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Review Article

# A Mini Review on Clinical Aspects of Cystic Fibrosis

**Nasim Eftekhari[1]*, Farokh Rokhbakhsh-Zamin[2], Amir Hossein Mohammad Bagheri[3]**

[1] Department of Biology, Zand Institute of Higher Education, Shiraz, Iran

[2] Department of Microbiology, Ke.C., Islamic Azad University, Kerman, Iran

[3] The Office of Vice-President for International Affairs, Department of Medical Education, Faculty of Medicine, Iran University of Medical Sciences (IUMS), Tehran, Iran.

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**ABSTRACT**

Cystic fibrosis (CF) is a rare autosomal disorder caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR). CF can lead to various health issues that affect the quality of life and can be challenging for both patients and healthcare providers. In this article, we conduct a thorough review of the clinical characteristics of cystic fibrosis in children. Classical cystic fibrosis is defined by chronic lung infections, pancreatic insufficiency, and male infertility, and may also include other conditions such as cystic fibrosis-related diabetes or liver disease. This genetic disease is diagnosed in many places through newborn screening, while in other areas, diagnosis is based on specific clinical symptoms, high sweat chloride levels, or known CFTR mutations. Management techniques, including improving mucus clearance and aggressively treating infections, have steadily increased the life expectancy of people with cystic fibrosis. Moreover, the development of new small-molecule drugs that can restore CFTR function is changing the outlook for many patients. Clinical trials are actively looking into various other approaches, which will become increasingly important as survival rates improve and the population of adults with cystic fibrosis grows. This review offers a comprehensive update on CF, covering screening as well as current and future treatments.

**Keywords**: Cystic fibrosis, CFTR, Clinical feature, Inflammation, *Pseudomans aeruginosa*.

* *Corresponding Author:*
*E mail: Nasim.eftekhari180@gmail.com*
*ORCID ID: 0000-0003-4083-6147*

## BACKGROUND

Cystic fibrosis (CF) is a multisystem disorder among children, caused by defects in the cystic fibrosis gene, which codes for a protein, transmembrane conductance regulator (CFTR), that functions as a chloride channel and is regulated by cyclic adenosine monophosphate (cAMP). Mutations in the CFTR gene result in abnormalities of cAMP-regulated chloride transport across epithelial cells on mucosal surfaces [1]. Recorded observations of children with this disease in the 1940s and 1950s. In the 1990s, it caused pancreatic damage that resulted in severe malabsorption, wasting, and infant mortality [1,2]. Children were found to be at risk for lung infections, although the pathogenic relationships between these various disease processes were unclear. The 1948 heat wave in New York, USA, which resulted in severe hyponatremic dehydration in many children with cystic fibrosis, led to the discovery of sweat salt loss and the development of diagnostic tests using sodium and chloride sweat tests [2]. Since 1989, the discovery of the CFTR gene that causes cystic fibrosis has greatly increased the understanding of the pathophysiology [3]. Over time, cystic fibrosis has become a model for the convergence of research and clinical development, with scientific advances in pathophysiology and cell biology leading to therapeutic advances directly linked to significant improvements in patient care and survival. Such examples include dietary supplements, including pancreatic enzyme supplements, airway, and long-term antimicrobial therapy to prevent respiratory infections [1,4,5,6]. The development of small molecules to improve the function of the CFTR protein, called CFTR modulators, has greatly benefited people with cystic fibrosis. As a result, the changing epidemiology of cystic fibrosis presents new challenges that may require different approaches to health care delivery. This article provides a comprehensive literature review of the clinical characteristics of cystic fibrosis.

## REVIEW OF THE LITERATURE

### *Clinical features of cystic fibrosis*

Cystic fibrosis is caused by a defect in the transport of chloride and other ions (such as sodium and bicarbonate). This leads to the formation of thick, viscous secretions, like mucus, in the lungs, liver, pancreas, intestines, and reproductive tract. It also results in an increased salt concentration in the secretions of sweat glands [7]. Progressive lung disease is the primary cause of CF complications and patient mortality. The course of the disease is highly variable and can begin from a few months after birth to decades after birth, and many patients have mild or atypical symptoms. Therefore, doctors should be careful not to dismiss CF as a possible diagnosis in cases where patients have only a few typical signs and symptoms of CF [7, 8].

### *Respiratory tract involvement*

The typical respiratory symptoms of cystic fibrosis (CF) include a persistent productive cough, hyperinflation of lung fields on a chest X-ray, and pulmonary function tests that suggest obstructive airway disease. As the disease progresses, repeated infections related to the buildup of inflammatory cells and the release of cell contents damage the bronchial walls. This leads to the loss of bronchial cartilage support and muscle tendons, eventually resulting in bronchitis [8]. Disease progression involves acute worsening of cough, rapid breathing (tachypnea), shortness of breath (dyspnea), increased sputum production, malaise, loss of

appetite (anorexia), and weight loss. These acute events are connected to a temporary loss of lung function that improves with therapy but often leads to a permanent loss of lung function over time. While CF patients experience diverse symptoms, transient respiratory infections caused by pathogenic bacteria often occur early in life. [8,9].

The infections are often detected by X-ray examination of bronchiectasis and microbiological culture of sputum [10]. *Staphylococcus aureus* is the most common type of bacteria found in the airways of people with cystic fibrosis, even before they show any symptoms. This can lead to both acute (sudden) and chronic (long-lasting) infections. Another common bacterium in the early years of life is *Haemophilus influenzae* (non-capsule), which can cause worsening of symptoms, though its role in causing ongoing inflammation in the airways is not fully understood. As individuals with cystic fibrosis get older, *Pseudomonas aeruginosa* becomes more prevalent in their airways compared to the earlier bacteria mentioned. In addition, the airways of CF patients may be colonized or infected with other microbial species, including *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, *Burkholderia cepacia* complex (Bcc), Non-tuberculous mycobacteria (NTM) (especially *Mycobacterium avium* complex and *Mycobacterium abscessus*), and the filamentous fungus *Aspergillus fumigatus*. Persistent airway colonization and bacterial infection (especially Pseudomonas aeruginosa) can increase the inflammatory response by triggering neutrophils that release large amounts of DNA and matrix proteins into the airways. These agents, along with CF-induced airway dysfunction and chronic inflammation, increase the viscosity of airway mucus. Studies are currently underway to identify other bacterial species in the airways of CF patients, including obligate anaerobes, which can be identified using next-generation sequencing technology (NGS) [ 8, 9,10].

***Sinusitis***

Sinus disease occurs when the lining of the sinuses becomes infected and inflamed. It's common in CF because the thicker mucus found in the lungs is also found in the sinuses, causing the mucus to get stuck and increasing the risk of infection [11]. Most CF patients develop sinus disease. Sinusitis can manifest as chronic nasal congestion, headaches, chronic postnasal drip, and sleep disorders. Sinus infections can cause lower respiratory tract exacerbations in some patients, although the organisms found in the sinuses do not always match those recovered from the lungs. Chronic rhinosinusitis (CRS) is nearly ubiquitous in patients with cystic fibrosis (CF). Cystic fibrosis CRS is a challenging entity to define, diagnose, and treat, as patients often have severe refractory sinus disease in addition to complex medical comorbidities. In one case-control study, the rate of single CFTR mutations in a group of CRS cases was significantly higher than the corresponding rate in the general population (7% versus 2%) [12].

***Poor Growth***

The growth of children with cystic fibrosis (CF) is a crucial aspect to monitor as it indicates their health status [12]. The growth of these children is closely connected to important CF outcomes like nutrition and lung function. It is standard practice to regularly check and monitor the growth and nutrition of CF patients during their medical visits. However, it is especially important to pay close attention to their growth during specific times, such as the first 12 months after diagnosis, whether it was before birth, through newborn screening, or later in life, as well as during the period around puberty.

Focusing on growth during these times is vital for providing optimal care for individuals with CF [12,13].

***Bone disorder***

Bone disease is a common comorbidity in patients with CF. Patients with CF have reduced bone mineral content and increased rates of fractures and kyphoscoliosis [14]. The cause of CF-related bone disease (CFBD) is likely multifactorial; CFBD is due to both suboptimal peak bone mass acquisition and increased bone loss during adulthood, affecting up to 20% of adolescent patients and 55-65% of patients 45 years of age or older. In addition to a lower bone mineral density, CF patients often exhibit altered bone microarchitecture, compromised bone strength, and increased risk of fractures. Furthermore, factors such as pancreatic insufficiency, malnutrition, chronic inflammation, and vitamin D deficiency contribute to the pathogenesis of CF-related bone disease. Early screening, nutritional optimization, physical activity, and appropriate supplementation are crucial in the management of CFBD to prevent further skeletal complications and enhance the overall quality of life for individuals living with CF [15].

***Gastrointestinal disease***

In cystic fibrosis, nutritional failure arises from various factors. A key factor is the body's ineffective absorption of fats, proteins, and fat-soluble vitamins caused by a deficiency in pancreatic enzymes. Complications in bile salts, particularly in the presence of liver disease, can exacerbate this issue. Furthermore, persistent lung infections can hinder breathing, decrease appetite, and heighten calorie requirements due to the body's inflammatory reaction. Additional factors influencing nutrition in cystic fibrosis encompass associated conditions such as diabetes, alterations in gastrointestinal function, and bacterial overgrowth in the small intestine [16].

The digestive issues seen in individuals with cystic fibrosis are mainly due to thick mucus and problems with muscle movement in the digestive tract. Some common symptoms include severe constipation, blockage of the lower part of the intestines (known as distal intestinal obstruction syndrome), acid reflux, and an overgrowth of bacteria in the small intestine. Distal intestinal obstruction syndrome happens when thickened intestinal contents block the small intestine, often at a specific junction [16,17]. This blockage is thought to be caused by a series of inflammatory reactions in the intestines due to the genetic defect seen in cystic fibrosis [18].

***Diagnosis of cystic fibrosis***

**Clinical diagnosis**

In 2017, the Cystic Fibrosis Foundation issued updated diagnostic consensus guidelines in partnership with global collaborators [19,20,21]. In regions lacking newborn screening programs, diagnostic criteria suggest assessing clinical symptoms, family history, presence of CFTR gene mutations, or identification of two disease-causing CFTR mutations [22,23]. For genotypes with varied clinical implications, diagnostic tests like sweat chloride or advanced electrophysiological examinations are necessary for confirming cystic fibrosis. A sweat test conducted in an accredited clinical lab remains the principal method for assessing CFTR function: chloride concentrations exceeding 60 mmol/L indicate diagnosis; concentrations between 30 and 59 mmol/L fall within an intermediate range; while concentrations below 30 mmol/L are considered normal [24].

***Newborn screening***

Several newborn screening strategies are utilized, many employing initial biochemical screening (typically measuring immunoreactive trypsinogen from a dried blood spot) followed by genetic testing, sweat chloride testing, or both. The selection of CFTR mutations included in newborn screening panels is based on local population prevalence and aims to detect as many cystic fibrosis patients as possible while minimizing false positive results. Newborn screening has had many benefits for people with cystic fibrosis and their families, with positive effects on physical and psychological health [25]. In the future, the health benefits of highly effective CFTR modulation therapies may prove synergistic with neonatal screening, as new intrauterine animal studies and postnatal treatment demonstrate disease attenuation [25, 26].

***Treatment***

CF treatment programs must be evaluated, improved, and managed with close monitoring to achieve early and active intervention for CF treatment. To achieve these goals, potential CF patients should be admitted to the hospital pending additional test results and other findings that support or rule out a CF diagnosis. Once a diagnosis of CF is made, the physician must begin treating the patient immediately and educate patients and their families about the effective management of the disease.

Treatment for CF lung disease includes giving mucus thinners, clearing the airways, and antibiotics. Inhalation therapy consists of hypertonic saline to hydrate the thick mucus in the CF patient's airways to thin the mucus [27].

The high osmotic pressure of the solution draws water out of the airway epithelial cells to rebuild a water-containing surface layer that is absent in CF patients. To treat the retention of purulent exudate, which obstructs airflow and damages the airways, the usual method of elimination of exudate in CF patients is chest physiotherapy based on positional drainage and percussion, which also uses bronchoscopic lavage. Although antibiotics are necessary for the treatment of chronic infections and acute exacerbations of CF, long-term oral antibiotics are generally not recommended for infection control. However, long-term use of Azithromycin is recommended for many CF patients because of its anti-inflammatory and/or antibacterial properties, while long-term therapy with aerosolized antibiotics against *P. aeruginosa* (like Tobramycin and Aztreonam) is recommended because of these useful properties' effect on lung function [27,28,29].

In particular, severe neutrophilic inflammation is the pathological hallmark of CF airways. In the past, inflammation was thought to be necessary to prevent the spread of infection, but accumulating evidence indicates that excessive inflammation is generally harmful. Thus, in clinical practice, Azithromycin is recommended for all CF patients older than 6 years of age with clinical signs of airway inflammation (like chronic cough), regardless of *P. aeruginosa* infection status. To further support growth and nutrition in CF patients, patients' diets should be supplemented with pancreatic enzymes, calories, and fat-soluble vitamins [27].

To further support CF patient growth and nutrition, the patient's diet must be supplemented with pancreatic enzymes, calories, and fat-soluble vitamins. Several new types of drugs are currently in development, some of which are well tolerated by patients, including those required to restore normal function of the damaged CFTR protein and those that directly affect mucociliary clearance. CFTR modulators such as ivacaftor (Kalydeco),

lumacaftor/ivacaftor (Orkambi), and tezacaftor/ivacaftor (Symdeko) target different potential defects in the CFTR protein caused by different gene mutations, making these drugs effective only in people with certain mutations [27,28]. Trikafta (tezacaftor, elexacaftor and ivacaftor) is the third drug approved by the FDA to rescue defects caused by better F508del than its predecessor. Trikafta is also effective in CF patients with one copy of the F508del CFTR mutation. It shows safety and sustained efficacy for 24 weeks or longer in people with CF and one or more F508del alleles [28,29,30].

***Pulmozyme (Dornase alfa)***

Dornase alfa is currently used as a mucolytic to treat pulmonary disease (the major cause of morbidity and mortality) in cystic fibrosis. It is a highly purified solution of recombinant human deoxyribonuclease (rhDNase), an enzyme that selectively cleaves DNA.

The enzyme hydrolyzes the DNA present in the sputum/mucus of patients with cystic fibrosis and reduces viscosity, thereby improving the clearance of secretions [ 31,32]. The use of dornase alfa in therapy has been proven to enhance lung function in short-term and longer trials lasting up to two years. In a three-year trial, there was no significant difference in lung function between groups, but the trial did not specifically focus on measuring changes in lung function.

Taking dornase alfa once daily lowers the risk of infective exacerbations. Although not everyone with cystic fibrosis experiences improved lung function with dornase alfa, most people can expect to see improvements within a month of starting the treatment.

It's important to understand that improvements in lung function may not always result in a decrease in exacerbations. Longer trials may be needed to fully comprehend this connection. The impact of dornase alfa on mortality remains uncertain due to the restricted duration of existing trials. Dornase alfa is generally well-tolerated, with the most commonly reported side effects being voice changes and rash. Comparative trials suggest that dornase alfa is more effective than hypertonic saline in improving lung function, but there were no significant differences in the frequency or timing of pulmonary exacerbations. Trials comparing dornase alfa with mannitol or a combination of dornase alfa with a hyperosmolar agent did not show any additional benefits in terms of lung function or exacerbation rates [32,33,34].

***Newer therapies and clinical trials***

Until the development of a class of small-molecule drugs now known as CFTR modulators, all available treatments targeted the symptoms and subsequent consequences of CFTR dysfunction rather than the underlying cause. Treating disease by restoring CFTR function was considered a breakthrough, yet proved challenging in the initial phase [35,36]. Two main groups of molecules have been developed: enhancers, which increase the effect of CFTR on the cell surface, and correctors, which help transport CFTR to the cell surface. In 2020, enhancers that increase the amount of CFTR mRNA (and therefore protein) in the cell entered clinical trials [35,36,37]. However, not all parts of the world have access to modulators, which is increasing health disparities. Patients who cannot use or do not have modulator drugs may benefit from alternative approaches that are being tested in clinical trials. Designing and implementing these trials will present challenges, but the existing global cystic fibrosis infrastructure provides a significant advantage in this process [38,39,40].

## CONCLUSION

Cystic fibrosis, a genetic condition without a cure, often reduces life expectancy. Nevertheless, over the past 50 years, the average lifespan of CF patients has notably increased, surpassing 40 years. This progress highlights that CF is no longer just a childhood disease: more than half of cases are now in adults, with some individuals living into their sixties. Successful treatments have improved prognosis, quality of life, and longevity for CF patients. Prognosis for CF patients is significantly influenced by factors such as early detection and treatment, the severity of lung disease, nutritional status, overall health, and mental well-being. To improve outcomes for pediatric CF cases, raising awareness and ensuring family members adhere to preventive measures, reduce infections, manage acute exacerbations, and follow care protocols are crucial. These strategies aim to enhance life quality and increase long-term survival rates for those with cystic fibrosis.

**Transparency declaration**

There is no conflict of interests.

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