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MULTISYSTEM MANIFESTATIONS OF CYSTIC FIBROSIS: A COMPREHENSIVE REVIEW

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ABSTRACT

Cystic fibrosis (CF) is a life-threatening autosomal recessive condition that primarily affects the secretory glands and has significant effects on the respiratory, digestive, and reproductive systems. Mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene induce improper ion transport and thick, sticky secretions. This paper thoroughly investigates CF's multi-systemic symptoms and emerging management techniques. Respiratory problems from cystic fibrosis continue to be the largest source of morbidity and mortality, with Pseudomonas aeruginosa dominating chronic lung infections. Gastrointestinal involvement includes pancreatic insufficiency, intestinal obstruction, and CF-related liver disease (CFLD), the latter of which is a major cause of non-pulmonary death. Male infertility is primarily caused by the congenital lack of the vas deferens. Advancements in CF management have transformed the disease paradigm, as seen by the development of CFTR modulators that target the basic defect. These modulators, particularly elexacaftor/tezacaftor/ivacaftor, have significantly improved clinical outcomes for the majority of CF patients. However, persistent hurdles remain in controlling resistant infections, liver consequences, and CF-related diabetes. In addition, new microbiome insights and upper airway sampling techniques are improving our understanding of CF-related respiratory dynamics. This review emphasizes the significance of customized treatment, early intervention through neonatal screening, and ongoing research into genetic modifiers and therapeutic innovation to improve the life expectancy and quality of life for people with cystic fibrosis.

INTRODUCTION

Cystic fibrosis (CF) is a genetic disorder of the secretory glands, including those responsible for sweat and mucus production **(1).** It is an autosomal recessive condition that primarily affects cells producing sweat, mucus, and digestive fluids **(2).** Cystic Fibrosis (CF) impacts multiple organs, including the lungs, liver, intestines, pancreas, sinuses, and sex organs, with the lungs being the most severely affected. **(1)** The disease arises from mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene, which encodes a regulated anion channel critical for maintaining ion and water balance across epithelial surfaces**. (3)** The CFTR protein functions as a chloride and bicarbonate channel located on the apical membrane of epithelial cells in various organs, including the lungs, pancreas, gastrointestinal tract, and liver. **(4)** Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) also regulates other chloride and sodium channels, maintaining proper hydration and electrolyte composition of secretions. Mutations in the CFTR gene disrupt this function, leading to impaired ion and water transport **(3).** Consequently, thick, sticky mucus accumulates in the airways and ducts of affected

organs, causing obstruction, infection, and inflammation. In the lungs, CFTR dysfunction results in the accumulation of mucus that traps bacteria, promotes chronic inflammation, and leads to progressive tissue fibrosis and airway destruction. This pulmonary involvement is the leading cause of morbidity and mortality in CF patients. Other systemic effects include pancreatic insufficiency, biliary cirrhosis, chronic sinusitis, and azoospermia due to the absence of the vas deferens. **(4)** Cystic fibrosis was first recognized as a distinct disease entity in 1938 when postmortem investigations differentiated "cystic fibrosis of the pancreas" from celiac syndrome in malnourished newborns. **(5)** Early symptoms of CF include failure to thrive and malnutrition, which were historically attributed to gastrointestinal involvement. Pancreatic enzyme supplements introduced later helped manage malnutrition, shifting CF's primary classification to a pulmonary disease due to the chronic lung infections and respiratory decline that now account for most CF-related deaths. **(4,6)** Recent advancements in understanding CFTR structure and function have driven the development of small-molecule CFTR modulators, significantly improving outcomes for over 90% of individuals with CF. These modulators correct the underlying defect in CFTR protein synthesis, trafficking, or function. Treatment innovations have transformed CF from a fatal pediatric disease to a manageable chronic condition in many patients. **(3)**

GENETICS OF CYSTIC FIBROSIS AND CYSTIC FIBROSIS GASTROINTESTINAL DISEASE: F508del, a three-base pair deletion of a phenylalanine residue at amino acid position 508 of the CFTR protein, is the most common CFTR gene mutation. Formerly known as F508, the protein is now referred to as p. Phe508del, and the cDNA as 1521_1523delCTT. In the United States, over 40% of people with cystic fibrosis (CF) are heterozygous for F508del, whereas 48% are homozygous. While genotype does not directly correlate with respiratory phenotype, it is a powerful predictor of pancreatic functional status. **(7)** Patients with pancreatic sufficiency (PS) typically have class IV-V mutations, which result in partially functioning CFTR on the cell surface. In contrast, patients with pancreatic insufficiency (PI) often have class I-III mutations, which result in either missing or nonfunctional CFTR at the cell surface, sometimes known as "severe" mutations. **(8)** Meconium ileus (MI), a form of neonatal bowel blockage, is frequently the first gastrointestinal sign of CF. Severe mutations, including F508del, G542X, W1282X, R553X, and G551D, are usually related to MI in babies. However, the majority of people with these mutations do not get MI **(9).** Genome-wide association studies show that non-CFTR genetic modifiers account for around 17% of phenotypic variability, **(10)** underscoring their relevance in clinical outcomes. Diagnosing cystic fibrosis-related liver disease (CFLD) can be difficult, but cirrhosis develops in 2% to 15% of people. **(11, 12,13)** No specific CFTR mutation has been found as a reliable predictor of CFLD, **(14)** albeit it is frequently connected to mutations associated with pancreatic insufficiency. CFTR2, an international, curated database of CF mutations, is a novel tool for patients and physicians to explore various genotypes. While modifier genes, such as the SERPINA1 Z variant, enhance the risk of CFLD, they do not account for the majority of affected patients. **(15)**

LIVER

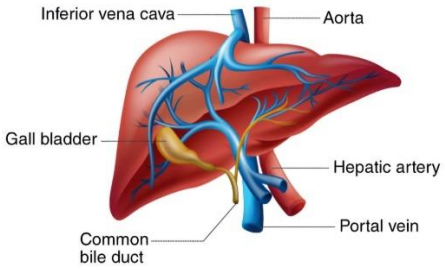


Fig. 1. Liver

INTRODUCTION TO CFLD: Liver disease is a serious consequence of cystic fibrosis and the third leading cause of death from non-pulmonary causes. Cystic Fibrosis Liver Disease (CFLD) is characterised by distinct liver alterations that can range from abnormal liver enzymes to cholestasis and sclerosing cholangitis-type lesions that progress to focal biliary cirrhosis and are frequently associated with micro gallbladder and liver steatosis. CFTR is expressed particularly on

the apical membrane of biliary epithelial cells (cholangiocytes), where it maintains the chloride ion gradient that drives bicarbonate secretion into the bile via anion exchange-2 (AE2) and, as a result, the bile's alkalisation and hydration. The pathogenetic pathways causing liver disease are constantly being investigated. The major event is CFTR dysfunction-induced biliary secretion, but additional insults can contribute to disease progression and severity. **(16)**

PATHOPHYSIOLOGY AND MECHANISMS:

The pathophysiology of CF liver damage is mostly unclear. CFTR is present only on the apical surface of the bile duct epithelium in the liver, not in hepatocytes. CFTR in the biliary epithelium stimulates apical biliary chloride secretion, which essentially enhances bile acid independent bile flow. In both the pancreas and the lung, CFTR is found in the apical epithelium. A malfunctioning or missing chloride channel affects these organ systems to variable degrees, causing thicker mucus discharges and clogging. A similar pathological mechanism has been proposed in the liver, with inspissated bile clogging small intrahepatic bile ducts. This has been linked to toxic bile acid buildup in the liver, depletion of hepatic antioxidants, and liver cell damage. Repeated liver cell injury can activate hepatic stellate cells, causing hepatic fibrosis and, in rare circumstances, cirrhosis. An alternate explanation of pathogenesis holds that increased intestinal permeability in CF leads to the absorption of pathogen-associated molecular patterns, which promote inflammation and fibrosis. It is unknown why just a small proportion of CF patients develop cirrhosis, whereas the majority of people with an identical CFTR deficiency do not. Cirrhosis is more common in those with severe class 1, 2, and 3 mutations and pancreatic insufficiency, but there is no clear genotype/phenotype association. In a study of genetic modifiers in CF cirrhosis, the PiZ heterozygote condition for Alpha-1 antitrypsin (SERPINA1 Z-allele) was related with an increased risk of cirrhosis and a population attributable risk of 7%, but only accounted for 9% of the cirrhosis cases. Other factors that have been inconsistently linked to cirrhosis include male sex, meconium ileus, and TGF-B1 polymorphisms. Further research into the etiology of CF cirrhosis will hopefully help in the development of targeted therapeutics. **(17)**

IMPACT AND TREATMENT OPTIONS: Liver disease is a key cause of morbidity in cystic fibrosis (CF), accounting for reduced survival and being the second leading cause of mortality. The pathognomonic hepatic lesion is localized biliary cirrhosis, which is usually asymptomatic and affects 25-30% of all CF patients; nevertheless, postmortem investigations show that the frequency of intrahepatic biliary abnormalities is frequently overestimated. The abnormal bile viscosity and increased concentration of bile components in CF-associated liver disease are attributed to impaired biliary epithelium secretion caused by the absence of Cystic Fibrosis Transmembrane Regulator (CFTR) regulatory function at the apical domain of epithelial bile duct cells. Ursodeoxycholic acid (UDCA) is a hydrophilic, benign bile acid that makes up almost 3% of the typical bile acid pool in humans. Around 1990, UDCA was launched for the treatment of CF-related liver damage. It is currently the sole approved medication for the treatment of chronic cholestatic liver disease and is thought to have immunomodulatory, cytoprotective, anti-apoptotic, membrane-stabilizing, and antioxidative properties. It is used to replace harmful bile acids that build up in the hepatocytes and to lessen the viscosity of bile in CF-related liver damage. These UDCA choleretic qualities were biochemically confirmed in human cholangiocarcinoma cells and revealed by scintigraphic studies in CF patients. **(18)**

PANCREAS: Pancreatitis has traditionally been uncommon in cystic fibrosis (CF) patients due to early pancreatic parenchymal loss during infant development, which restricts exocrine pancreatic function. However, as CF patients' CFTR modulator medications, newborn screening, and genetic technologies have advanced, so has the occurrence of pancreatitis. These advancements enable early detection of CF patients, even before symptoms manifest, via neonatal screening. Furthermore, the use of whole gene sequencing and broader genetic testing has enhanced the

discovery of patients with mild or limited symptoms, particularly those with exocrine pancreatic insufficiency (EPI), who would otherwise go misdiagnosed until later in life. The Increased proportion of CF patients with pancreatic sufficiency (CF-PS) is mostly responsible for the rise in pancreatitis cases. Ooi et al. suggested a scenario in which persons with near-normal CFTR function or severe CFTR impairment are less likely to develop pancreatitis. However, people with intermediate degrees of CFTR impairment are more vulnerable. Decades of research have shown that CFTR mutations are linked to the pathophysiology of pancreatitis, and newer studies have confirmed these findings. This evolving understanding emphasizes the necessity of recognizing and treating pancreatitis in CF patients, especially given shifting CF demographics. **(19)**

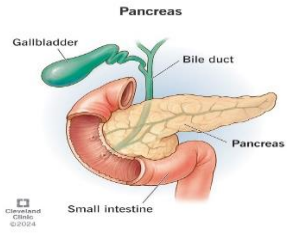


Fig. 2. Pancreas

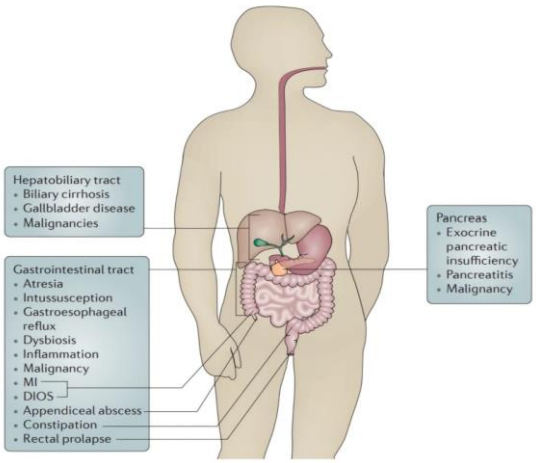


Fig. 3. Gastrointestinal, hepatobiliary and pancreatic manifestations and complications of cystic fibrosis.

Diagnosing symptomatic pancreatitis in CF is difficult and requires a high level of suspicion. Pancreatitis affects around 20% of CF-PS individuals, and it is the presenting symptom in 25% of these instances, frequently leading to a CF diagnosis in late adolescence or adulthood. Symptoms often include abdominal pain, especially in the epigastric region, as well as nausea and vomiting to varied degrees. The diagnostic criteria for acute pancreatitis frequently rely on serum pancreatic enzyme levels, with a "cut-off" number typically described as two to three times the upper range of normal. Imaging tests that reveal acute pancreatic inflammation can also confirm the diagnosis. Imaging in pancreatic insufficiency (PI) patients frequently reveals chronic alterations such as atrophy, calcifications, and ductal abnormalities. However, these findings do not always indicate clinical pancreatitis because the exocrine pancreatic tissue in PI patients is extensively damaged and non-functional. It is critical to distinguish between these chronic alterations and acute pancreatitis, as the clinical consequences and therapy differ. To get the best possible outcomes, children with CF who develop acute pancreatitis should follow established guidelines and recommendations for addressing the disease. **(20)**

RESPIRATORY SYSTEM:

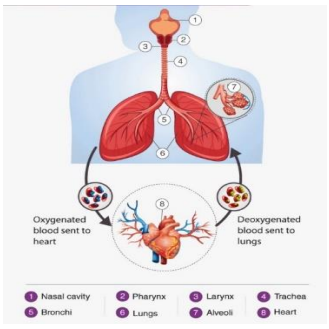


Fig. 4. Respiratory system

INTRODUCTION: Cystic fibrosis (CF) is a hereditary disorder characterized by chronic respiratory infections and reduced life expectancy. Persistent bacterial lung infections remain the leading cause of morbidity and mortality among people with CF (pwCF). These infections are particularly difficult to treat due to

the ability of pathogens to form biofilms, resist antibiotics, and evade immune responses.

PSEUDOMONAS AERUGINOSA AND CHRONIC INFECTIONS: Pseudomonas aeruginosa, a common environmental bacterium, is frequently isolated from the lungs of CF patients. It adapts its virulence gene expression from acute to chronic infection states, forming dense biofilms composed of polysaccharides, proteins, DNA, and lipids. Biofilms protect bacterial cells from immune system attacks and hinder phagocytosis. Chronic P. aeruginosa infection affects nearly 80% of CF patients by the age of 20 and significantly contributes to disease progression and mortality. **(21)**

OTHER GRAM-NEGATIVE PATHOGENS: In addition to P. aeruginosa, other Gram-negative bacteria complicate CF management. The Burkholderia cepacia complex (BCC) includes multiple species that cause rapid lung function decline and exhibit multi-drug resistance. Stenotrophomonas maltophilia, a rising multidrug-resistant pathogen, thrives in hospital environments and is associated with worsened symptoms, strong immune responses, and increased mortality. Other Gram-negative organisms, including Haemophilus influenzae and Achromobacter xylosoxidans, further deteriorate lung function in pwCF. (**22,23)**

GRAM-POSITIVE PATHOGENS: Staphylococcus aureus is the most frequently isolated Gram-positive bacterium in CF patients, particularly in younger populations. Despite advancements in treating S. aureus infections, it continues to play a role in pulmonary exacerbations. **(21)**

ADVANCES IN CF TREATMENT AND MICROBIOME INSIGHTS: Groundbreaking research has improved CF management and life expectancy. Highly effective modulator treatments (HEMT), particularly elexacaftor/tezacaftor/ivacaftor (ETI), have transformed CF care. Approved for pwCF over two years old with at least one F508del mutation, ETI significantly improves quality of life and clinical outcomes. Studies show reduced bacterial load and pathogen abundance, along with increased commensal flora in the CF lung after ETI initiation.

MICROBIOME PROFILING AND AIRWAY DYSBIOSIS: Microbiome profiling in CF reveals complex microbial communities involving bacteria, viruses, and fungi. Reduced bacterial diversity correlates with disease progression and decreased lung function. Although lower airway samples dominate research, the upper airway microbiota, including sinus samples, remain underexplored despite their role in respiratory health.

THE ROLE OF THE UPPER AIRWAY IN CF: Chronic rhinosinusitis (CRS) is a common comorbidity in CF. It is characterized by sinonasal epithelium inflammation, nasal congestion, sinus pressure, and diminished olfactory perception. Viscous mucus impairs mucociliary clearance, fostering chronic bacterial infections. Notably, bacteria from the sinuses can aspirate into the lungs, contributing to lower respiratory infections. Functional endoscopic sinus surgery (FESS) is often performed to improve mucus clearance and airflow, but it alters the sinus microbiota. According to the united airway theory, the upper and lower airways share immunologic and physiological properties. **(24)**

SAMPLING CHALLENGES AND THE NEED FOR MINIMALLY INVASIVE TECHNIQUES: While bronchoalveolar lavage is the gold standard for lung microbiological sampling, it is rarely performed during routine CF clinic visits. Sputum sampling, a common alternative, is becoming less feasible as HEMT reduces sputum production. Thus, developing minimally invasive methods, such as endoscopically guided sinus sampling, is critical for pathogen monitoring. Preliminary studies suggest that sinus samples may offer valuable insights into lung infections.

INFECTION DYNAMICS IN OTHER CHRONIC LUNG DISEASES: P. aeruginosa infections in non-CF bronchiectasis, chronic obstructive pulmonary disease (COPD), and intensive care unit patients range from colonization to severe necrotizing bronchopneumonia. In non-CF bronchiectasis,

common pathogens include Haemophilus influenzae, Streptococcus pneumoniae, and Moraxella catarrhalis. Severe COPD patients with frequent hospitalizations face increased nosocomial P. aeruginosa infections, often linked to contaminated equipment or bacteraemia. Complications such as abscesses and empyema exacerbate disease outcomes. **(25)**

ENDOCRINE COMORBIDITIES

CF-RELATED DIABETES: Diabetes is the most prevalent endocrine consequence of CF, and it is caused by increasing pancreatic fibrosis, which eventually damages the insulae. CF-related diabetes differs from type 1 and type 2 diabetes in that it is caused by decreased insulin secretion as well as insulin resistance, especially during acute pulmonary exacerbations. Prevalence increases after the age of ten and reaches 40-50% in elderly cases. Its recurrence is connected with worsening of the respiratory disease, whereas adequate hyperglycemia control minimizes the number of respiratory exacerbations and slows pulmonary disease progression. Diabetes due to cystic fibrosis is linked to an increased risk of death. There is conflicting evidence about the effect of gender, as well as the alleged poorer severity and higher mortality rate in CF diabetic female patients. Annual screening with oral glucose tolerance testing is recommended beginning at the age of ten to detect diabetes or prediabetes. Insulin therapy is recommended. Many people with normal or borderline glycemic profiles develop diabetes following a lung transplant. **(26)**

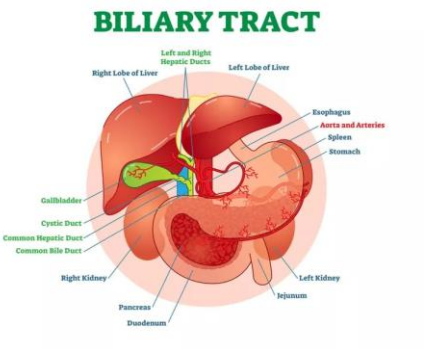
BONE DISEASE: As survival has gradually increased, CF-related bone disease has been appearing concurrently. According to dual-energy X-ray absorptiometry (DEXA), 10–15% of patients have poor bone mineral density, and this number rises to 50% in late-stage disease. These patients are at risk for osteopenia, osteoporosis, and vertebral fractures. Malnutrition, low body mass index, the severity of lung illness, and a number of other variables, including impaired mobility, low vitamin D and K absorption, steroid usage, circulating inflammatory cytokines, and accelerated bone turnover, are all associated with an increased risk of bone disease. Since CFTR is expressed in bone cells, it is impossible to rule out the possibility that the protein directly affects bone metabolism. **(27,28,29)**

MALE INFERTILITY: Up to 90% of CF males have male infertility, known as Congenital Bilateral Absence of Vas Deferens (CBAVD). It is also a distinct clinical characteristic of illnesses connected to CFTR. In mono organ situations, the most common genotype is the in trans combination of the IVS8-5T polymorphism plus a mutation that causes cystic fibrosis. **(30,31,32)**

GROWTH: It has been documented that in children with cystic fibrosis, puberty spurt retardation decreased growth velocity and GH secretion under suitable stimuli. Low levels of insulin-like growth factor 1 (IGF1) in CF pigs and patients point to a function for CFTR in pituitary growth hormone release, even though starvation and the severity of the disease are partially to blame for short height. **(33,34)**

GALLBLADDER AND BILIARY TRACT: The biliary tree has been shown to exhibit extrahepatic abnormalities in cystic fibrosis. Gallbladder imaging may show a tiny, nonvisualized, malformed, or enlarged gallbladder. Autopsies have revealed micro-gallbladders in 23 percent of cystic fibrosis patients. In about 25% of patients, gallstones and biliary sludge are also frequently discovered. In rare cases, imaging reveals PSC-like alterations, including bile duct stricturing and beading. Significantly, PSC patients have been reported to exhibit CFTR impairment and a higher frequency of CFTR mutations. Nonetheless, the vast majority of these biliary anomalies are accidental, asymptomatic, and untreated. **(35)**

SWEAT GLANDS: The weather is a major factor in identifying sweat gland function in people with cystic fibrosis (CF). Shortly after Guido Fanconi found a connection between lung disease and fibrocystic pancreata, a severe heat wave hit New York City in the summer of 1949. Dorothy Andersen, who was the first to identify cystic fibrosis as a genetic disorder, observed that heat prostration was a common occurrence for several of her patients around the same time.



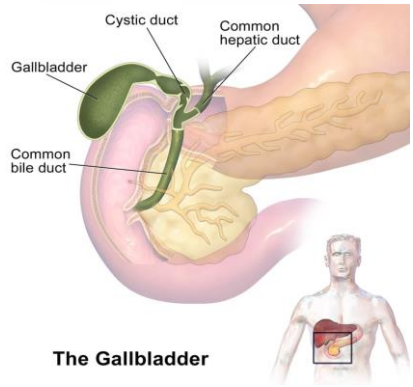


Fig. 5. Biliary Tract & Fig. 6. Gallbladder

Paul di Sant'Agnese, a young assistant professor who worked with Andersen at Babies Hospital (Columbia Presbyterian Medical School), postulated that the crisis was brought on by pure salt loss, which led to dehydration. He meticulously illustrated how the sweat glands were the source of this loss. Over the following ten years, these results were confirmed. In the past, the patient was placed in a rubber or plastic body bag to collect perspiration, which was a dangerous practice that could result in lethal hyperpyrexia. When the Quantitative Pilocarpine Iontophoresis Sweat Test (QPIT) was developed, this risk was removed. In QPIT, a potent sweat stimulant called pilocarpine was iontophoressed through the skin to increase sweat production in a limited area (30–40 cm2), typically on the forearm. Chloride (Cl–) was measured in the sweat that was hermetically collected from this location for approximately half an hour. Extensive analysis revealed that, particularly in young patients, perspiration with Cl– concentrations more than 60 mEq/L was suggestive of cystic fibrosis. Healthy people usually have less than 40 mEq/L of Cl– in their sweat. After half a century, the sweat test is still the most reliable method for diagnosing cystic fibrosis. The most efficient and quick method of diagnosing cystic fibrosis was shown to be the measurement of Cl– in a little sweat sample. **(36)**

CONCLUSION

Cystic fibrosis, a once fatal pediatric ailment, has transformed into a tolerable chronic condition as a result of groundbreaking advances in understanding and treating its genetic underpinnings. Despite great improvements, CF continues to pose severe clinical difficulties that necessitate extensive, multidisciplinary therapy. Innovations such as very effective CFTR modulator medications have significantly increased survival rates and quality of life. Nonetheless, the disease's complexities, which include increasing lung impairment, gastrointestinal difficulties, endocrine dysfunctions, and reproductive issues, necessitate ongoing vigilance and tailored methods to management.

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