Cystic Fibrosis:

Manifests as mucosal obstruction of exocrine glands caused by defective ion transport within epithelial cells.

EPIDEMIOLOGY AND ETIOLOGY

In the United States (US), CF most commonly occurs in whites, affecting from 1 in 1900 to 3700 individuals.

CF is inherited as an autosomal recessive trait, and approximately 1 in 25 whites are heterozygous carriers.

The gene mutation is found on the long arm of chromosome 7 and encodes for the CF transmembrane regulator (CFTR) protein, which functions as a chloride channel to transport water and electrolytes.

Over 1900 mutations have been described in the CF gene; however, the F508del mutation is most common and is present in 70% to 90% of CF patients in the United States.
PATHOPHYSIOLOGY

CF is a disease of exocrine gland epithelial cells where CFTR Expression is prevalent. Normally, these cells transport chloride through CFTR chloride channels with sodium and water accompanying this flux across the cell membrane.

In CF, the CFTR chloride channel is dysfunctional and usually results in decreased chloride secretion and increased sodium absorption, leading to altered viscosity of fluid excreted by the exocrine glands and mucosal obstruction.

Pulmonary disease:

Is characterized by thick mucus secretions, impaired mucus clearance, chronic airway infection and colonization, obstruction, and an exaggerated neutrophil-dominated inflammatory response. This process leads to air trapping, atelectasis, mucus plugging, bronchiectasis, cystic lesions, pulmonary hypertension, and eventual respiratory failure.

Early infection is most often caused by Staphylococcus aureus and nontypeable Haemophilus influenzae. Pseudomonas aeruginosa infection is the most significant CF pathogen among all age groups.

Organisms identified later in the disease course include Stenotrophomonas maltophilia, Achromobacter xylosoxidans, Burkholderia cepacia, fungi including Candida and Aspergillus species, and nontuberculous mycobacteria among others.

Gastrointestinal System

Gastrointestinal (GI) involvement often presents as:

- meconium ileus
- Small-bowel obstruction shortly after birth due to abnormally thick meconium.
- Older CF patients may develop (DIOS).
- Maldigestion due to pancreatic enzyme insufficiency is present in 85% to 90% of CF patients.
- Thick pancreatic secretions
- Volume and concentration of pancreatic enzymes and bicarbonate are reduced, leading to maldigestion of fat and protein and subsequent malabsorption of fat-soluble vitamins (A, D, E, and K).
- Symptoms include abdominal distention, steatorrhea, flatulence, and malnourishment despite voracious appetite.

Hepatobiliary disease occurs due to bile duct obstruction from abnormal bile composition and flow.

Hepatomegaly, splenomegaly, and cholecystitis may be present. Hepatic steatosis may be present due to effects of malnutrition. Progression from cholestasis (impaired bile flow) to cirrhosis, esophageal varices, and portal hypertension takes several years.

**Endocrine System**

CF-related diabetes (CFRD):

Although it shares characteristics of both type 1 and type 2 diabetes mellitus, CFRD is categorized separately.

Reduced functional pancreatic islet cells and increased islet amyloid deposition results in insulin insufficiency, the primary cause of CFRD.

Postprandial hyperglycemia is common, but because some basal insulin secretion is maintained, fasting hyperglycemia is less severe and ketosis is rare.

Diet, acute and chronic infection, and corticosteroid use lead to fluctuation in glucose tolerance over time.

**Reproductive System**

CF patients often experience delayed puberty.

In females, menarche occurs 18 months later than average; menstrual irregularity is common, and fertility is reduced due to increased cervical mucus viscosity. Due to increasing life expectancy, pregnancy is becoming more common; however, outcomes depend on prepartum nutritional and pulmonary status.

Almost all males with CF are azoospermic due to congenital absence of the vas deferens with resultant obstruction; however, conception still occurs occasionally.

**Musculoskeletal System**

Several factors contribute to development of bone disease in CF:

(a) Malabsorption of vitamins D and K and calcium
(b) Poor nutrition and decreased body mass

(c) Physical inactivity

(d) Corticosteroid therapy

(e) Delayed puberty.

Chronic pulmonary infection, through release of inflammatory cytokines, can increase bone resorption and decrease formation.

Osteopenia, osteoporosis, pathological fractures, and kyphosis can occur. Episodic or chronic arthritis may occur due to immune complex formation in response to chronic inflammation.

Digital clubbing is commonly observed and is a marker for hypoxia.

**Hematological System**

Anemia may be present due to impaired erythropoietin regulation, nutritional factors (vitamin E and iron malabsorption), or chronic inflammation.

Increased cytokine production can lead to shortened red blood cell survival, reduced erythropoietin response, and impaired mobilization of iron stores. Additionally, with chronic hypoxia, normal hemoglobin and hematocrit values may represent relative anemia.

Abnormal bleeding or clotting may also be observed as a result of vitamin K malabsorption, antibiotic-associated depletion of GI flora and vitamin K synthesis, reduced coagulation factor synthesis due to liver disease, and/or a procoagulant state due to inflammation.

**Integumentary System**

Sweat contains abnormally high concentrations of sodium and chloride due to impaired reabsorption within the sweat duct from loss of CFTR channels. Patients are usually asymptomatic (other than a characteristic salty taste to the skin).

In rare instances such as hot weather or excessive sweating during physical activity, patients may become dehydrated and experience symptoms of hyponatremia (nausea, headache, lethargy, and confusion).

**Clinical Presentation of Cystic Fibrosis**

• General Usually diagnosed in neonates or during early childhood. May present later in life due to less severe symptoms or misdiagnosis
Symptoms

• Pulmonary: Chronic cough, sputum production, decreased exercise tolerance, and recurrent pneumonia and sinusitis. Exacerbations may be marked by increased cough, sputum changes (darker, thicker), hemoptysis, dyspnea, and fever.

• GI: Foul-smelling loose stools (steatorrhea), flatulence, and abdominal pain. Intestinal obstruction may present as abdominal pain and decreased bowel movements.

• Nutritional: Poor weight gain despite voracious appetite and hunger. Dry skin, skin rash, and visual disturbances may be noted in vitamin deficiency.

• Cystic fibrosis-related diabetes (CFRD): Weight loss, increased thirst, and more frequent urination.

Signs

• Obstructive airways disease: Tachypnea, dyspnea, cyanosis, wheezes, crackles, sternal retractions, digital clubbing, and barrel chest.

• Failure to thrive: Below age-based normal in both height and weight in children; adults may be near/below ideal body weight or have a low body mass index (BMI).

• Salty taste to the skin.

• Hepatobiliary disease: Hepatomegaly, splenomegaly, and prolonged bleeding may occur.
• Recurrent pancreatitis (usually in pancreatic-sufficient patients): Episodic epigastric abdominal pain, persistent vomiting, and fever.

**Laboratory Tests**

• Leukocytosis with increase in polymorphonuclear (PMN) leukocytes and bands may occur in acute pulmonary exacerbations.

• Malnutrition: Decreased serum levels of fat-soluble vitamins (A, D, E, and K). Decreased vitamin K levels may result in elevated prothrombin time (PT) and international normalized ratio (INR).

• Glucose intolerance: Blood glucose between 140 and 199 mg/dL (7.8–11.0 mmol/L) 2 hours after an oral glucose-tolerance test.

• CFRD: Blood glucose 200 mg/dL (11.1 mmol/L) or higher 2 hours after an oral glucose-tolerance test or fasting hyperglycemia (fasting blood glucose 126 mg/dL [7.0 mmol/L] or more regardless of the postglucose challenge level.)

• Hepatobiliary disease: Serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyltransferase, and bilirubin may be elevated.

**Other Tests**

• Microbial cultures (sputum, throat, bronchoalveolar lavage, or sinus): Isolation of P. aeruginosa, S. aureus, S. maltophilia, and other CF-related organisms.

• Pulmonary function tests (PFTs): Decreased forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC), typically lower during acute pulmonary exacerbations.

• Chest x-ray or CT: Infiltrates, atelectasis, bronchiectasis, and mucus plugging.

• Abdominal x-ray or CT: Intestinal obstruction may be manifested as meconium ileus, DIOS, or intussusception. Rectal prolapse may be noted on physical examination.

• Malnutrition: Elevated fecal fat content, reduced pancreatic stool elastase (less than 200 mcg/g of feces.)

**Diagnosis**

Testing for CF is part of required newborn screening panels in all US states in an effort to identify patients prior to symptom development. All “positive screens,” as well as individuals presenting with signs and symptoms of CF, are referred to a CF care center. Diagnosis of CF is based on:
1-Two separate elevated sweat chloride concentrations of 60 mEq/L (60 mmol/L) or greater obtained through pilocarpine iontophoresis (“sweat test”)

2- Genetic testing (CFTR mutation analysis)

Cystic Fibrosis TREATMENT

Desired Outcomes:

Therapeutic outcomes in CF care relate to chronic and acute treatment goals.

Maximizing nutritional status through pancreatic enzyme replacement and vitamin and nutritional supplements is necessary.

Reduction of airway inflammation and infection through aggressive airway clearance and antibiotic therapy with a goal of returning lung function to pre-exacerbation levels or greater.

Nonpharmacological Therapy

»» Airway Clearance Therapy:

Airway clearance therapy is a necessary routine for all CF patients to clear secretions and control infection, even at diagnosis prior to becoming symptomatic.

The traditional form of chest physiotherapy (CPT) is percussion and postural drainage. Areas of the patient’s chest, sides, and back are rapidly “clapped” by hand in different patient positions, followed by cough or forced expiration to mobilize secretions.

Effective cough and expectoration of mucus are essential for good clearance technique. Airway clearance therapy is typically performed once or twice daily for maintenance care and is increased to three or four times per day during acute exacerbations.
Nutrition:

Most CF patients have increased caloric needs due to increased energy expenditure through increased work of breathing, increased basal metabolism, and maldigestion. Nutrition in malnourished patients consists of baseline required calories plus additional calories for weight gain. Collaboration with dieticians specially trained in CF nutrition is essential.

Pharmacologic Therapy

Airway Clearance Therapy:

Airway clearance therapy is usually accompanied by bronchodilator treatment with albuterol to stimulate mucociliary clearance and prevent bronchospasm, associated with therapy mucolytic agent is administered afterward to reduce sputum viscosity and enhance clearance.

- Nebulization of dornase alfa: improves daily pulmonary symptoms and function, reduces pulmonary exacerbations, and improves quality of life.
- Daily dosing is most common, but some patients benefit from twice daily administration.
- Hypertonic saline for inhalation (HyperSal) 7% or 3.5% is often used as an alternative or add-on mucolytic agent for osmotic effects or sputum induction.

- N-acetylcysteine is another mucolytic agent, but its unpleasant odor and taste limit patient acceptance.
- Montelukast, antihistamines, and/or intranasal steroids are used for CF patients with allergic or rhinosinusitis symptoms.
- Inhaled corticosteroids may attenuate reactive airways and reduce airway inflammation in some patients; however, clear benefit in CF has not been established.
- Systemic corticosteroids may be used short term in acute exacerbations or for treatment of allergic response to Aspergillus colonization (allergic bronchopulmonary aspergillosis, or ABPA); however, dose and duration of therapy should be minimized.
- High-dose ibuprofen targeting peak concentrations of 50 to 100 mcg/mL (243–485 μmol/L) has been shown to slow disease progression, particularly in children 5 to 13 years of age with mild lung disease.
- Azithromycin is a macrolide antibiotic commonly used in CF as an anti-inflammatory agent to improve overall lung function.
- Due to its long tissue half-life, azithromycin is typically dosed 3 days per week (Monday, Wednesday, and Friday).
Alternatively, patients may take 500 or 250 mg either daily or only Monday through Friday, based on the same weight parameters.

-screening acid-fast bacillus sputum culture.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pediatric Dose</th>
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<tbody>
<tr>
<td>Albuterol (salbutamol)</td>
<td>2.5 mg nebulized with chest physiotherapy two to four times daily; alternatively, two puffs via metered-dose inhaler may be substituted</td>
</tr>
<tr>
<td>Dornase alfa</td>
<td>2.5 mg nebulized once or twice daily</td>
</tr>
<tr>
<td>Hypertonic saline 7%, 3.5%, or 3%</td>
<td>4 mL nebulized one to four times per day</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Body weight 25–39 kg: 250 mg on Mondays, Wednesdays, and Fridays</td>
</tr>
<tr>
<td>Ibuprofena</td>
<td>20–30 mg/kg/dose given twice daily</td>
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</tbody>
</table>
**Antibiotic Therapy**

*Oral Antibiotic Therapy:*

- For recent-onset or mild symptoms, patients may be treated with outpatient oral and inhaled antibiotics for 14 to 21 days.

- Oral fluoroquinolones are a mainstay for *P. aeruginosa* treatment in CF, even in children.

- To prevent development of resistance and promote synergy, inhaled tobramycin, aztreonam, or colistin is usually added for double coverage.

- Methicillin-sensitive *S. aureus* (MSSA) may be treated with oral amoxicillin–clavulanic acid, dicloxacillin, first- or second-generation cephalosporins, trimethoprim–sulfamethoxazole, clindamycin, doxycycline, or minocycline, depending on sensitivity.

- Methicillin-resistant *S. aureus* (MRSA) may be treated with oral trimethoprim–sulfamethoxazole, clindamycin, doxycycline, minocycline, or linezolid.

- *H. influenzae* often produces β-lactamases but can usually be treated with amoxicillin–clavulanic acid, a cephalosporin, or trimethoprim–sulfamethoxazole.

*Intravenous antibiotic therapy:*

For severe infection or patient failing outpatient therapy, IV antibiotic therapy is prescribed for 2-3 weeks as inpatient therapy.

Some patients may be discharged to finish their IV course or even receive their entire IV course at home.

Typical regimen for severe infection include an antipseudomonal β-lactam (piperacillin, ceftazidime, cefpirome, imipenem, aztreonam) plus an aminoglycoside (tobramycin, amikacin) or fluoroquinolone (ciprofloxacin, levofloxacin).

*Inhaled Antibiotic Therapy:*

- Inhaled tobramycin (TOBI, Bethkis) is typically administered to patients 6 years of age and older in alternating 28-day cycles of 300 mg nebulized twice daily, followed by a 28-day washout period to minimize development of resistance.

- A dry powder formulation of tobramycin (TOBI Podhaler™, 112 mg inhaled twice daily) can also be used in 28-day on/off cycles with reduced administration time.

- Aztreonam lysine for inhalation (Cayston) is also used for *P. aeruginosa* suppression in 28-day on/off cycles for CF patients 6 years of age and older.

A dose of 75 mg three times daily is given via the Altera nebulizer system, a high-efficiency drug delivery device with shorter administration time.
-Nebulized colistin using the IV formulation may be an option in patients with tobramycin-resistant strains or intolerance to inhaled tobramycin or aztreonam lysine. Pretreatment with albuterol is necessary due to increased risk of bronchoconstriction.

»» Gastrointestinal Therapy

**Pancreatic Enzyme Replacement:**

-This is the mainstay of GI therapy.

-Capsules may be opened and the microbeads swallowed with food (for infants and young children), as long as they are not chewed or mixed with alkaline or hot foods (which denature enzymes).

-Pancreatic enzymes are initiated at 500 to 1000 units/kg/meal of lipase component (because fats are most difficult to digest) with half-doses given for snacks.

-Doses are titrated at 2- to 3-week intervals in increments of 150 to 250 units of lipase/kg/meal (or the next easily administered capsule or half-capsule) up to 2500 units/kg/meal.
- Separate 3 hours between Pancreatic Enzyme Replacement and nutritional supplements.

- Patients responding poorly to maximal doses of one product may benefit from changing to another product and/or addition of a histamine H2-receptor antagonist or proton pump inhibitor. Acid suppression may boost the effective enzyme dose, if the duodenal pH is not alkaline enough to neutralize residual gastric acid and dissolve enteric coating. Acid suppression also treats concomitant GERD, which is common in CF.

<table>
<thead>
<tr>
<th>Table 16-4</th>
<th>Common Pancreatic Enzyme Replacement Products</th>
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<tbody>
<tr>
<td><strong>Trade Name</strong></td>
<td><strong>Lipase (Units)</strong></td>
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<tr>
<td>Creon 3000</td>
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<td>Creon 6000</td>
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<td>Pancreaze MT 4*</td>
<td>4200</td>
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<tr>
<td>Pancreaze MT 10*</td>
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<tr>
<td>Pancreaze MT 16*</td>
<td>16,800</td>
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<tr>
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<td>21,000</td>
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<tr>
<td>Pertzye 8000</td>
<td>8000</td>
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<tr>
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<tr>
<td>Ultresa</td>
<td>13,800</td>
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<tr>
<td>Ultresa</td>
<td>20,700</td>
</tr>
<tr>
<td>Ultresa</td>
<td>23,000</td>
</tr>
<tr>
<td>Viokase*</td>
<td>10,440</td>
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<tr>
<td>Viokase*</td>
<td>20,880</td>
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<tr>
<td>Zenpep 3000</td>
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<td>Zenpep 10,000</td>
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<td>Zenpep 25,000</td>
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<tr>
<td>Zenpep 40,000</td>
<td>40,000</td>
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</tbody>
</table>

*a The number after a trade name refers to the approximate number of thousands of units of lipase contained per dosage form.

*b Nonenteric coated enzyme. Must be given with a gastric acid suppressant. Often administered via feeding tube.
**Fat-Soluble Vitamin Supplementation:**

- This is usually required in pancreatic insufficiency. Specially formulated products for CF patients (AquADEKs, Vitamax, MVW Complete, Choiceful) are usually sufficient to attain normal serum vitamin levels at a dose of 1 mL daily for infants, one tablet daily for younger children, and one tablet/capsule twice daily for teenagers and adults.

- Appetite stimulants such as cyproheptadine may be an option for promoting nutrition and weight gain, but efficacy has not been established.

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>>> Liver Disease

*Ursodiol at 20 mg/kg/day in two divided doses.*

It may slow progression of liver disease. It improves bile flow and may displace toxic bile acids that accumulate in a cholestatic liver, stimulate bicarbonate secretion into the bile, offer a cytoprotective effect, and reduce elevated liver enzymes.

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>>> Intestinal Obstruction

Treatment of DIOS consists of enteral administration of polyethylene glycol (PEG) electrolyte solutions.

- Enemas may also be used to facilitate stool clearance.

- IV fluids are often required to correct dehydration due to vomiting or decreased oral Intake.

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>>> CF-Related Diabetes

Many patients can be successfully managed by meal coverage with short- or rapid-acting insulin (regular, lispro, or aspart) dosed per carbohydrate counting.

Patients with fasting hyperglycemia or patients receiving nighttime tube feedings typically also require longer-acting basal insulin.

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>>> Bone Disease and Arthritis

CF patients with low bone mineral density and low serum vitamin D levels may improve bone health through supplemental vitamin D analogs beyond those found in standard CF vitamins.

- For cholecalciferol (or ergocalciferol), a minimum of 400 to 500 IU and 800 to 1000 IU should be taken daily by infants and patients older than 1 year of age, respectively.
- Vitamin D concentrations should be measured annually in the winter for evaluation of dosing. Total weekly or biweekly doses of 12,000 IU for children younger than 5 years of age and 50,000 IU for patients 5 years of age and older may be required to achieve target vitamin D concentrations.

- Supplemental calcium should be provided if 1300 to 1500mg of elemental calcium intake cannot be achieved through diet.

- Antiresorptive agents (oral or IV bisphosphonates) may be used to treat adult CF patients with Osteoporosis.

- Pamidronate 30 mg IV every 3 months has been shown to increase bone mineral density in adult CF patients.

>>>Pharmacogenomic Therapy

- **Ivacaftor** (Kalydeco, VX-770) is a CFTR potentiator that activates defective CFTR at the cell surface and improves CFTR function in patients with gating mutations.

- Ivacaftor is indicated for treatment of CF patients 6 years and older who have at least one G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R, or R117H CFTR gene mutation.

- Ivacaftor treatment (added to standard CF care) is associated with improved lung function, decreased pulmonary exacerbations, weight gain, and increased quality of life.

- The ivacaftor dose is 150 mg orally every 12 hours with food containing at least 20 g of fat for patients age six years and older.

Patients 2 to 5 years of age should receive 50 mg (<14 kg) or 75 mg (> 14 kg) orally every 12 hours.

**Reference:**