

Cystic Fibrosis:

Summary

Cystic fibrosis (CF) is an **autosomal recessive disorder** that is **common in individuals of European descent**. It is caused by **mutations in the CFTR gene**, which encodes the CF transmembrane conductance regulator (CFTR) protein. These **mutations result in defective chloride (Cl⁻) channels**. Mandated newborn screening (NBS) in many countries can frequently detect CF during the asymptomatic newborn period. **Initial manifestations may include meconium ileus, failure to thrive, and symptoms of malabsorption**, and later in life, patients may experience symptoms such as **recurrent respiratory infections, recurrent pancreatitis, and infertility**. As the disease progresses, **defective Cl⁻ channels in the respiratory tract result in thickened bronchial mucus and impaired mucociliary clearance**, which leads to **chronic respiratory infections, pulmonary colonization with multiresistant bacteria, and a progressive decline in lung function**. Patients often experience acute episodes of worsening respiratory symptoms, known as pulmonary exacerbations. CFTR dysfunction in the exocrine pancreas and biliary tract can ultimately lead to CF-related liver disease (CFLD) and CF-related diabetes (CFRD). If CF is suspected, the first diagnostic study is a sweat test, usually followed by **genetic testing**, and if the diagnosis remains unclear, CFTR physiologic testing. Patients with CF should be managed at a CF-accredited center, if possible. Management should focus on slowing the progression of lung disease, eradicating and/or suppressing chronic infections, preventing and/or treating exacerbations, and addressing complications and comorbidities. Many patients may also benefit from novel treatments such as CFTR modulators, which can partially restore CFTR function. With the recent advances in treatment, the predicted median life expectancy of a patient born in 2021 with CF is estimated to be ~ 45 years. Complications due to lung disease are the most common cause of death in CF.

Definition and Etiology:

- Second most common genetic metabolic disorder in individuals of Northern European descent after hemochromatosis [1][2][3]
- Incidence: approx. 1:3500 in the US [4]

Etiology

- CF is a hereditary **autosomal recessive disorder** caused by defective **CFTR** (cystic fibrosis transmembrane conductance regulator) protein due to mutation in the CFTR gene located on the long arm of **chromosome 7**. [5]
- The most common mutation causing CF is delta F508 (ΔF508), a codon deletion that leads to the **absence of phenylalanine (F)** in position 508 of the CFTR protein.



Children whose parents are both heterozygous carriers of cystic fibrosis have a 25% chance of being affected by the condition.

- Expressed mostly on epithelial cells of airways, gastrointestinal tract, sweat glands, genitourinary (GU) system
- Not all children with CF can be identified by DNA testing; may need to sequence CFTR gene

Pathophysiology:

- Mutations in the CFTR gene damage chloride and water transport across the apical surface of epithelial cells in exocrine glands throughout the body → abnormally thick mucus in the lungs**, as well as damage to the **pancreas, liver, sinuses, intestines, and genitourinary tract. They all clog up.**
- Damaged mucus clearance decreases the ability to get rid of inhaled bacteria.**
- Neutrophils in CF dump tons of DNA into airway secretions, clogging them up.**
- Four long-standing observations are of fundamental pathophysiologic importance:**
 - failure to clear mucous secretions**
 - paucity of water in mucous secretions**
 - elevated salt content of sweat and other serous secretions**
 - chronic infection limited to the respiratory tract.**
 - Desiccated secretions become more viscous and elastic (rubbery) and are harder to clear by mucociliary and other mechanisms.
 - Altered mucus rheology can be aggravated by low HCO₃⁻ and a more acidic pH.
 - These secretions are retained and obstruct airways, starting with those of the smallest caliber, the bronchioles.
 - Airflow obstruction at the level of small airways is the earliest observable physiologic abnormality of the respiratory system.**

RESPIRATORY

Bronchiectasis, bronchitis, bronchiolitis, pneumonia

Atelectasis

Hemoptysis

Pneumothorax

Nasal polyps

Sinusitis

Reactive airway disease

Cor pulmonale

Respiratory failure

Mucoid impaction of the bronchi

Allergic bronchopulmonary aspergillosis

GASTROINTESTINAL

Meconium ileus, meconium plug (neonate)

Meconium peritonitis (neonate)

Distal intestinal obstruction syndrome (non-neonatal obstruction)

Rectal prolapse

Intussusception

Volvulus

Fibrosing colonopathy (strictures)

Appendicitis

Intestinal atresia

Pancreatitis

Biliary cirrhosis (portal hypertension: esophageal varices, hypersplenism)

Neonatal obstructive jaundice

Hepatic steatosis

Gastroesophageal reflux

Cholelithiasis

Inguinal hernia

Growth failure (malabsorption)

Vitamin deficiency states (vitamins A, K, E, D)

Insulin deficiency, symptomatic hyperglycemia, diabetes

Malignancy (rare)

OTHER

Infertility

Delayed puberty

Edema-hypoproteinemia

Dehydration-heat exhaustion

Hypertrophic osteoarthropathy-arthritis

Clubbing

Amyloidosis

Diabetes mellitus

• General considerations

- The CFTR gene encodes the CFTR protein, which is an important component of the ATP-gated chloride channel in cell membranes.
- **Mutated CFTR gene** → **misfolded protein** → retention for degradation of the defective protein in the rough endoplasmic reticulum (rER) → **absence of ATP-gated chloride channel** on the cell surface of epithelial cells throughout the body (e.g., intestinal and respiratory epithelia, sweat glands, exocrine pancreas, exocrine glands of reproductive organs) [6][7]

• In sweat glands

- The chloride channel is responsible for transporting Cl^- from the lumen into the cell (reabsorption).
- Defective ATP-gated chloride channel → **inability to reabsorb Cl^-** from the lumen of the sweat glands → reduced reabsorption of Na^+ and H_2O → excessive loss of salt and **elevated levels of NaCl in sweat**

• In all other exocrine glands (e.g., in the GI tract or lungs)

- The chloride channel is responsible for transporting Cl^- from the cell into the lumen (secretion).
- Defective ATP-gated chloride channel → inability to transport intracellular Cl^- across the cell membrane → **reduced secretion of Cl^-** and H_2O → accumulation of intracellular Cl^- → $\uparrow \text{Na}^+$ reabsorption (via ENaC) → $\uparrow \text{H}_2\text{O}$ reabsorption → formation of **hyperviscous mucus** → accumulation of secretions and **blockage of small passages** of affected organs → **chronic inflammation** and remodeling → **organ damage** (see "Clinical features" below)
- $\uparrow \text{Na}^+$ reabsorption → **transepithelial potential difference** between interstitial fluid and the epithelial surface **increases** (i.e., negative charge increases; e.g., from normal -13 mv to abnormal -25 mv)

Clinical findings:

Respiratory Tract:

- **Presentation:**
- Major cause of **severe chronic lung disease** and most common cause of **exocrine pancreatic deficiency** in children.
- Over one-third of CF patients are adults. Look for a young adult with chronic lung disease (cough, sputum, hemoptysis, bronchiectasis, wheezing, and dyspnea) and recurrent episodes of infection. Sinus pain and polyps are common.
- Lung disease accounts for 95% of deaths in CF.

- **physical findings** include:
 1. increased anteroposterior diameter of the chest
 2. generalized hyperresonance
 3. scattered or localized coarse crackles
 4. digital clubbing
 5. Expiratory wheezes, especially in young children.
 6. Cyanosis is a late sign.
- Common pulmonary complications include: (beyond the 1st decade of life)
 1. atelectasis
 2. hemoptysis
 3. pneumothorax
 4. cor pulmonale

Intestinal tract:

- **meconium ileus** the ileum is completely obstructed by meconium
 - ◊ 15-20% of newborn infants with CF.
 - ◊ The frequency is greater (≈30%) among siblings born subsequent to a child with meconium ileus.
 - ◊ Abdominal distention, emesis, and failure to pass meconium appear in the 1st 24-48 hr of life.
 - ◊ Abdominal radiographs show dilated loops of bowel with air-fluid levels and, frequently, a collection of granular, "ground-glass" material in the lower central abdomen.
- Rarely, **meconium peritonitis** results from intrauterine rupture of the bowel wall and can be detected radiographically by the presence of peritoneal or scrotal calcifications.
- **Meconium plug syndrome** occurs with increased frequency in infants with CF but is less specific than meconium ileus.
- **distal intestinal obstruction syndrome or meconium ileus equivalent:** Ileal obstruction with fecal material occurs in older patients, causing cramping abdominal pain and abdominal distention.
- > 85% of affected children show evidence of maldigestion from exocrine **pancreatic insufficiency**.
- Symptoms : frequent, bulky, greasy stools and failure to gain weight even when food intake appears to be large.
- Less common , **intussusception**, fecal impaction of the cecum with an asymptomatic right lower quadrant mass, and epigastric pain owing to duodenal inflammation.
- **Acid or bile reflux with esophagitis** symptoms is common in older children and adults.
- **Subacute appendicitis and periappendiceal abscess** have been encountered.
- **rectal prolapse** occurs much less frequently as the result of earlier diagnosis and initiation of pancreatic enzyme replacement therapy.
- **hypoproteinemia** with anasarca appears in malnourished infants, especially if children are fed soy-based preparations.
- **vitamin E deficiency:** Neurologic dysfunction (dementia, peripheral neuropathy) and hemolytic anemia.
- **Hypopro-thrombinemia** owing to vitamin K deficiency may result in a bleeding diathesis.
- Clinical manifestations of other fat-soluble vitamin deficiencies: decreased bone density and night blindness, Rickets is rare.

Biliary Tract:

- liver dysfunction is most often detected in the 1st 15 yr of life (30% of cases).
- Liver disease occurs independent of genotype but is associated with meconium ileus and pancreatic insufficiency.
- **Biliary cirrhosis** : symptomatic in only 2-3% of patients: icterus, ascites, hematemesis from esophageal varices, and evidence of hyper-splenism.
- **Steatosis**: A neonatal hepatitis-like picture and massive hepatomegaly .
- Biliary colic secondary to **cholelithiasis** may occur in the 2nd decade or later.

Pancreas:

Pancreatic insufficiency (in 90%) with steatorrhea and vitamin A, D, E, and K malabsorption.

Recurrent pancreatitis.

- exocrine pancreatic insufficiency
- **insulin-dependent diabetes**: 8 % of 11-17 yr old patients and 18% of 18-24 yr olds.
- **Ketoacidosis** usually does not occur, but eye, kidney, and other vascular complications have been noted in patients living ≥ 10 yr after the onset of hyperglycemia.
- **Recurrent acute pancreatitis** occurs in individuals who have residual exocrine pancreatic function and may be **the sole manifestation of two CFTR mutations**.

Genitourinary:

- **delayed Sexual development** by an average of 2 yr.
- > 95% of males are **azoospermic** because of failure of development of Wolffian duct structures, but sexual function is generally unimpaired.
- The incidence of **inguinal hernia, hydrocele, and undescended testis** is higher.
- **secondary amenorrhea**, especially with exacerbations of pulmonary disease.
- **Cervicitis** and accumulation of tenacious mucus in the cervical canal have been noted.
- The **female fertility rate is diminished**.
- Pregnancy is generally tolerated well by women with good pulmonary function but may accelerate pulmonary progression in those with moderate or advanced lung problems.

- Genitourinary Involvement:

- Almost all male patients with cystic fibrosis have **obstructive azoospermia from congenital bilateral absence of the vas deferens**. The vas deferens fails to develop due to accumulation of inspissated mucus in the fetal genital tract, resulting in infertility.
- Women are **infertile** because **chronic lung disease alters the menstrual cycle** and **thick cervical mucus blocks sperm entry**.

Notes:

Sweat Gland:

- Excessive loss of salt in the sweat predisposes young children to salt depletion episodes, especially during episodes of gastroenteritis and during warm weather.
- These children present with **hypochloremic alkalosis**.
- parents notice salt "frosting" of the skin or a salty taste when they kiss the child.
- A few genotypes (**3849 + 10 kb C >T**) are associated with normal sweat chloride values.

Newborn Screening:

Newborn screening (NBS) for CF is essential for early detection and treatment, which can improve health outcomes. In many countries, including the US, it is mandatory to screen for CF. [10][15]

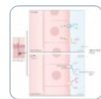
- **Sample collection:** newborn blood spot test, performed via heel prick blood sampling in the first 24 and 48 hours of life
- **Screening tests** [16]
 - **Immunoreactive trypsinogen (IRT)** : initial screening test
 - An immunofluorescence assay that measures levels of IRT [17]
 - Normal IRT levels: CF unlikely
 - Elevated IRT levels: CF possible; additional screening tests required [16]
 - **CFTR mutation testing (DNA testing):** second-tier screening test
 - Identifies the most common CF-causing CFTR mutations, including CF carriers
 - Cannot detect uncommon CFTR mutations that are not included on the panel.
- **Screening protocols:** a combination of CF screening methods to minimize false-positive and false-negative NBS results [18]
- **Next steps after positive NBS:** Refer patients promptly to a specialist for a complete diagnostic workup and to start treatment if required.

! Patients who test positive for CF during NBS should undergo a sweat test, ideally in the first 4 weeks of life. [10]

Diagnosis:

Sweat test (quantitative pilocarpine iontophoresis) [15]

- Indications: preferred initial test in all patients with suspected CF [10]
- Method [10]
 - Pilocarpine and an electrical current are applied to the skin to stimulate sweat production.
 - Sweat is collected with absorbent pads and the Cl^- concentration is measured.



! CFTR dysfunction is confirmed with a positive sweat test ($\geq 60 \text{ mmol/L}$). If the result is borderline ($30\text{--}59 \text{ mmol/L}$), proceed to genetic testing and, if the diagnosis is still unclear, consider physiologic testing (NPD or ICM).

! In most exocrine glands, intracellular Cl^- is transported across the cell membrane into the lumen through the CFTR Cl^- channel. In sweat glands, Cl^- is transported in the opposite direction, from the lumen into the cell. In CF, a defect in the CFTR Cl^- channel results in an accumulation of Cl^- and, subsequently, of Na^+ in the lumen of the sweat gland, leading to an increased concentration of NaCl in the sweat.

- Non-CF conditions associated with positive sweat test:

1. untreated adrenal insufficiency
2. ectodermal dysplasia
3. hereditary nephrogenic diabetes insipidus
4. G6PD
5. hypothyroidism
6. hypoparathyroidism
7. familial cholestasis
8. pancreatitis
9. mucopolysaccharidoses
10. fucosidosis
11. malnutrition

CFTR genetic testing [15][20][21]

- **Indication**
 - Carrier screening [10]
 - Confirmatory test after equivocal sweat test
 - Guidance of targeted therapy (e.g., CFTR modulators)

- Genotyping with CFTR is not as accurate as finding an increased sweat chloride level. This is because there are so many different types of mutations leading to CF.

Pulmonary function tests

- Modalities: predominantly spirometry
- Findings: obstructive pattern, e.g., $\downarrow$ FEV₁:FVC ratio (see "Obstructive lung diseases") [25][26]

Imaging: chest x-ray or chest CT

- Early findings: may be normal or show subtle signs of air trapping and hyperinflation
- Late findings
 - Signs of obstructive lung disease (e.g., air trapping, hyperinflation)
 - Reticular nodular pattern
 - Bronchiectasis [27]

Microbiology: findings can help prevent and treat exacerbations [27][20]

- Bacterial sputum cultures

! Monitoring with sputum cultures helps guide the selection of antibiotics to prevent and treat exacerbations. [27][20]

Additional screening and monitoring

- Routine laboratory studies
 - CBC; may show anemia; potentially leukocytosis during exacerbations
 - BMP; findings are variable, e.g., contraction alkalosis and hypokalemia
- Nutritional assessment
 - Stool tests: low levels of pancreatic elastase suggest exocrine pancreatic insufficiency
- CT head may show opacification of sinuses in patients with features of chronic sinusitis

! Sweat losses of NaCl and H_2O lead to contraction of the ECF volume and RAAS activation (similar to the effects of loop diuretics). This can result in increased renal reabsorption of NaCl and H_2O and excretion of H^+ and K^+ , causing alkalosis and hypokalemia.

In general:

Additional Diagnostic Tests:

- Chest x-ray and CT: There is no single abnormality on imaging of the chest to confirm a diagnosis of CF. Findings include:
 - Bronchiectasis.
 - Pneumothorax.
 - Scarring.
 - Atelectasis.
 - Hyperinflation.
- Arterial blood gas may show hypoxemia and, in advanced disease, a respiratory acidosis.
- PFTs show mixed obstructive and restrictive patterns; decrease in FVC and total lung capacity; and decreased diffusing capacity for carbon monoxide.
- Sputum Culture:
 - Pseudomonas aeruginosa.
 - Nontypable Haemophilus influenzae.
 - Staphylococcus aureus.
 - Burkholderia cepacia.
- The most common pathogen isolated from sputum cultures in infants and young children is Staphylococcus aureus. Pseudomonas aeruginosa is the most common cause of CF-related pneumonia in adults and contributes to life-threatening decline of pulmonary function.

DIAGNOSTIC CRITERIA FOR CYSTIC FIBROSIS (CF)

Presence of typical clinical features (respiratory, gastrointestinal, or genitourinary) or
A history of CF in a sibling or
A positive newborn screening test

PLUS

Laboratory evidence for CFTR dysfunction:

Two elevated sweat chloride concentrations obtained on separate days or
Identification of two CF mutations or
An abnormal nasal potential difference measurement

Management:

General principles [28][20]

- All patients with CF require periodic follow-up with a multidisciplinary team for specialized management.
- Management should include the following goal-directed interventions:
 - Preservation of lung function
 - Pharmacological and nonpharmacological interventions
 - Prevention of infection and reduction of exacerbations
 - Optimization of nutrition
 - Screening and monitoring for comorbidities and complications
- Patients with certain mutations may benefit from treatment with CFTR modulators.
- Acute pulmonary exacerbations require rapid and effective treatment.

A. Clear airway secretions and control infections:

- Aerosol treatment; albuterol/saline.
- Daily dose of human recombinant DNase (mucolytic; breaks down the massive amounts of DNA in respiratory mucus that clogs up the airways).
- Chest physical therapy with postural drainage: 1-4 times per day.

B. Antibiotics:

- For acute infections (change in baseline condition).
- Most frequent is P. aeruginosa (also non-typable H. influenzae, S. aureus, B. cepacia).
- Must base choice on culture and sensitivity.
- Aerosolized antibiotics: tobramycin.

C. Hospitalization (Progressive despite intensive home measures):

- Typical 14-day treatment.
- Two-drug regimens to cover pseudomonas. Ex: piperacillin plus tobramycin or ceftazidime.

D. Nutritional: pancreatic enzyme replacement with meals/snacks; vitamin supplementation (ADEK).

E. Adequate fluid replacement when exercising or hot weather.

F. Ivacaftor for certain mutations (increases the activity of CFTR in the 5% of patients who have a specific mutation).

G. Lung transplant: Lung transplantation is used only in advanced disease not responsive to the therapy previously listed.

- ❖ N.B:
- CF variably affects multiple organ systems, but almost all patients have debilitating infections of the respiratory tract.
 - Accumulation of inspissated mucus allows bacteria to proliferate and invade the sinuses and predisposes patients to recurrent rhinosinusitis.
 - Up to 40% of patients have nasal polyps, which are benign outgrowths of chronically inflamed mucosa that further obstruct the nasal passages and exacerbate sinusitis.
 - Symptomatic relief of polyps includes intranasal glucocorticoids and, in some cases, surgical resection.

Prevention:

- Annual influenza vaccine for all affected individuals > 6 months with inactivated influenza vaccine
- **Pneumococcal vaccine** (see "Immunization schedule")
- Palivizumab: antibody against respiratory syncytial virus (RSV) for infants < 24 months
- Long-term treatment with azithromycin may be used to prevent recurrent pulmonary infections.

Complication:

↳ Acute pulmonary exacerbations

General principles [27][8][20]

- Increased severity or new onset of clinical symptoms can be a sign of acute pulmonary exacerbation.
 - There are no universally accepted diagnostic criteria.
 - Findings are varied and include increased dyspnea or cough, changes in sputum production, weight loss, and fever
- Start culture-guided antibiotic therapy for pulmonary exacerbations.

⚠ Treat pulmonary exacerbations quickly and aggressively to prevent an irreversible decline in lung function. [30]

Antibiotics [27]

Antibiotic therapy in patients with CF is challenging because of a high prevalence of antibiotic resistance following frequent antibiotic use and the presence of multiple pathogenic organisms. 💬

⚠ Choose initial antibiotics based on the speciation and sensitivities of the patient's recent routine sputum cultures. Adjust the antibiotics, if needed, once the results from the new sputum culture have been reported.

Antibiotic therapy for CF pulmonary exacerbations 💬 [27]

Pathogen	Example regimens
Staphylococcus aureus	• MSSA [37] ◦ Nafcillin ◦ OR oxacillin • MRSA ◦ Vancomycin ◦ OR linezolid
Pseudomonas aeruginosa	• Select two antipseudomonal antibiotics (double coverage) with different mechanisms of action. [27] ◦ Antipseudomonal beta-lactam antibiotics: e.g., ceftazidime, meropenem ◦ Fluoroquinolones: e.g., ciprofloxacin ◦ Aminoglycosides: e.g., tobramycin, amikacin
Other pathogens	• H. influenzae: often susceptible to antipseudomonal antibiotics 💬 • Other gram-positive infections: should be covered by antibiotics that are used to treat S. aureus • Drug-resistant pathogens (e.g., B. cepacia, S. maltophilia, Achromobacter spp.) ◦ Known to be resistant to many antibiotics and often require double coverage ◦ Treatment should be decided in consultation with an infectious diseases specialist.