prompting a severe inflammatory reaction to pathogens, unrivaled in its immediacy, persistence, and intensity within the CF airway. Individuals with CF endure pronounced systemic inflammation, marked by heightened serum acute phase reactants, elevated antibody titers against a plethora of foreign and self-antigens, heightened susceptibility to ileitis including Crohn's disease, atopic tendencies, and heightened Th2 responses [4,5]. Various animal models of CF have been devised based on specific human CFTR mutations, each exhibiting discrepancies in their ability to emulate human CF-associated pathology. For instance, the murine CF model deviates significantly from human CF on a pathological level, while though the CFTR genes of pigs and humans demonstrate high homology at a molecular level, their respective CFTR protein structures and functions diverge considerably. Presently, ferret and rabbit CF models show potential as human CF proxies, though the exploration of additional models from diverse species remains imperative for comprehensive evaluation [6].

Historical context

The discovery of the CFTR gene in 1989 marked a pivotal moment in medical science, yet initially, few enterprises seized the opportunity to leverage this knowledge for novel therapeutic developments, citing the perceived inadequacy of the market size. It is thus noteworthy that numerous entities are currently engaged in the pursuit of cystic fibrosis (CF) research [7]. In parallel to how children with CF have colloquially dubbed the condition as "65 roses," there exists a tendency to oversimplify this ostensibly intricate monogenic disorder. Fundamentally, the genetic underpinning of CF is well understood, as is its clinical manifestation, notably advanced pulmonary complications, which constitute the primary cause of fatality among CF patients. However, the precise mechanistic link between CFTR dysfunction and the CF phenotype remains somewhat elusive [8]. CF is inherited in an autosomal recessive manner, arising from mutations in the CFTR gene located on chromosome 7. This gene encodes an ion channel integral to epithelial cell membranes, facilitating the transport of sodium and bicarbonate ions. Beyond its role in chloride secretion, this channel modulates the activity of other membrane-bound transport proteins. Collectively, these channels are pivotal in maintaining epithelial water balance, particularly crucial for mucosal surfaces. Consequently, malfunctioning CFTR leads to abnormal fluid absorption and desiccation of epithelial surfaces, culminating in the production of viscous, dehydrated secretions. Over 1900 CFTR mutations have been identified, with F508del being the most prevalent, accounting for approximately 90% of cases [9]. These mutations impede protein synthesis and are categorized into six functional classes. Class II, exemplified by the notorious F508del mutation, encompasses variants that impede channel trafficking to the cell surface due to protein misfolding and premature degradation by the cellular quality control apparatus. However, the classification of variants into discrete classes poses challenges, as a single mutation can impact multiple aspects of CFTR synthesis and function. For instance, despite being categorized as a Class II mutation, the impact of F508del on CFTR spans across at least three functional classes [10].

Epidemiology and genetics

Globally, an estimated 89,000 individuals are currently managing cystic fibrosis, with around 31,450 cases reported in the United States alone. The prevalence of this condition remains comparable between the US (7.97 per 100,000) and the European Union (7.37 per 100,000). In the US, demographics among those affected show that approximately 3.5% identify as Black or African American, 91.4% as White, and 5.1% as other ethnicities, encompassing a variety of racial backgrounds such as American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, as well as mixed races. Hispanic individuals constitute around 9.8% of the affected population, while the majority, approximately 91.2%, identify as non-Hispanic. Regarding genetic markers, about 85.5% of individuals in the US exhibit the p. Phe508del gene variant, commonly known as F508del. A comprehensive meta-analysis identified 24 to 54 CFTR gene variants across regions in South Asia, the Middle East, and East Asia, though it's acknowledged that populations of non-European descent may be underrepresented due to inherent biases in data collection. Across ten Latin American countries, F508del emerged as the predominant CFTR variant, found in proportions ranging from 23% to 59%. Furthermore, rare variants (<1% prevalence) in Latin American populations reflect the diverse ancestral heritage of Native, African, and European origins [11,12].

The identification of the CFTR gene in 1989 marked a significant breakthrough in cystic fibrosis research, sparking optimism within the medical and scientific communities. An extensive collaborative effort, involving over 100 laboratories worldwide and facilitated by the Cystic Fibrosis Genetic Analysis Consortium, has led to the discovery of over 2000 distinct CFTR mutations [13]. Molecular investigations into this gene have deepened our understanding of genotype/phenotype correlations, enhancing both the diagnosis and management of CF patients and their families. Furthermore, these advancements have paved the way for mutation-specific therapies, reshaping the epidemiological landscape of cystic fibrosis [14].

Figure 1: Lung white patches following fixation, accompanied by distinct cystic alterations.

- Study of Genotype/Phenotype Correlations: The growing number of mutations identified in the CFTR gene and the variability observed in the phenotypic expression of CF have led the researchers to try to establish genotype/phenotype correlations [15,16]. Quickly after the gene discovery, the CFTR mutations could be classified into six classes according to their impact on the level of protein function [17]. Schematically, mutations in classes I, II, and III are usually associated with a classical form of CF (severe mutations), while those in classes IV, V, and VI are related to a milder phenotype (mild mutations) characterized by pancreatic sufficiency and later bacterial colonization. The estimated median age of survival of patients carrying at least one mild mutation is generally ten years higher than that of patients with severe mutations [18].
- Advent of CFTR Modulator Therapies: Deciphering of the molecular bases of CF has also led to the development of novel therapeutic approaches and the search for pharmaceutical treatments aiming at correcting the defective CFTR protein. These drugs, called CFTR modulators, search to improve the production, processing or expression of the protein and include correctors, potentiators, stabilizers, amplifiers and read through agents [19]. This approach is said to be "targeted" or "mutation specific" because the type of molecules to be administered to patients depends on the type of CFTR mutations they carry. Many studies have been carried out in that field over the past decade and have led to major clinical advances in treatment, with significant improvements in biological and clinical endpoints of CF (as sweat chloride concentration orFEV1) [20].

Pathophysiology of cystic fibrosis

The pathophysiological alterations observed in cystic fibrosis primarily stem from the dysfunctional CFTR protein and its pivotal role as an anion channel in epithelial cells located at the apical surface. Disruption of CFTR function disturbs the balance of hydration and pH levels within exocrine ducts, resulting in obstruction and dilation of exocrine glands across multiple organs. This dysfunction manifests in various ways, such as increased salt loss and elevated chloride concentrations in sweat due to reduced CFTR activity in sweat glands [21]. Moreover, mucous blockages in pancreatic acini and ducts, biliary ducts, as well as glandular obstructions in the vas deferens and submucosal glands of the airways, lead to structural damage and fibrosis within affected organs. In individuals with cystic fibrosis, the endobronchial space of the airways is typically colonized first by bacterial pathogens like Staphylococcus aureus and Haemophilus influenzae, followed by Pseudomonas aeruginosa. These infections provoke a neutrophilic inflammatory response and persistent mucopurulent plugging, ultimately resulting in bronchiectasis [22]. The advent of CFTR modulator therapies has altered the landscape of cystic fibrosis pathogenesis, offering the potential for early intervention to mitigate the development of multiorgan pathology. For instance, in utero administration of the CFTR modulator ivacaftor to ferret fetuses with specific CFTR variants has shown promising outcomes, including reduced meconium ileus and improved pancreatic exocrine function, growth, and survival. With over 700 identified disease-causing CFTR gene variants, these variants are categorized into six classes based on the mechanisms underlying CFTR dysfunction [23,24]. Classes I, II, and III typically result in minimal or absent CFTR function and are often associated with severe lung disease, pancreatic insufficiency, and elevated sweat chloride values. Conversely, classes IV, V, and VI are associated with residual protein function, lower sweat chloride levels, and milder disease presentations. While some variants may impact multiple mechanisms, understanding the alignment of cystic fibrosis variants with biological pathways is crucial [25].

The CFTR gene encodes the CFTR protein, a chloride channel present in various epithelial tissues. This channel utilizes ATP to transport chloride ions against their concentration gradient. Within the airway, defective CFTR disrupts chloride ion movement and sodium reabsorption, leading to decreased water content in secretions and reduced airway surface liquid. Consequently, impaired mucus clearance occurs, fostering an environment conducive to bacterial growth, particularly in biofilm formations that shield bacteria from the immune system and antibiotics. This inflammatory cascade further exacerbates tissue damage.

Symptom's	Description
Most children with CF display symptoms before their first birthday.	CF symptoms typically appear early in life, often before the age of one.
Some children may not show signs of CF until they are older.	While most children display symptoms early on, some may not show signs until later in childhood.
Meconium ileus	Newborns may experience this bowel obstruction, where thick meconium blocks the intestines.
Salty-tasting skin	Individuals with CF often have skin that tastes salty due to high levels of salt in sweat.
Excessive sweating	CF can cause increased sweating, especially during physical activity or in warm environments.
Recurrent lung infections or sinus infections	CF patients are prone to frequent infections in the lungs and sinuses, leading to chronic respiratory issues.
Persistent coughing, wheezing, or other asthma-like symptoms	CF can cause ongoing respiratory symptoms such as coughing, wheezing, and breathlessness, similar to asthma.
Shortness of breath, even at rest	Breathing difficulties, including shortness of breath, can occur even when the individual is at rest.
Coughing up blood or thick mucus	CF can lead to coughing up blood or thick mucus from the lungs.
Chronic diarrhea or stools that are smelly or greasy	Digestive issues like chronic diarrhea or foul-smelling, greasy stools are common in CF.
Difficulty absorbing certain nutrients	CF can impair the body's ability to absorb essential nutrients from food.
Poor growth	Children with CF may experience slowed growth and development due to nutritional deficiencies.
Difficulty putting on weight	Weight gain can be challenging for individuals with CF, despite adequate food intake.
Abdominal pain	CF can cause abdominal discomfort or pain due to digestive issues or complications.
Round and enlarged fingers and toes	Clubbing, or round and swollen fingers and toes, may occur due to chronic oxygen deprivation in CF.
Enlargement of the heart	CF can lead to cardiac complications, including the enlargement of the heart muscle.
Growths in the nose, called nasal polyps	Nasal polyps, benign growths in the nasal passages, are common in CF patients and can cause breathing difficulties.
Rectal prolapse	CF can lead to rectal prolapse, where the lower intestine protrudes from the anus.
Liver problems	CF may affect liver function, leading to liver complications such as jaundice or liver disease.
Diabetes	CF-related diabetes can develop due to pancreatic damage, resulting in insulin insufficiency.

Table 1: Symptoms Shown in CF infected patient [26].

Clinical manifestations and diagnosis

The confirmation of a diagnosis typically involves genetic testing and/or a positive sweat test, where elevated chloride concentrations are detected. In the sweat test, localized sweating is induced using pilocarpine-soaked gel pads applied to the patient's limb, while a mild and painless electric current is passed between them. A small duct is then affixed to the area to collect sweat, which is subsequently sent to the laboratory for analysis. Sometimes, the test may need to be repeated if insufficient sweat is collected or if the result is inconclusive. In certain cases, clinical diagnosis of cystic fibrosis (CF) can be made based on symptoms, even if the sweat test is equivocal and genetic testing shows normal results [27].

The diagnosis of CF relies on compatible clinical presentations alongside biochemical or genetic confirmation. While the sweat chloride test serves as the primary method for laboratory confirmation, other tests such as mutation-specific tests, nasal potential difference (NPD), immunoreactive trypsinogen (IRT), stool fecal fat analysis, or pancreatic enzyme secretion evaluation may also prove beneficial in specific instances.

Diagnostic criteria for CF include meeting both of the following conditions:

- Manifestation of clinical symptoms consistent with CF in at least one organ system, a positive result from newborn screening, or having a sibling diagnosed with CF.
- Indication of dysfunction in the cystic fibrosis transmembrane conductance regulator (CFTR), demonstrated by any of the following:
- Elevated sweat chloride levels equal to or exceeding 60 mmol/L
- Identification of two disease-causing mutations in the CFTR gene, one from each parental allele
- Abnormal results from NPD testing

Test	Methodology	Indications
Sweat Chloride Testing	Collection of sweat with pilocarpine iontophoresis followed by chemical determination of chloride concentration	Infants with positive CF newborn screening results (perform after two weeks of age and >2 kg if asymptomatic) Infants with symptoms suggestive of CF (eg, meconium ileus) Older children and adults with symptoms suggestive of CF (eg, male infertility, chronic respiratory infections, or chronic sinusitis) Siblings of a patient with confirmed CF, if the diagnosis cannot be established based on genetic testing
Molecular Diagnosis	CFTR gene mutation screening panels Gene sequencing Further molecular testing	Newborns with positive CF screening results Patients with intermediate sweat chloride results Patients with confirmed or suspected CF if genotype is unknown Patients with normal sweat chloride results but strong clinical suspicion of CF
Other Diagnostic Tests	Measurement of fecal elastase Direct measurement of pancreatic exocrine function Pulmonary evaluation Nasal sinus CT scan	For patients with unclear CF diagnosis despite repeated sweat chloride testing and expanded DNA analysis Evaluation of pancreatic exocrine function in individuals with CF symptoms Pulmonary evaluation for respiratory symptoms CT scan for chronic pansinusitis Monitoring individuals with intermediate sweat chloride results for symptom development

Table 2: Overview of Diagnosis tests for CF.

Cystic fibrosis (CF) is a genetic disorder inherited in an autosomal recessive pattern, impacting approximately 1 in 2500 infants born in the UK. It arises due to mutations in the CFTR gene, responsible for encoding chloride channels crucial for the regulation of exocrine secretions. These secretions display heightened viscosity and adhesiveness, leading to complications in the respiratory, gastrointestinal, biliary, pancreatic, and reproductive systems. Historically, diagnosis predominantly occurred during infancy or later childhood. The manifestation and severity of the disease vary depending on the specific CFTR gene mutation, with over 1900 mutations identified thus far. Notably, false negatives can occur in both screening and genetic testing for the disorder.

Management strategies

Managing Cystic Fibrosis Related Diabetes (CFRD) involves a complex nutritional strategy requiring collaboration between CF and endocrine specialists. Although evidence is limited, current CFRD management integrates principles from CF and diabetes care, aiming to maintain normal nutrition and BMI, particularly focusing on adolescent growth and adult BMI within 20 to 25 kg/m^2. Unlike traditional diabetes management, CFRD insulin therapy must consider CF-specific energy needs, with fat intake at 35-40% of calories and balanced carbohydrate intake. Structured meal plans with three main meals and three snacks are recommended. About

System involved	Manifestation
Lower respiratory	Recurrent chest infections Bronchiectasis Pneumothorax Haemoptysis Respiratory failure Cor pulmonale
Upper respiratory	Sinusitis Nasal polyps
Gastrointestinal	Malabsorption Steatorrhea Failure to thrive Constipation Meconium ileus Distal intestinal obstruction syndrome Rectal prolapse Intussusception
Hepatobiliary/pancreatic	Prolonged jaundice Gallstones CF-related diabetes Pancreatitis CF-related liver disease including cirrhosis and portal hypertension
Musculoskeletal	Arthritis Hypertrophic pulmonary osteoarthropathy Osteoporosis/osteopenia Clubbing
Reproductive	Absence of vas deferens leading to infertility in males

Table 3: Among the numerous different ways that cystic fibrosis manifests itself [27].

15% of CFRD patients experience fasting hyperglycemia, necessitating insulin therapy for lung function and nutritional stability. Insulin regimens typically include basal bolus schedules with additional doses at meals. Monitoring HbA1c levels and screening for microvascular complications are essential. Recent studies suggest insulin therapy benefits CFRD patients without fasting hyperglycemia, while oral hypoglycemic agents provide short-term benefits. Treatment initiation isn't recommended for those with impaired glucose tolerance, pending further evidence [29].

Patients with cystic fibrosis (CF) can employ various strategies to ameliorate their symptoms. Daily physiotherapy aids in airway clearance and mucus mobilization within the lungs, with tailored techniques addressing specific issues like urinary incontinence and ensuring optimal inhalation medication adherence. Regular physical exercise is strongly recommended, facilitating sputum expectoration, enhancing respiratory muscle endurance, and reducing residual lung volume. Maintaining adequate nutrition is crucial, as it correlates directly with improved lung function and reduced susceptibility to chest infections. However, CF patients often face challenges related to malabsorption due to gastrointestinal congestion, particularly in early stages, necessitating increased caloric intake and the administration of digestive enzyme supplements to facilitate food breakdown. Despite these interventions, CF imposes a substantial metabolic burden, often doubling the body's energy requirements, particularly challenging for those with diminished appetite. In cystic fibrosis management, patients adopt various approaches to alleviate symptoms and improve overall health. Daily physiotherapy routines are vital, aiding in airway clearance and mucus mobilization, with personalized techniques addressing specific challenges like urinary incontinence and medication compliance. Regular exercise complements these efforts, enhancing sputum clearance, bolstering respiratory muscle endurance, and minimizing residual lung volume. Nutritional upkeep is paramount, directly impacting lung function and infection resilience, although gastrointestinal complications often hinder nutrient absorption, necessitating heightened caloric intake and enzyme supplementation. Despite these measures, cystic fibrosis imposes significant metabolic demands, exacerbating psychological distress, with elevated rates of depression and anxiety observed among patients and caregiver [30].

Psychosocial and quality of life considerations

In light of the impact that early encounters with medical challenges can have on both psychological and physiological outcomes over time, it is crucial to provide children with developmentally appropriate yet accurate information regarding their illness, even from a young age. Recent findings suggesting that children may comprehend the causes of their illnesses at a more advanced level than previously assumed are promising. This understanding should be leveraged to help children grasp the connection between their illness and the necessary medical procedures and treatments they undergo daily. Interventions aimed at enhancing coping mechanisms for early distress caused by cystic fibrosis (CF) experiences are essential for both present and future interactions with healthcare providers. Research indicates that effective pain management techniques, including non-pharmacological methods such as distraction, can mitigate aversive responses to procedural anxiety and pain [31].

Maintaining healthy family dynamics amid the demands of treatment is a priority for children in this age group. While behavioral therapy has primarily been applied to dietary interventions, it can be extended to improve adherence to all aspects of CF care. Equipping parents with knowledge of behavioral management strategies is vital to positively influence their child's health behaviors, fostering prosocial actions and enhancing parental self-confidence. Assessing the functioning of individual family members and overall family interaction patterns can identify areas for targeted intervention. Despite the challenges presented by CF, it has been observed that parents of children with CF tend to spend more quality time engaging in play activities with their child, potentially reflecting a conscious allocation of time resources in the face of a life-limiting illness [32]. Emphasizing the importance of prioritization to parents, coupled with effective parenting strategies, may enable them to allocate their limited time and energy more effectively, including towards self-care, nurturing marital relationships, and maximizing quality time spent with all their children.

Behavioral and cognitive-behavioral interventions are widely recognized as first-line treatments for depression and anxiety among school-aged children in the general population. However, there is a lack of literature applying these evidence-based treatments to improve adjustment in the CF population [33]. Nonetheless, recent studies have incorporated cognitive-behavioral elements such as problem-solving, anticipatory guidance, behavioral modeling, and relaxation training into interventions for children with CF. For instance, one study implemented a "Building CF Life Skills" intervention targeting problem-solving and social skills in children aged 8 to 12, which resulted in improvements in loneliness and perceived impact of CF immediately post-intervention and at the 9-month follow-up. Another study utilized a CD-ROM program to enhance CF-related knowledge and coping skills in children aged 10 to 17, demonstrating increased disease-related knowledge and coping strategies compared to a control group [34-37].

Key Points	Details
Importance of Balanced Diet for CF Patients	Essential for maintaining well-being, controlling symptoms, and combating infections. Helps in improving nutritional status.
Specific Dietary Needs of CF Patients	Require up to twice as many calories as individuals without CF due to increased energy usage from chronic chest infections.
Pancreatic Problems and Nutritional Deficiencies	Some CF patients experience pancreatic issues leading to difficulties in digesting foods and absorbing nutrients, particularly fats. Result in nutritional deficiencies and poor weight gain.
Loss of Appetite and Malnutrition Risk	Many CF patients may experience loss of appetite, increasing the risk of malnutrition.
Recommended Diet for CF Patients	Should include a balanced mix of carbohydrates, fats, and proteins. Incorporating specific types of food into the diet is beneficial.

Table 4: Key points for the Balanced diet for the CF infected patient.

Category	Food Items	Key Nutrients	Benefits
Fruits	Apricots, Bananas, Blueberries, Cantaloupes, Grapefruit, Mangoes, Oranges, Peaches, Strawberries	Antioxidants (e.g., Vitamin C), Fiber	Rich in antioxidants and fiber, which can aid in reducing intestinal blockages and fighting infections; convenient snack options for individuals on the go and versatile additions to various meals and snacks.
Vegetables	Arugula, Bok Choy, Broccoli, Brussels Sprouts, Collard Greens, Kale, Mustard Greens, Spinach	Antioxidants, Fiber, Iron, Vitamin A, Vitamin K	Provide essential vitamins, minerals, and antioxidants; dark leafy greens offer iron, vitamin A, and vitamin K, which support immunity, blood clotting, and infection prevention; diverse vegetable options ensure a well-rounded diet.
Eggs	Egg Yolk and Albumen	Protein, Vitamin B-12	Protein-rich source aiding muscle maintenance; contains essential vitamin B-12 necessary for red blood cell formation and nerve function; versatile food option for various meal preparations.
Fish and Seafood	Salmon, Herring, Trout, Shellfish (e.g., Oysters)	Protein, Iron, Vitamin D, Zinc	Rich in protein, iron, and vitamin D; fatty fish provide healthful fats and calories, essential for individuals with CF; shellfish contain high levels of zinc, crucial for growth, development, healing, and immunity.
Nuts	Almonds, Peanuts, Brazil Nuts	Protein, Healthful Fats, Fiber, Vitamin E, Selenium	High-calorie snack option with healthful fats and protein; rich in vitamin E and selenium, offering antioxidant and infection protection benefits; versatile inclusions in various dishes and snacks for both children and adults.
Dairy Products	Greek Yogurt, Cream Cheese, Cheese, Full Fat Milk, Powdered Milk, Parmesan Cheese	Calcium, Healthful Fats, Calories	Excellent source of calcium for bone health; full-fat dairy products offer significant healthful fats and calories; diverse options for increasing dairy intake, including adding to meals, snacks, and beverages.

Table 5: Overview of Balanced Diet for CF infected patient [46-50].

Current research and future directions

Gene therapy

Cystic Fibrosis (CF) was initially characterized as a distinct ailment in 1938, with the discovery of the CFTR gene occurring in 1989. Various mutations, notably the prevalent F508del mutation, have been linked to CF. Following the identification of CFTR, the pursuit of gene therapy for CF lung disease gained traction within the scientific community and industry. In 1993, a seminal study attempted to rectify defective CFTR in the nasal airway using an E1-deleted recombinant adenoviral (rAd) vector to introduce normal CFTR complementary DNA (cDNA). Although this study lacked a placebo group, it demonstrated proof-of-concept for gene therapy by transiently correcting Cl− transport post-vector inoculation. Subsequent trials with rAd vectors revealed limitations due to transient gene expression and strong immunogenicity [38]. Recombinant adeno-associated virus (rAAV) vectors emerged as the most promising candidates for human gene therapy, with several rAAV-based therapies gaining clinical approval. Between 1998 and 2007, CF lung disease gene therapy trials employing rAAV-2 vectors were conducted by the Targeted Genetics Corporation. Phase I trials established the safety of the gene transfer agent, tgAAVCF, and its successful delivery to the sinuses and lungs of CF patients. Despite detectable transient functional restoration, Phase II trials failed to meet the primary efficacy endpoint of improved lung function, although a subset of patients demonstrated notable improvement in forced expiratory volume in 1 second (FEV1) following treatment with tgAAVCF [39].

CF gene therapy has undergone significant advancements, transitioning from initial attempts with rAd vectors to promising trials utilizing rAAV vectors. While Phase II trials with tgAAVCF showed partial success in improving lung function for some patients, challenges persist in achieving consistent therapeutic outcomes. Continued research is warranted to address these challenges and refine gene therapy approaches for CF lung disease [40].

Stem cell therapy

Regenerative medicine aims to achieve stem cell homing and engraftment in various organs for tissue regeneration. Notably, hematopoietic stem cells (HSCs) exhibit developmental plasticity akin to embryonic stem cells and have shown potential to transdifferentiate into epithelial cells. Bone marrow-derived cells (BMDCs) or enriched HSCs have been detected in the epithelia of organs like the liver, lung, gut, and skin post-transplantation, highlighting their therapeutic promise [35]. Cystic fibrosis (CF), characterized by a single-gene defect primarily affecting the lungs, presents an opportune target for gene therapy due to its accessible pathology and potential therapeutic window. However, despite the potential of gene therapy to restore CFTR function, clinical trials have yielded inconsistent results. Alternatively, stem cell therapy offers promise, with recent studies showing bone marrow-derived stem cells homing to damaged respiratory epithelium and contributing to non-hematopoietic tissues [41].

Recent research explores the use of various stem cell types, including bone marrow-derived stem cells and BASCs, for CF cell therapy. Techniques such as fluorescence-activated cell sorting (FACS) enable the isolation of BASCs, which have demonstrated proliferative and multipotent capabilities in clonal assays. These advancements hold potential for innovative treatments in CF management [42].

Precision medicine approaches

Personalized medicine, tailored to individual clinical profiles and genetic traits, has revolutionized treatment approaches, notably in cystic fibrosis (CF) and other diseases. For instance, CF treatment customizes enzyme supplementation dosages based not only on physiological factors but also on specific patient responses to enzymes, food intake volume and type, body metrics, and growth rate. However, current perspectives question traditional symptom-centered treatments, emphasizing the need to address underlying disease mechanisms. In CF, chronic pulmonary infections exemplify this challenge, demanding further research to understand the progressive impact of inflammation and antibiotic resistance [43].

Precision medicine, emerging as an extension of personalized medicine, integrates molecular data to categorize and treat patients accurately. This approach identifies disease endotypes based on gene-environment interactions, offering insights into complex conditions like CF. However, challenges persist, including regulatory hurdles, high implementation costs, ethical considerations, and technological limitations [44]. Despite advancements, achieving holistic precision medicine remains a goal, necessitating a paradigm shift towards comprehensive, individualized care. The CF model illustrates the potential of precision medicine, yet obstacles such as genetic variability and treatment efficacy underscore the need for continued research and education in genetics and medical practice [45].

Conclusion

Cystic fibrosis (CF) is a commonly occurring genetic disorder characterized by a range of organ changes. Failure to diagnose and treat CF properly can lead to severe complications. While classical cystic changes have been well-documented, renal changes, particularly lumen compaction and calcification, are often overlooked in literature but serve as primary histological indicators in CF patients' kidneys. Advancements in understanding the fundamental defect and pathobiology of CF have led to the development of new treatments, contributing to improved outcomes. Enhanced comprehension of the basic defect and access to epidemiological data in the United States have enabled the identification of predictors of survival and factors—genetic, environmental, and therapeutic—that may influence it. Identifying genetic modifiers may offer new targets for therapy, while environmental factors can be modified, and novel therapeutic agents and aggressive treatment strategies can be better understood and implemented.

Functional CFTR is crucial for appropriate airway inflammation in response to pathogens. However, in CF, the inflammatory response to lung infections is ineffective, severe, and persistent. This high-intensity inflammation leads to permanent structural damage to the airways, impairs lung function, and, if left unchecked, results in respiratory failure and death. Extensive research has linked

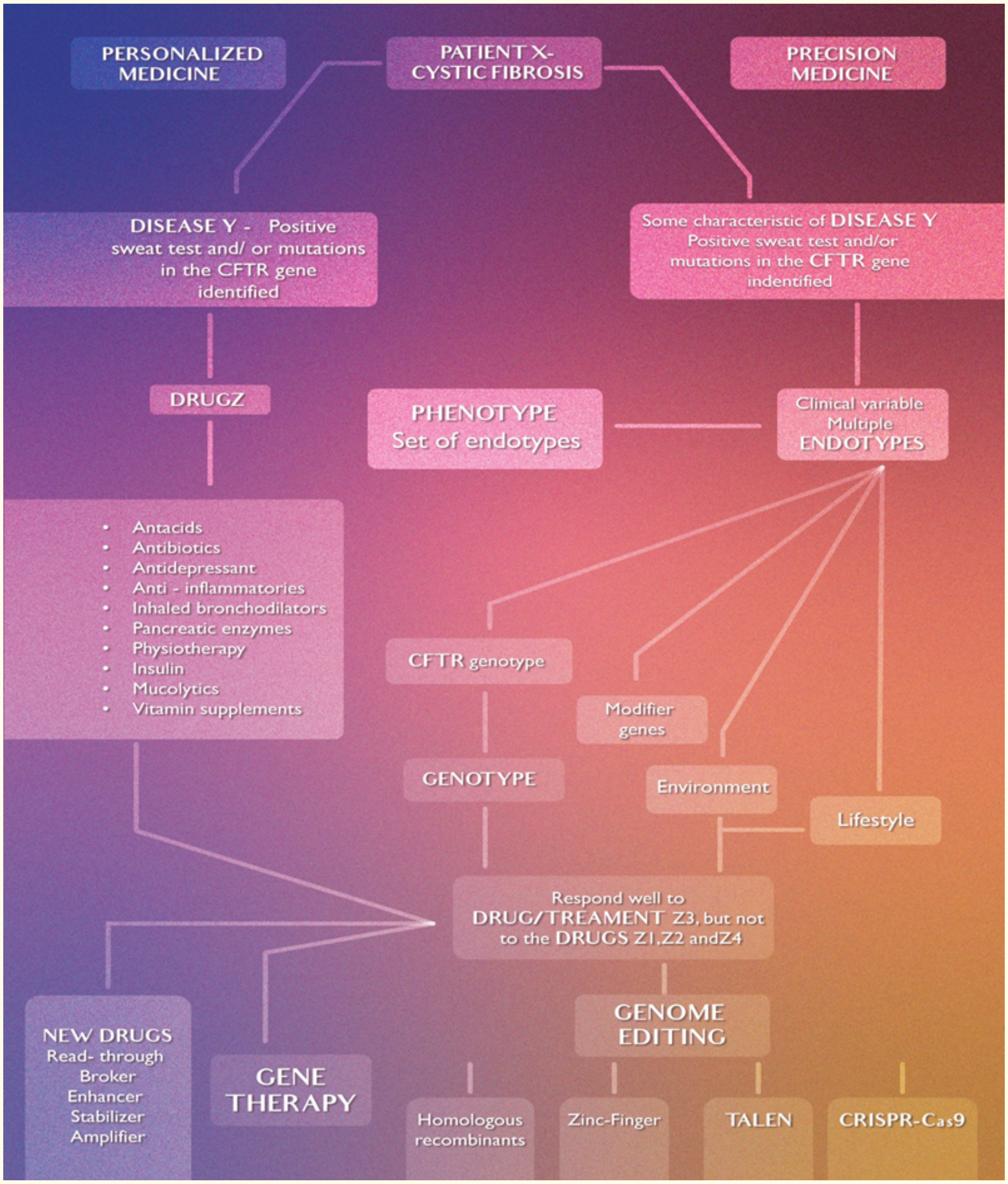

Figure 2: Techniques of Precision Medication to a CF infected Patient.

CFTR deficiency to various innate and acquired immune dysfunctions. Clinical trials of anti-inflammatory therapies show promise but also warrant caution.

Bibliography

1. Andersen D. "Cystic fibrosis of the pancreas and its relation to celiac disease". *American Journal of Diseases of Children* 56 (1938): 344-399.

2. Meyerholz DK., *et al*. "Loss of cystic fibrosis transmembrane conductance regulator function produces abnormalities in tracheal development in neonatal pigs and young children". *American Journal of Respiratory and Critical Care Medicine* 182 (2010): 1251-1261.

3. Stoltz DA., *et al*. "Cystic fibrosis pigs develop lung disease and exhibit defective bacterial eradication at birth". *Science Translational Medicine* 2.29 (2010): ra31.

4. Tiringer K., *et al*. "A Th17- and Th2-skewed cytokine profile in cystic fibrosis lungs represents a potential risk factor for Pseudomonas aeruginosa infection". *American Journal of Respiratory and Critical Care Medicine* 187 (2013): 621-629.

5. Lloyd-Still JD. "Crohn's disease and cystic fibrosis". *Digestive Diseases and Sciences* 39 (1994): 880-885.

6. Chen Q., *et al*. "A review of cystic fibrosis: Basic and clinical aspects". *Animal Models and Experimental Medicine* 4.3 (2021): 220-232.

7. "A disease called 'sixty-five roses'". *Nature Structural and Molecular Biology* 9 (2002): 887.

8. Stoltz D., *et al*. "Origins of Cystic Fibrosis Lung Disease". *New England Journal of Medicine* (2015).

9. Derichs N. "Targeting a genetic defect: cystic fibrosis transmembrane conductance regulator modulators in cystic fibrosis". *European Respiratory Review* 22.127 (2013): 58-65.

10. Cutting G. "Cystic fibrosis genetics: from molecular understanding to clinical application". *Nature Reviews Genetics* 16.1 (2014): 45-56.

11. Cystic Fibrosis Foundation. National Patient Registry 2021: Annual Data Report (2023).

12. Pérez MM., *et al*. "CFTR gene analysis in Latin American CF patients: heterogeneous origin and distribution of mutations across the continent". *Journal of Cystic Fibrosis* 6.3 (2007): 194-208.

13. Cystic Fibrosis Mutation Database (2020).

14. Farrell PM., *et al*. "The Impact of the CFTR Gene Discovery on Cystic Fibrosis Diagnosis, Counseling, and Preventive Therapy". *Genes* 11 (2020): 401.

15. Kerem E., *et al*. "The relation between genotype and phenotype in cystic fibrosis - analysis of the most common mutation (delta F508)". *The New England Journal of Medicine* 323 (1990): 1517-1522.

16. "The Cystic Fibrosis Genotype-Phenotype Consortium. Correlation between genotype and phenotype in patients with cystic fibrosis". *The New England Journal of Medicine* 329 (1993): 1308-1313.

17. Welsh MJ and Smith AE. "Molecular mechanisms of CFTR chloride channel dysfunction in cystic fibrosis". *Cell* 73 (1993): 1251-1254.

18. Scotet V., *et al*. "The changing epidemiology of cystic fibrosis: incidence, survival and impact of the CFTR gene discovery". *Genes* 11.6 (2020): 589.

19. Clancy JP., *et al*. "CFTR Modulator Theratyping: Current Status, Gaps and Future Directions". *Journal of Cystic Fibrosis* 18 (2019): 22-34.

20. Accurso FJ., *et al*. "Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation". *The New England Journal of Medicine* 363 (2010): 1991-2003.

21. Ong T and Ramsey B W. "Cystic fibrosis: a review". *Jama* 329.21 (2023): 1859-1871.

22. Sun X., *et al*. "In utero and postnatal VX-770 administration rescues multiorgan disease in a ferret model of cystic fibrosis". *Science Translational Medicine* 11.485 (2019): eaau7531.

23. Veit G., *et al*. "From CFTR biology toward combinatorial pharmacotherapy: expanded classification of cystic fibrosis mutations". *Molecular Biology of the* Cell 27.3 (2016): 424-433.

24. Welsh MJ and Smith AE. "Molecular mechanisms of CFTR chloride channel dysfunction in cystic fibrosis". *Cell* 73.7 (1993): 1251-1254.

25. Mall MA., *et al*. "Cystic fibrosis: emergence of highly effective targeted therapeutics and potential clinical implications". *American Journal of Respiratory and Critical Care Medicine* 201.10 (2020): 1193-1208.

26. http://www.childrenshospital.org/conditions-and-treatments/conditions/c/cystic-fibrosis/symptoms-and-causes

27. Davies J C., *et al*. "Clinical review: Cystic fibrosis". *BMJ: British Medical Journal* 335.7632 (2007): 1255.

28. Katkin JP. "Cystic fibrosis: Clinical manifestations and diagnosis" (2012).

29. Kendig E L., *et al*. "Kendig and Chernick's disorders of the respiratory tract in children". Elsevier Health Sciences (2012).

30. Jaques R., *et al*. "Novel therapeutic approaches for the management of cystic fibrosis". *Multidisciplinary Respiratory Medicine* 15.1 (2020).

31. Ernst MM., *et al*. "Developmental and psychosocial issues in cystic fibrosis". *Child and Adolescent Psychiatric Clinics* 19.2 (2013): 263-283.

32. Quittner AL., *et al*. "Role strain in couples with and without a child with a chronic illness: associations with marital satisfaction, intimacy, and daily mood". *Health Psychology* 17.2 (1998): 112-124.

33. Birmaher B. "Practice parameter for the assessment and treatment of children and adolescents with depressive disorders". *Journal of the American Academy of Child and Adolescent Psychiatry* 46.11 (2007): 1503-1526.

34. Rapee RM., *et al*. "Anxiety disorders during childhood and adolescence: origins and treatment". *Annual Review of Clinical Psychology* 5 (2008): 311-341.

35. Christian BJ and D'Auria JP. "Building life skills for children with cystic fibrosis: effectiveness of an intervention". *Nursing Research* 55.5 (2006): 300-307.

36. Davis MA., *et al*. "Controlled evaluation of the STARBRIGHT CD-ROM program for children and adolescents with cystic fibrosis". *Journal of Paediatrics Psychology* 29.4 (2004): 259-267.

37. Ziaian T., *et al*. "Treatment burden and health-related quality of life of children with diabetes, cystic fibrosis and asthma". *Journal of Paediatrics and Child Health* 42.10 (2006): 596-600.

38. Conese M and Rejman J. "Stem cells and cystic fibrosis". *Journal of Cystic Fibrosis* 5.3 (2006): 141-143.

39. Sui H., *et al*. "Gene therapy for cystic fibrosis: Challenges and prospects". *Frontiers in Pharmacology* 13 (2022): 1015926.

40. Guggino W B and Cebotaru L. "Adeno-associated virus (AAV) gene therapy for cystic fibrosis: current barriers and recent developments". *Expert Opinion on Biological Therapy* 17.10 (2017): 1265-1273.

41. Alton E., *et al*. "Repeated nebulisation of non-viral CFTR gene therapy in patients with cystic fibrosis: a randomised, double-blind, placebo-controlled, phase 2b trial". *Lancet Respiratory Medicine* 3.9 (2015): 684-691.

42. Reynolds SD., *et al*. "Conditional Clara cell ablation reveals a selfrenewing progenitor function of pulmonary neuroendocrine cells". *American Journal of Physiology-Lung Cellular and Molecular Physiology* 278 (2000): L1256-1263.

43. Dorin JR., *et al*. "A demonstration using mouse models that successful gene therapy for cystic fibrosis requires only partial gene correction". *Gene Therapy* 3 (1996): 797-801.

44. Marson FA., *et al*. "Personalized or precision medicine? The example of cystic fibrosis". *Frontiers in Pharmacology* 8 (2017): 271586.

45. Yuan B. "How do precision medicine and system biology response to human body's complex adaptability?". *Chinese Journal of Integrative Medicine* 22.12 (2016): 883-888.

46. Calcium: Fact sheet for health professionals (2019).

47. Egg, whole, cooked, hard-boiled (2019).

48. Engelen M P., *et al*. "Protein is an important but undervalued macronutrient in the nutritional care of patients with cystic fibrosis". (2014).

49. Iron: Fact sheet for health professionals (2019).

50. Nutrition and your digestive system. (n.d.).