Current Trends in Medicine and Clinical Research
*Nagora et al. Curr. Trends Med. Clin. Res. 2025 Aug;1(1):1-8.*
https://ctpcr.org
ISSN 0000-0000

**REVIEW** **Open Access**

# Revolutionising Cystic Fibrosis: Unwinding the Complexities for Innovative Therapeutic Insights

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## ABSTRACT

Cystic fibrosis (CF) is a life-threatening autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. These genetic alterations impair chloride and bicarbonate ion transport across epithelial surfaces, resulting in thick, sticky mucus that accumulates in the lungs, pancreas, and other organs. The consequences include recurrent respiratory infections, progressive lung damage, and nutritional deficiencies, making CF a complex multisystem disease requiring lifelong management. Recent decades have witnessed major advancements in CF therapy. The development of CFTR modulators, such as ivacaftor and triple-combination regimens (elexacaftor/tezacaftor/ivacaftor), has revolutionised care by directly targeting the underlying molecular defect rather than just managing symptoms. These therapies have demonstrated improvements in lung function, quality of life, and life expectancy, marking a paradigm shift in treatment. In parallel, nanotechnology has emerged as a powerful tool for drug delivery, enabling nanoparticles to enhance drug stability, improve bioavailability, and deliver therapies more precisely to affected tissues, thereby minimising systemic side effects. Cutting-edge genetic approaches, particularly CRISPR-Cas9–based genome editing, hold promise for correcting CFTR mutations at their source. Although still experimental, these strategies could provide long-term or even curative solutions. Alongside pharmacological and genetic interventions, epidemiological research and improved diagnostic techniques are shaping early detection and personalised treatment plans.

**Keywords:** Cystic Fibrosis, CFTR Modulators, Nanotechnology, CRISPR-Cas9, Personalised Medicine

## INTRODUCTION

Cystic fibrosis (CF) is a progressive genetic disorder caused by mutations in the CFTR gene, leading to thick mucus production that obstructs airways and impairs digestion. This results in recurrent respiratory infections, lung damage, and malabsorption of nutrients, often causing malnutrition. Advances in CF treatment include CFTR modulator therapies (e.g., ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor, and elexacaftor/tezacaftor/ivacaftor), which improve lung function and quality of life by targeting the underlying defect [1–5].

Nanotechnology offers promising solutions through targeted drug delivery systems, facilitating precise administration of CFTR modulators, mucus-clearing enzymes, and gene-editing tools, enhancing efficacy and minimizing side effects [4,6]. Additional interventions like airway clearance techniques, antibiotics, nutritional support, and lung transplantation further optimise CF management. Emerging approaches, including personalised medicine and gene-editing technologies, aim to address individual genetic variations, paving the way for more effective and holistic treatments [5–6].

## EPIDEMEOLOGY

Cystic fibrosis (CF) prevalence varies globally, with rates of 1 in 2000-3000 in Europe, where F508del mutation prevalence ranges from 100% in the Faroe Islands to 20% in Turkey. North America reports 1 in 3500 cases, with 79.7% involving 10 common CFTR mutations. In Latin America, incidence ranges from 1 in 3900 to 1 in 8500, with F508del mutation rates of 59% in Argentina and 29% in Chile. In Africa and the Middle East, CF prevalence ranges from 1 in 2560 to 1 in 15,876, influenced by ethnicity and consanguinity. Asia shows lower rates, from 1 in 10,000 in the UK to 1 in 100,000-350,000 in Japan, with F508del mutation rates of 60% in Pakistan, 20% in India, and 10% in Japan. Limited Indian studies estimate prevalence between 1 in 10,000 and 1 in 50,000, with chronic infections as a primary mortality cause. A 2014 study noted life expectancy below 15 years in low-resource settings like India, though improvements are likely due to recent advances. Further research is essential to clarify Indian CF prevalence and life expectancy [7–15].

## ETIOLOGY AND RISK FACTORS

Cystic fibrosis (CF) is caused by mutations in the CFTR gene on chromosome 7, with over 1,700 identified variations. The most common, ΔF508, accounts for ~70% of cases and involves the deletion of three nucleotides, leading to defective chloride channels and impaired CFTR protein function [11,12]. Risk factors include a family history of CF, European ancestry (especially Northern European), advanced maternal age (>35), previous CF pregnancies, and environmental exposures like tobacco smoke or respiratory infections. While CF is genetic, these factors can influence disease severity. CF is slightly more prevalent in females than males [11,12].

## PATHOPHYSIOLOGY

CFTR is a membrane protein that regulates chloride and bicarbonate ion transport in epithelial tissues, enabling passive ion flow driven by ATP hydrolysis [13–15]. Located in the apical membranes of exocrine cells, CFTR facilitates ion and water secretion, crucial for maintaining mucociliary clearance and fluid balance in respiratory and digestive systems [16]. Dysfunctional CFTR impairs hydration, leading to mucus buildup, ciliary dysfunction, and tissue damage in organs like the lungs, pancreas, and bile ducts, disrupting glandular secretion and causing obstruction.[17]

Abnormal CFTR protein disrupts ion transport, reducing chloride secretion and increasing sodium absorption, leading to dehydrated protective fluid and thick, sticky mucus that blocks airways [18]. This impairs cilia function, hinders mucus clearance, and promotes bacterial growth, especially *Pseudomonas aeruginosa*, causing chronic respiratory infections and inflammation, which damage lung tissue and reduce lung function [19].

CF also causes pancreatic insufficiency, reducing enzyme secretion and impairing nutrient absorption, leading to malnutrition [2,18]. Gastrointestinal effects include bile duct blockages causing liver disease and thickened secretions causing intestinal obstruction [18].

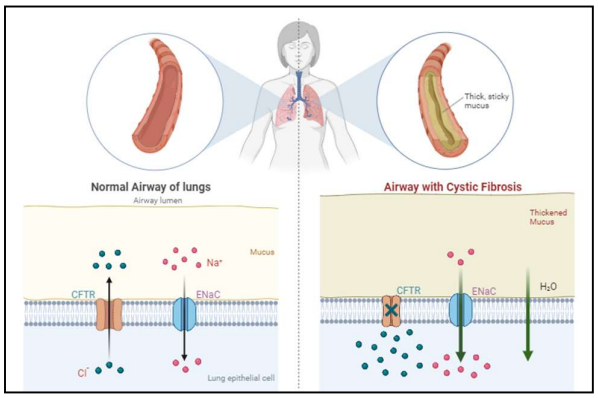


**Figure 1:** Diagram representing Normal Airway of lungs and Airway with Cystic fibrosis

## CLINICAL MANIFESTATIONS

Cystic fibrosis (CF) causes persistent cough, frequent lung infections, shortness of breath, wheezing, poor growth, malnutrition, vitamin deficiencies, greasy stools, abdominal pain, and bloating. It results in pancreatic insufficiency, liver disease, diabetes, delayed puberty, infertility in males, osteoporosis, and sinus issues like nasal polyps and chronic sinus infections. Severe complications include respiratory failure, Cor pulmonale, pneumothorax, rectal prolapse, gallstones, and heat intolerance. CFTR protein defects disrupt ion transport, leading to thick mucus, airway blockage, bacterial growth, chronic inflammation, and lung damage. Reduced enzyme secretion and bile duct blockages cause nutrient malabsorption, intestinal obstruction, and liver disease [1,2,6].

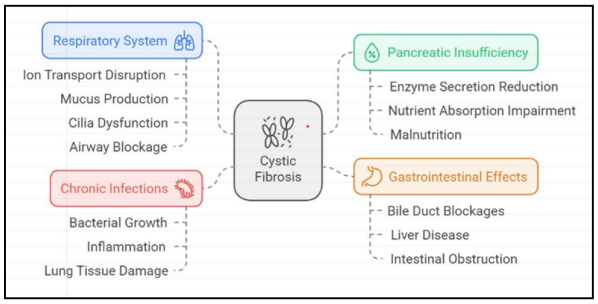


Figure 2: This figure is a mind map illustrating the effects of cystic fibrosis (CF) on different body systems

## DIAGNOSIS

Diagnostic evaluations for cystic fibrosis (CF) include the sweat test, which measures elevated sweat chloride levels due to impaired CFTR channels, following standardized methods involving pilocarpine iontophoresis and chloride analysis [20–23]. Newborn screening uses immunoreactive trypsinogen (IRT) assays to detect pancreatic injury, requiring confirmation for positive cases and early treatment at specialised centres [3,20,24,25]. The R117H mutation, often identified in newborn screenings, has uncertain clinical significance due to asymptomatic cases [20,26]. The beta-adrenergic sweat test assesses CFTR function by analysing CFTR-dependent and independent sweat secretion components [20,27].

## MANAGEMENT OF CYSTIC FIBROSIS

Pharmacological treatment for cystic fibrosis (CF) includes bronchodilators to widen airways and improve airflow, short- and long-acting agents being key options [28–30]. Mucolytic agents, such as dornase alfa, reduce mucus thickness and enhance clearance [31]. Antibiotics target infections, with inhaled, oral, or specific agents addressing bacteria like *Pseudomonas aeruginosa* [32–35]. Pancreatic enzyme replacement therapy (PERT) assists in digestion by supplementing enzymes for fats, proteins, and carbohydrates [36,37]. Anti-inflammatory drugs, including corticosteroids, reduce airway inflammation and prevent lung damage [38,39].

Non-pharmacological strategies include nutritional support with high-calorie, high-fat diets and micronutrient supplementation to address deficiencies in vitamins (A, D, E, K) and minerals like calcium and zinc [40–46]. Salt supplementation compensates for excessive salt loss through sweat [47]. Exercise improves lung function, muscle strength, and mucus clearance [49]. Airway clearance techniques (ACTs) use methods like chest physiotherapy, vibration vests, and breathing exercises to remove mucus [50]. In end-stage CF, lung transplantation is a life-extending option for those with severe lung damage unresponsive to other treatments [59]. Regular monitoring ensures personalized care and optimized outcomes.

## CFTR MODULATOR THERAPY

CFTR modulator therapy is a novel approach in cystic fibrosis (CF) management, targeting the dysfunctional CFTR protein responsible for chloride and fluid homeostasis. By improving CFTR function, these therapies address the root cause of CF [2,11,51,52]. There are several classes of CFTR modulators, each tailored to specific mutations. Potentiators enhance intrinsic CFTR channel activity, while correctors increase functional CFTR protein at the cell surface, improving chloride and fluid conductance [54]. Approved therapies target mutations such as G551D, F508del, and others, with eligibility determined by genetic testing and patient-specific factors [53–55,58]. CFTR modulators significantly enhance pulmonary function, reduce respiratory exacerbations, and improve weight gain and nutritional status, leading to better quality of life for CF patients [56,57].

Ongoing research aims to develop therapies for broader mutation coverage, further advancing CF treatment options [54], see figure 3.

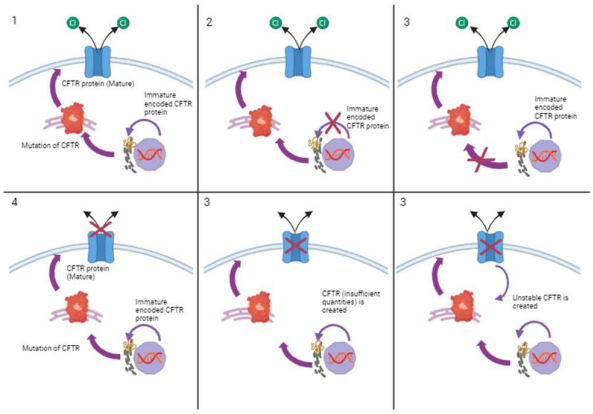


**Figure 3**: A simplified diagram illustrating how mutations in CFTR contribute to cystic fibrosis; (A) CFTR functions normally without any mutations, (B) Mutations belonging to Class I and VII, (C) Mutations classified as Class II, (D) Mutations falling under classes III and IV, (E) Class V mutation and (F) Class VI mutations [84].

## TRIPLE COMBINATION THERPY/TRIKAFTA/KAFTRIO-

Trikafta, a combination of elexacaftor, tezacaftor, and ivacaftor, is a targeted therapy for CF patients with specific CFTR mutations, particularly those with at least one F508del mutation. It enhances CFTR protein function by improving chloride ion transport across cell membranes, alleviating the molecular pathophysiology of CF. Trikafta improves pulmonary function (evidenced by increased FEV1), reduces mucus viscosity to enhance mucociliary clearance, and supports nutrient absorption, addressing weight gain and improving overall clinical outcomes.[23]

## NANOTECHNOLOGY IN CYSTIC FIBROSIS

Nanotechnology offers innovative strategies for enhancing the treatment of cystic fibrosis (CF) by enabling targeted drug delivery, advanced diagnostics, and gene therapy. Nanoparticles are engineered to deliver medications directly to the lungs, bypassing mucus barriers and enabling controlled or sustained drug release. This approach enhances therapeutic efficacy while minimizing systemic side effects. Liposomal nanoparticles and dry powder formulations have been developed for delivering antibiotics, mucolytic agents, and bronchodilators to the respiratory system, improving drug targeting and patient adherence. Nanofiber-based systems further ensure sustained therapeutic effects through controlled drug release [60–70]. Nanotechnology also advances gene therapy by providing non-viral nanoparticles as carriers for functional CFTR genes. These nanoparticles protect and deliver genetic material to airway cells, aiming to restore CFTR protein production and chloride ion transport.

Ongoing research and clinical trials are optimizing delivery methods and evaluating the safety and efficacy of gene therapy to address CF's root cause [2,12,71–74]. Nanosensors, or nanoprobes, enable early disease detection, real-time monitoring of treatment response, and assessment of CF progression. They identify CF-specific biomarkers in fluids like sputum or sweat, aiding in personalized treatment plans and early interventions. Surface nanocoatings on medical devices prevent bacterial colonization and biofilm formation, reducing infection risks. Additionally, nanotechnology contributes to personalized medicine by tailoring therapies based on an individual's genetic profile and disease characteristics, further improving outcomes and minimizing adverse effects [63,65,70,75–77].

## CRISPR-Cas9

CRISPR-Cas9 is a powerful genome-editing tool derived from the bacterial immune system. CRISPR sequences act as a genetic memory of past viral infections, producing guide RNAs (gRNAs) that direct the Cas9 enzyme to specific DNA sequences, leading to targeted cleavage. Cas9, functioning as molecular scissors, introduces precise DNA cuts, allowing cellular repair mechanisms to correct or modify the DNA sequence [78,79]. In cystic fibrosis (CF), CRISPR-Cas9 targets disease-causing mutations in the CFTR gene, such as ΔF508. The system is programmed to recognize and bind to specific mutated regions within the gene. Cas9 then induces a double-strand break (DSB) at the target site, triggering the cell's natural DNA repair mechanisms. The homology-directed repair (HDR) pathway is preferred for CFTR gene correction, as it enables the accurate insertion of a corrected DNA sequence. This repair restores normal CFTR protein function, facilitating proper ion transport across cell membranes and addressing the root cause of CF. By correcting the genetic defect, CRISPR-Cas9 holds significant potential to alleviate CF symptoms and improve patient outcomes as shown in the figure 4. [80–83]

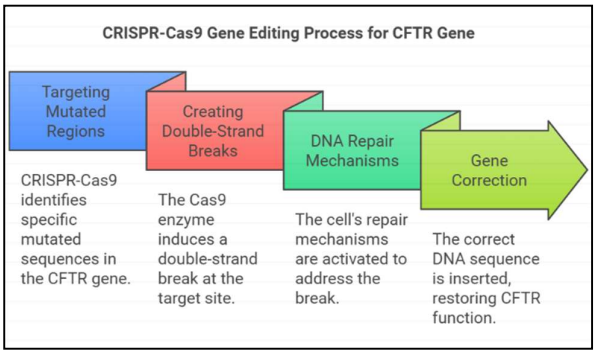


Fig 4: This figure is illustrating the CRISPR-Cas9 Gene Editing Process for the CFTR Gene, specifically detailing the steps involved in correcting mutations in the CFTR gene associated with Cystic Fibrosis.

## DISCUSSION

Cystic fibrosis represents a significant global health challenge, with notable disparities in prevalence, diagnosis, and outcomes across regions. Despite being primarily prevalent among Caucasians, emerging studies from Asia and Africa indicate an evolving epidemiological landscape. This review underscores the transformative role of CFTR modulators, such as Trikafta, in altering the disease trajectory by directly targeting defective ion transport. Furthermore, advancements in nanotechnology provide innovative solutions for overcoming physiological barriers and delivering therapies with unparalleled precision. Gene-editing technologies, particularly CRISPR-Cas9, hold promise for correcting the underlying genetic mutations, potentially offering a permanent cure [84]. However, the translational gap from research to clinical application highlights the need for rigorous safety and efficacy evaluations. Additionally, integrating personalized medicine into clinical practice remains pivotal for tailoring interventions to individual genetic and phenotypic profiles. Challenges persist in resource-limited settings where access to advanced diagnostic tools and therapies remains constrained. Strengthening global health initiatives, fostering collaborations, and ensuring equitable distribution of emerging treatments are critical for addressing these gaps. This discussion emphasizes the importance of interdisciplinary research, patient-centered care, and proactive public health strategies in transforming the landscape of CF management.

## CONCLUSION

The advancements in cystic fibrosis research and treatment underscore a paradigm shift toward precision medicine and targeted interventions. Innovative therapies, such as CFTR modulators, nanotechnology-driven drug delivery, and CRISPR-Cas9 gene editing, hold the potential to significantly improve outcomes and quality of life for CF patients. However, addressing disparities in access and developing scalable solutions for resource-constrained regions are essential. Continued investment in research, clinical trials, and healthcare infrastructure will be pivotal in translating these innovations into universal standards of care. With sustained efforts, the prospect of a cure for cystic fibrosis becomes increasingly attainable.

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## Ethical Matters

This manuscript does not involve any in vivo experiments with animals or humans. Therefore, there are no ethical concerns requiring permissions from an ethics committee or an Institutional Review Board. Additionally, I confirm that I have no conflicts of interest related to this manuscript and that there is no copyright issues associated with this submission.

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**Cite this article as:**

Nagora A, Soni V, Sharma A, et al. Revolutionising cystic fibrosis: unwinding the complexities for innovative therapeutic insights. Curr Trends Med Clin Res. 2025 Sep;1(1):1-8.