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Mini-Review

Cystic Fibrosis: A Brief Review of Pathogenesis, Clinical Features, Diagnosis and Therapies

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Abstract: Cystic fibrosis (CF) is an autosomal recessive disorder caused by variants in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, which encodes CFTR protein, a chloride and bicarbonate channel essential for epithelial ion transport. CF occurs across all racial and ethnic groups, though incidence is highest among individuals of Northern European ancestry. Advances in newborn screening, diagnosis, and treatment have transformed CF from a fatal childhood disease into a chronic, manageable condition extending into adulthood. Over 2000 CFTR variants have been identified and classified into six groups based on their impact on protein production, processing, and function. Variants in Classes I–III generally result in more severe disease, while Classes IV–VI are associated with milder phenotypes. CF primarily affects the lungs, pancreas, gastrointestinal tract, hepatobiliary system, and reproductive system. Progressive pulmonary disease remains the leading cause of morbidity and mortality, driven by mucus obstruction, chronic infection, and neutrophil-mediated inflammation. Pancreatic insufficiency, malabsorption, CF-related diabetes, liver disease, and infertility are common systemic features. Modern management combines symptomatic therapies with CFTR modulators such as ivacaftor and triple-combination regimens which have revolutionized outcomes. Median survival now exceeds 50 years, with ongoing research targeting universal therapies and gene-based approaches.

Keywords: cystic fibrosis; CF; CFTR; newborn screening; pulmonary disease; CFTR modulators

1. Introduction

First described in 1949, cystic fibrosis (CF) is a monogenic, autosomal recessive disorder caused by pathogenic variants in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Although historically associated with individuals of Northern European descent, clinical and genetic studies have shown that CF occurs across all racial and ethnic groups. Once considered a fatal disease of early childhood, advances in diagnosis and management have transformed CF into a chronic, multisystem disorder that now typically extends into adulthood, with steadily improving quality of life.

The incidence of CF is highest among individuals of Northern European ancestry, at approximately 1 in 2000–3000 live births. Rates are lower in other populations, estimated at about 1 in 13,500 among Hispanic individuals, 1 in 15,000 among individuals of African descent, and 1 in 35,000 among those of Asian descent. In the United States, more than 30,000 people are currently living with cystic fibrosis (CF), with approximately 1000 new diagnoses each year, while globally the CF population exceeds 90,000 [1,2]. With the widespread

adoption of newborn screening and advances in diagnostic technologies, the reported prevalence of CF has continued to rise.

2. Genetics and Pathogenesis of CF

Cystic fibrosis (CF) is caused by pathogenic variants in *CFTR*, located on chromosome 7q31.2, which encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein composed of 1480 amino acids. CFTR is a member of the ATP-binding cassette (ABC) transporter superfamily and functions as a cAMP-regulated chloride channel embedded in the apical membrane of epithelial cells [3]. In addition to chloride, CFTR also modulates the transport of sodium and bicarbonate ions. Defects in the CFTR protein impair chloride and bicarbonate secretion as well as sodium reabsorption, leading to disrupted ion and water transport across epithelial membranes. This leads to the accumulation of thick, viscous mucus in multiple organs, including the lungs, pancreas, gastrointestinal tract, and reproductive system. Although CFTR is heavily expressed in the nervous system and kidneys, no direct pathogenic effects have been clearly demonstrated in these organs.

To date, over 2000 variants in *CFTR* have been identified, with approximately 700 confirmed to cause cystic fibrosis (CF) [2,4]. Based on how these variants affect CFTR protein production, processing, expression, and function, they are categorized into six classes [2,4].

- Class I variants are caused by nonsense, frameshift, or splice-site variants that result in the absence of CFTR protein.
- Class II variants, including the most common F508del variant in white population, produce a misfolded and unstable CFTR protein that is degraded before reaching the cell surface.
- Class III variants lead to defective channel regulation due to impaired ATP binding.
- Class IV variants result in reduced chloride conductance through CFTR channels.
- Class V variants cause decreased levels of functional CFTR protein, often due to impaired mRNA splicing or reduced protein stability.
- Class VI variants affect the stability of CFTR at the plasma membrane, leading to its accelerated degradation.

In general, variants in Classes I to III are associated with more severe disease as compared to those in Classes IV to VI. Table 1 provides a summary of CFTR defects classified by type, their prevalence, representative variants, and associated therapeutic strategies.

Table 1. CFTR classes by type of defects, prevalence, example variants, and corresponding therapeutic approaches.

	Class I	**Class II**	**Class III**	**Class IV**	**Class V**	**Class VI**
CFTR Defect	No CFTR	Trafficking	Regulation	Conductance	Synthesis	Stability
Variant Type	Nonsense, frameshift, splice defect	Missense, amino acid substitution	Missense, amino acid substitution	Missense, amino acid substitution	Missense, splice defect	Missense, amino acid substitution
Relative Prevalence	5%	86%	4%	3%	2%	<1%
Variant Examples	G542X W1282X R553X	F508del N1303K 1507del	G551D S549N V520F	R117H D1152H R334W	A455E 3272-26A > G 2789 + 5G > A	4326delTC 4279insA Gln1412X
Therapeutic Approach	Suppressor—read through premature stop codons	Corrector + Potentiator—improve folding and increase gating	Potentiator—increase gating activity	Potentiator—improve channel function	Potentiator—improve splice efficiency	Stabilizer—improve protein stability at cell surface

3. Clinical Presentation

Cystic fibrosis (CF) is a multisystem disorder that primarily affects epithelial tissues of the respiratory tract, exocrine pancreas, gastrointestinal tract, hepatobiliary system, and sweat glands [2,4,5]. Among these, progressive pulmonary disease remains the principal source of morbidity and mortality in individuals with CF.

In the countries with newborn screening for CF, infants are largely diagnosed through NBS. In countries without newborn screening, a typical presentation would include poor weight gain, extreme hunger, and steatorrhea. This is followed by lower respiratory signs and symptoms caused by a cycle of airway inflammation, obstruction, and infection. CFTR dysfunction leads to the obstruction of airways by thick and tenacious mucus which promotes chronic infection and worsening neutrophilic inflammation. Cough and sputum production are the clinical hallmarks of CF lower respiratory disease. The commonly found bacteria are *Staphylococcus aureus, Pseudomonas aeruginosa*, and methicillin-resistant *S. aureus* (MRSA). Persistent inflammation and infections cause structural lung damage, including bronchiectasis, characterized by abnormal airway dilation. Persons with

CF (PwCF) frequently experience acute pulmonary exacerbations marked by increased cough, tachypnea, dyspnea, increased sputum production, malaise, anorexia, and weight loss. Recurrent pulmonary exacerbations often result in irreversible declines in lung function. Most individuals with CF also develop upper airway involvement, including chronic sinus disease characterized by nasal congestion, sinus headaches, and nasal polyposis [4,6].

Pancreatic and intestinal involvement is another hallmark feature of CF. 80–85% of PwCF experience exocrine pancreatic insufficiency (PI) [7]. Thickened secretions obstruct the pancreatic ducts, leading to impaired enzyme secretion and eventual destruction of pancreatic tissue, resulting in malabsorption, particularly of fats and fat-soluble vitamins. Clinically, this manifests as steatorrhea, poor weight gain, and failure to thrive, particularly in infants and young children. Focal biliary cirrhosis from thickened bile is a common finding in CF and may progress to periportal fibrosis, cirrhosis, portal hypertension, and variceal bleeding [6,8].

Intestinal involvement may include meconium ileus, a form of congenital bowel obstruction present at birth in approximately 10–20% of newborns with CF [6,9]. In older children and adults, distal intestinal obstruction syndrome (DIOS) is a potential complication, characterized by partial or complete obstruction of the ileocecal region. Rectal prolapse may also occur, particularly in younger children, due to chronic straining during stooling and malnutrition. Intestinal malabsorption may also lead to frequent deficiencies in fat-soluble vitamins (A, D, E, and K) [5,6,10].

In contrast, individuals with class IV–VI *CFTR* variants who retain partial pancreatic function may be pancreatic sufficient (PS) but are at increased risk for recurrent pancreatitis, often presenting as abdominal pain. Many PwCF who are PI may exhibit elevated pancreatic enzymes from early pancreatic inflammation, which may progresses to pancreatic insufficiency.

Over time, ongoing pancreatic injury may lead to cystic fibrosis related diabetes (CFRD), a distinct form of diabetes caused by progressive destruction of islet cells [2,5,6]. The prevalence of CFRD increases with age, affecting approximately 20% of adolescents and up to 50% of adults with CF [11]. Early recognition and management of pancreatic manifestations are essential to optimizing growth, nutrition, and overall health outcomes in CF.

CF also affects the reproductive systems in both males and females. More than 95% of males with CF are infertile due to congenital bilateral absence of the vas deferens, although spermatogenesis is typically preserved. In females, fertility may be reduced due to malnutrition and thick cervical mucus, but pregnancy is still possible [12,13].

Additional clinical manifestations of CF include reduced bone mineral density, increased fracture risk, kyphoscoliosis, osteopenia, and osteoporosis. Digital clubbing of the fingers and toes may develop in PwCF with long-standing disease. Compared with the general population, individuals with CF also experience central nervous system complications, particularly anxiety and depression, at rates two to three times higher [6,14].

4. Diagnosis

Historically, the diagnosis of CF was challenging and often delayed due to its broad and variable clinical presentation. Symptoms may range from classic multisystem involvement to milder or atypical phenotypes, depending on the level of residual CFTR function. These challenges are further amplified in non-white populations, where CF is often underrecognized due to its lower prevalence, reduced clinical suspicion, and the limited sensitivity of standard genetic testing panels, which are primarily based on variants common among individuals of Northern European descent.

Current consensus is that the diagnosis of CF should be based on the presence of a clinical feature consistent with CF

- Typical phenotypic feature
- Sibling with CF
- Abnormal newborn screening for CF

And an objective measure of CFTR dysfunction

- Elevated sweat chloride concentration (≥60 mmol/L) on two separate occasions
- Identification of two disease-causing *CFTR* variants in *trans* configuration
- Abnormal nasal potential difference measurements indicating CFTR dysfunction

In the United States and many other developed countries, newborn screening for CF is universal. Although not standardized, typical screening algorithms involve the measurement of immunoreactive trypsinogen (IRT) concentrations in a neonatal dried blood spot followed by genetic testing. IRT, a pancreatic enzyme precursor, is elevated in most infants with CF, even those who are pancreatic sufficient. If IRT concentrations are above a predefined threshold, the sample undergoes reflex molecular testing for common *CFTR* variants to confirm the

likelihood of CF and identify carriers [4–6]. Early detection through this two-tiered approach facilitates prompt diagnostic evaluation (sweat chloride testing) and initiation of care.

Sweat chloride measurement is the primary test for the diagnosis of CF. It is typically performed on individuals who have abnormal newborn screening or those with clinical features suggestive of CF. However, sweat collection for chloride testing presents several challenges. The procedure is relatively complex and can be uncomfortable, particularly in newborns. Sweat collection takes approximately one hour and involves pilocarpine iontophoresis followed by sweat collection using absorbent pads or coils [15]. One of the most common issues is obtaining a sufficient volume of sweat for analysis, particularly in premature, underweight newborns and young infants. In addition, variability in staff training, deviations from Clinical and Laboratory Standards Institute (CLSI) guidelines, and lack of standardization across institutions can contribute to inconsistent results [15]. Once collected, sweat is analyzed for chloride either directly, if collected in coils, or after elution, if collected on absorbent pads. The preferred method for chloride analysis is coulometric titration using a silver electrode, performed with a chloridometer [15].

Sweat chloride values are interpreted as follows [2,6]:

- ≥60 mmol/L: Indicative of CF. These values are generally associated with the presence of clinical symptoms and indicate significant CFTR dysfunction.
- 30–59 mmol/L: Intermediate or borderline range. Additional testing, such as *CFTR* genetic analysis and/or nasal potential difference (NPD) testing is generally warranted to clarify the diagnosis.
- <30 mmol/L: CF is unlikely. However, rare cases with mild *CFTR* variants or atypical clinical presentations have been reported in this range.

Genetic testing is widely used to confirm the diagnosis of cystic fibrosis, particularly in individuals with intermediate sweat chloride values. It identifies pathogenic variants in *CFTR* and plays a critical role in both establishing the diagnosis and guiding treatment decisions. This is especially important for determining eligibility for CFTR modulator therapies, which are tailored to specific *CFTR* variants.

The Nasal Transmembrane Epithelial Potential Difference (NPD) test is an indirect measure of CFTR function that assesses ion transport across the nasal epithelium. Though not diagnostic, NPD test can be particularly useful in cases where sweat chloride testing and genetic analysis yield inconclusive results. Its use is largely limited to research activities.

5. Management, Treatment and Prognosis

Over the past several decades, CF management has undergone a remarkable transformation, shifting from a focus on symptomatic relief to an integrated approach that combines targeted therapies addressing the underlying genetic defect with comprehensive supportive care. This modern model relies on multidisciplinary teams comprising of pulmonologists, gastroenterologists, endocrinologists, nurses, dietitians, respiratory therapists, mental health professionals, social workers, and laboratorians. These teams work collaboratively to provide early, proactive disease management aimed at improving quality of life and extending survival.

Current treatment strategies can be broadly divided into traditional symptomatic therapies and targeted CFTR modulator therapies.

Symptomatic treatments have been an essential part of care, focusing on controlling symptoms and preventing complications, and include the following [2,4,6]:

- Mucus Thinners and Airway Clearance: Inhaled hypertonic saline hydrates airway surfaces and improves mucociliary clearance. Recombinant human DNase reduces mucus viscosity by breaking down extracellular DNA. Airway clearance techniques include postural drainage and percussion, oscillatory positive expiratory pressure devices, and high-frequency chest wall oscillation. These measures are recommended for all PwCF, even when symptoms are minimal, as mucus plugging can occur silently.
- Infection Control: Chronic infection with pathogens such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* is common, making infection control a priority. Strategies include culture-directed antibiotic therapy, long-term azithromycin for combined antibacterial and anti-inflammatory effects, and chronic inhaled antibiotics such as tobramycin or aztreonam for persistent *Pseudomonas* infections. These approaches can improve lung function and reduce exacerbations.
- Anti-inflammatory Medications: Chronic neutrophil-driven inflammation in CF has been addressed with several anti-inflammatory medications. Though no longer commonly used, high-dose ibuprofen demonstrated efficacy in managing CF airway disease. Azithromycin continues to be commonly used for it's anti-inflammatory properties. Systemic steroids are generally avoided except for specific inflammatory comorbidities such as asthma or allergic bronchopulmonary aspergillosis (ABPA). Conversely, inhaled

corticosteroids are commonly used despite limited evidence of efficacy and the risk of adverse effects.Nutritional Support: Optimal nutrition through high-calorie diets, pancreatic enzyme replacement therapy, and supplementation with fat-soluble vitamins (A, D, E, and K) is strongly linked to better pulmonary function and resistance to infection.

- Other Symptomatic Measures: These may include laxatives for distal intestinal obstruction syndrome, surgical management for bowel obstruction, oral ursodiol for biliary complications, and supplemental oxygen for advanced respiratory disease.

The roll of all of these therapies is being reevaluated in the era of highly effective CFTR modulator therapy (HEMT). Early evidence suggests that many respiratory therapies may be safely discontinued among healthy PwCF who are consistent with HEMT.

The introduction of CFTR modulator therapies has been a turning point in CF care, establishing them as a central pillar of treatment [2,4,16–18]. These targeted small-molecule drugs correct specific functional defects in the CFTR protein, restoring chloride and bicarbonate transport across cell membranes. They are broadly categorized as potentiators and correctors. Potentiators (e.g., ivacaftor) increase the likelihood that the CFTR channel remains open, and correctors (e.g., lumacaftor, tezacaftor, elexacaftor) improve protein folding and trafficking of CFTR to the cell surface.

Ivacaftor, the first approved modulator, benefits PwCF with gating variants (Class III–V), such as G551D, improving lung function, nutritional status, and sweat chloride concentrations. Lumacaftor/ivacaftor and tezacaftor/ivacaftor combinations provide modest benefits for PwCF homozygous for the F508del variant (Class II). The triple therapy elexacaftor/tezacaftor/ivacaftor has produced transformative improvements in lung function, BMI, quality of life, and exacerbation rates, while expanding eligibility for modulator therapy to about 90% of the CF population [16,19,20]. Vanzacaftor, tezacaftor, and deutivacaftor has recently been approved by the FDA and allows once daily dosing compared to other modulators [21].

Surgical interventions remain important for advanced disease, with lung transplantation improving survival in end-stage pulmonary disease and other surgical options addressing severe liver disease or intestinal obstruction. Lung transplantation can significantly improve survival and quality of life in end-stage pulmonary disease, with median post-transplant survival of 8–10 years [2,6]. Liver transplantation may be required for severe CF-related liver disease, and bowel surgery is sometimes necessary for complications such as meconium ileus or DIOS.

In addition to the targeted therapies mentioned above, emerging treatments are being developed to extend benefits to all PwCF, regardless of genotype. Gene therapy (DNA or mRNA replacement) aims to restore wild-type *CFTR* expression, while CRISPR/Cas9 gene editing offers the potential for correction of specific variants. Alternative ion channel modulators such as ENaC inhibitors, TMEM16A potentiators, and SLC26A9 modulators seek to bypass CFTR dysfunction and improve mucus hydration. Variant-specific strategies include read-through agents (e.g., ELX-02, ataluren) for Class I nonsense variants and antisense oligonucleotides for correcting splicing defects in variants such as 3849 + 10 kb C → T and W1282X. Additional novel approaches include advanced mucolytics, phage therapy for antibiotic-resistant infections, protease inhibitors to reduce inflammation and structural lung damage, and nitric oxide pathway regulators to enhance airway function [2,6,17,20].

Advances in CF therapies have dramatically improved survival among PwCF. In the 1960s, median survival was under 10 years; today, in many high-income countries, it exceeds 50 years [2]. The median predicted survival age of an individual born with CF in 2023 was 68.0 years (95.0 percent confidence interval: 63.4–71.5 years) [1]. These gains are driven by newborn screening, improved infection control, and the impact of CFTR modulators.

In summary, cystic fibrosis, once considered a uniformly fatal childhood illness, is now recognized as a chronic and manageable condition. Modern care combines aggressive symptom control, targeted molecular therapies, and comprehensive support for both physical and mental health. Looking ahead, priorities include expanding effective treatments to all genotypes and reducing the long-term economic and psychological burdens of the disease, with the overarching goal of extending survival while maintaining a high quality of life.

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Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

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