Cystic Fibrosis 1

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- Cystic fibrosis (CF) is an inherited multisystem disorder of children and adults; it is the most common life-limiting recessive genetic trait among whites.
- Dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, the primary defect, leads to a wide and variable array of presenting manifestations and complications.
- CF is responsible for most cases of exocrine pancreatic insufficiency in early life and is the major cause of severe chronic lung disease in children.
- It is also responsible for many cases of hyponatremic salt depletion, nasal polyposis, pansinusitis, rectal prolapse, pancreatitis, cholelithiasis, and nonautoimmune insulin-dependent hyperglycemia.

- The prevalence in these populations varies but approximates 1 in 3,500 live births (1 in 9,200 individuals of Hispanic descent and 1 in 15,000 African Americans).
- Although less frequent in African, Hispanic, Middle Eastern, South Asian, and eastern Asian populations, the disorder does exist in these populations as well .

- CF is inherited as an autosomal recessive trait.

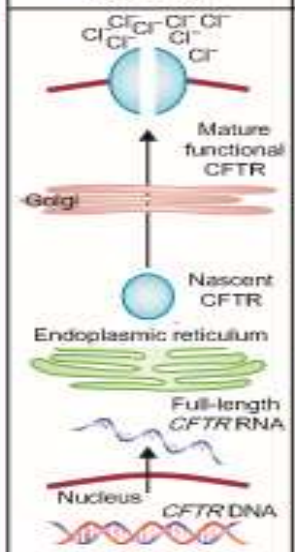
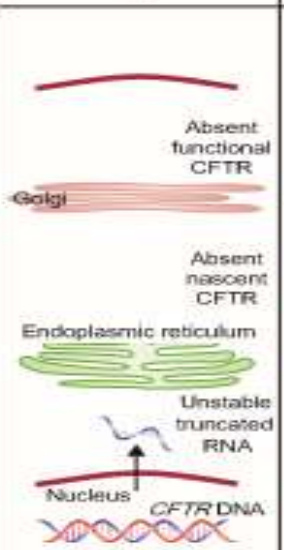
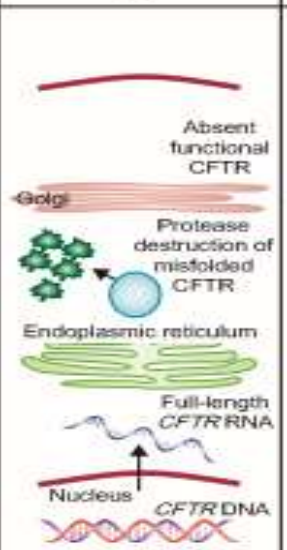
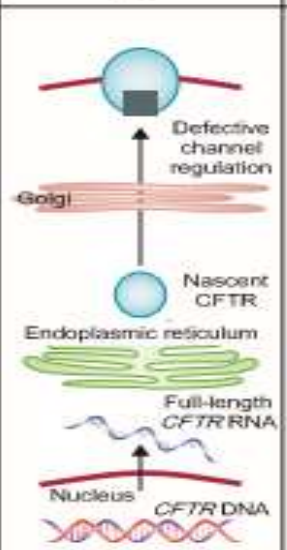
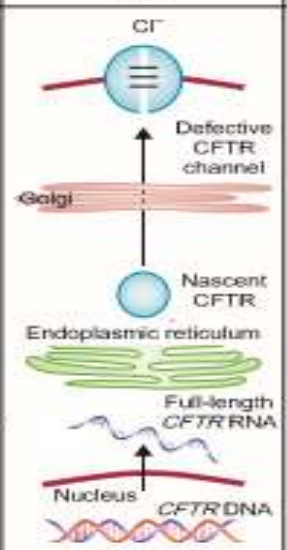
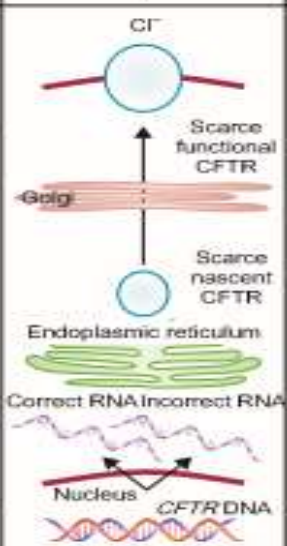
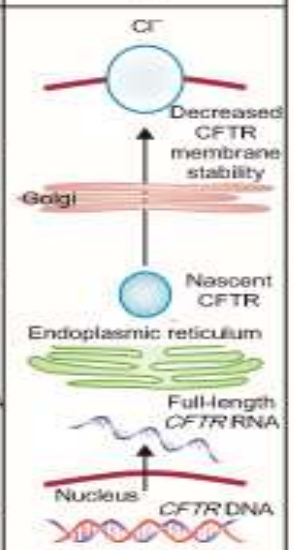
- CFTR is expressed largely in epithelial cells of airways, the gastrointestinal tract (including the pancreas and biliary system), the sweat glands, and the genitourinary system.

Table 432.2 One Proposed Classification of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Mutations

CLASS	EFFECT ON CFTR	FUNCTIONAL CFTR PRESENT?	SAMPLE MUTATIONS
I	Lack of protein production	No	Stop codons (designation in X; e.g., Trp1282X, Gly542X); splicing defects with no protein production (e.g., 711+1G→T, 1717-1G→A)
II	Defect in protein trafficking with ubiquitination and degradation in endoplasmic reticulum/ Golgi body	No/substantially reduced	Phe508del, Asn1303Lys, Gly85Gly, leu1065Pro, Asp507, Ser549Arg
III	Defective regulation; CFTR not activated by adenosine triphosphate or cyclic adenosine monophosphate	No (nonfunction CFTR present in apical membrane)	Gly551Asp, Ser492Phe, Val520Phe, Arg553Gly, Arg560Thr, Arg560Ser
IV	Reduced chloride transport through CFTR at the apical membrane	Yes	Ala455Glu, Arg117Cys, Asp1152His, Leu227Arg, Arg334Trp, Arg117His*
V	Splicing defect with reduced production of CFTR	Yes	3849+10kbC→T, 1811+16kbA→G, IVS8-5T, 2789+5G→A

*Function of Arg117His depends on the length of the polythymidine track on the same chromosome in intron 8 (IVS8): 5T, 7T, or 9T. There is more normal CFTR function with a longer polythymidine track.

From O'Sullivan BP, Freedman SD: Cystic fibrosis, *Lancet* 373:1891–1902, 2009.

Normal	I	II	III	IV	V	VI
						
CFTR defect	No functional CFTR protein	CFTR trafficking defect	Defective channel regulation	Decreased channel conductance	Reduced synthesis of CFTR	Decreased CFTR stability
Type of mutations	Nonsense; frameshift; canonical splice	Missense; aminoacid deletion	Missense; aminoacid change	Missense; aminoacid change	Splicing defect; missense	Missense; aminoacid change
Specific mutation examples	Gly542X Trp1282X Arg553X 621+1G→T	Phe508del Asn1303Lys Ile507del Arg560Thr	Gly551Asp Gly178Arg Gly551Ser Ser549Asn	Arg117His Arg347Pro Arg117Cys Arg334Trp	3849+10kbC→T 2789+5G→A 3120+1G→A 5T	4326delTC Gln1412X 4279insA

- Mutation class I-III are generally considered to be severe mutations in that they lead to a complete or nearly complete absence of CFTR function, whereas class IV-VI mutations are associated with some residual functional protein.

- The most prevalent mutation of CFTR is the deletion of a single phenylalanine residue at amino acid 508 (F508del).

- The high-frequency of CFTR mutations has been ascribed to resistance to the morbidity and mortality associated with infectious dysenteries through the ages.
- Cultured CF intestinal epithelial cells homozygous for the F508del mutation are unresponsive to the secretory effects of cholera toxin.

Table 432.1	Complications of Cystic Fibrosis
RESPIRATORY	
Bronchiectasis, bronchitis, bronchiolitis, pneumonia	
Atelectasis	
Hemoptysis	
Pneumothorax	
Nasal polyps	
Sinusitis	
Reactive airway disease	
Mucoid impaction of the bronchi	
Allergic bronchopulmonary aspergillosis	
Cor pulmonale	
Respiratory failure	

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
Aquagenic palmoplantar keratoderma (skin wrinkling)

PATHOGENESIS

- A number of long-standing observations of CF 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

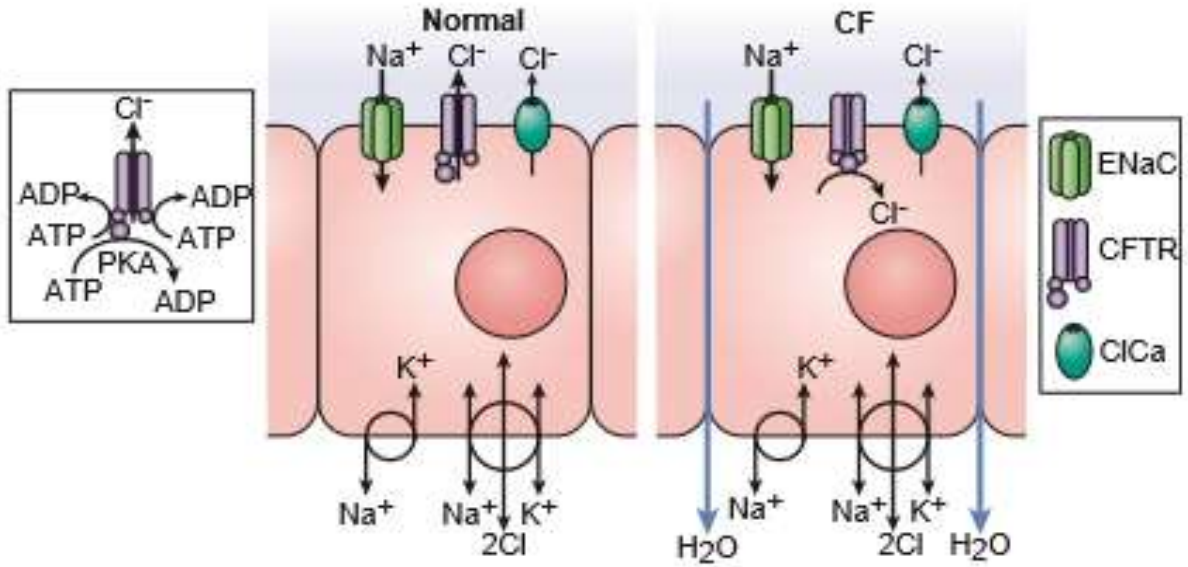
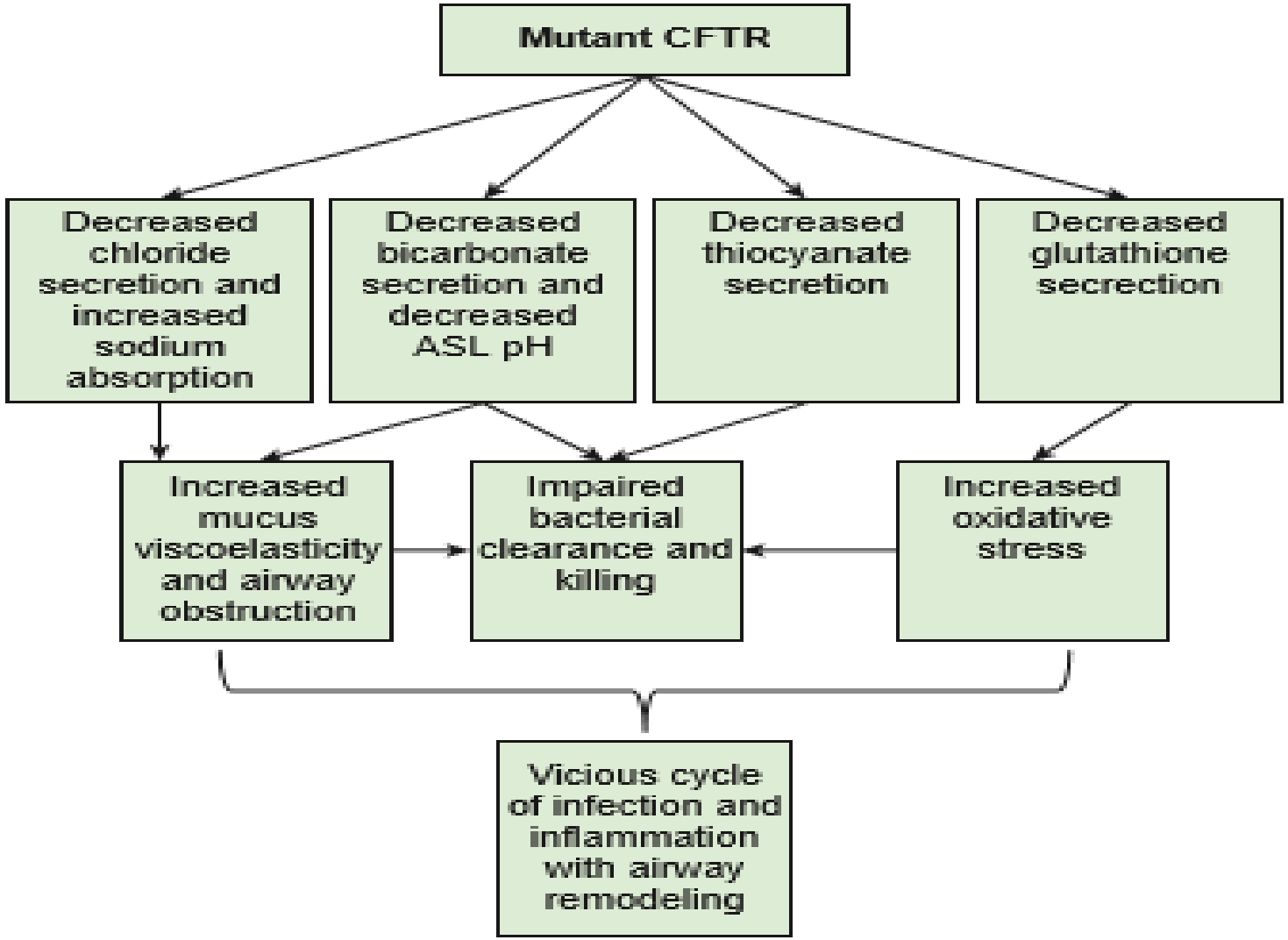


Fig. 432.3 Schematic diagram depicting cystic fibrosis *(CF)* epithelial channel defects, characterized by impaired chloride secretion, massive sodium absorption, and movement of water through the epithelium, leading to a dehydrated airway surface. *ADP*, Adenosine diphosphate; *ATP*, adenosine triphosphate; *CFTR*, cystic fibrosis transmembrane conductance regulator; *ClCa*, alternative chloride channel; *ENaC*, epithelium sodium channel; *PKA*, protein kinase A. *(From Michelson P, Faro A, Ferkol T: Pulmonary disease in cystic fibrosis. In* Kendig's Disorders of the Respiratory Tract in Children, *ed 9, Philadelphia, 2019, Elsevier, [Fig. 51.1, p. 778].)*


Mutant CFTR
Decreased chloride secretion and increased sodium absorption
Decreased bicarbonate secretion and decreased ASL pH
Decreased thiocyanate secretion
Decreased glutathione secretion
Increased mucus viscoelasticity and airway obstruction
Impaired bacterial clearance and killing
Increased oxidative stress
Vicious cycle of infection and inflammation with airway remodeling

- A central feature of lung disease in patients with CF is the high prevalence of airway infection with Staphylococcus aureus , Pseudomonas aeruginosa , and Burkholderia cepacia complex , organisms that rarely infect the lungs of other individuals.
- Exposure to environmental tobacco smoke and outdoor air pollutants, and early acquisition of respiratory virus infections, as well as pathogenic organisms like P. aeruginosa and methicillin-resistant S. aureus, have been implicated as causes of worsening disease.
- Sex/gender disparities also seem to exist, with females having a poorer prognosis.

PATHOLOGY

- The earliest pathologic lesion in the lung is that of bronchiolitis (mucous plugging and an inflammatory response in the walls of the small airways); with time, mucous accumulation and inflammation extend to the larger airways (bronchitis) .
- Goblet cell hyperplasia and submucosal gland hypertrophy become prominent pathologic findings, which is most likely a response to chronic airway infection.
- With long-standing disease, evidence of airway destruction such as bronchiolar obliteration, bronchiolectasis, and bronchiectasis becomes prominent.

- Bronchiectatic cysts and emphysematous bullae or subpleural blebs are frequent with advanced lung disease, the upper lobes being most commonly involved.
- These enlarged air spaces may rupture and cause pneumothorax.
- Bronchial arteries are enlarged and tortuous, contributing to a propensity for hemoptysis in bronchiectatic airways.
- Small pulmonary arteries eventually display medial hypertrophy, which would be expected in secondary pulmonary hypertension

- The paranasal sinuses are uniformly filled with secretions containing inflammatory products, and the epithelial lining displays hyperplastic and hypertrophied secretory elements .
- Polypoid lesions within the sinuses and erosion of bone have been reported.
- The nasal mucosa may form large or multiple polyps, usually from a base surrounding the ostia of the maxillary and ethmoidal sinuses.

- The pancreas is usually small, occasionally cystic, and often difficult to find at postmortem examination.
- In 85–90% of patients, the lesion progresses to complete or almost complete disruption of acini and replacement with fibrous tissue and fat.
- Infrequently, foci of calcification may be seen on radiographs of the abdomen.
- The islets of Langerhans contain normal-appearing β cells, although they may begin to show architectural disruption by fibrous tissue in the 2nd decade of life.

- The intestinal tract shows only minimal changes.
- Esophageal and duodenal glands are often distended with mucous secretions.
- Concretions may form in the appendiceal lumen or cecum.
- Crypts of the appendix and rectum may be dilated and filled with secretions.

- Focal biliary cirrhosis secondary to blockage of intrahepatic bile ducts is uncommon in early life, although it is responsible for occasional cases of prolonged neonatal jaundice.

- This process can proceed to symptomatic multilobular biliary cirrhosis that has a distinctive pattern of large irregular parenchymal nodules and interspersed bands of fibrous tissue.

- Approximately 30–70% of patients have fatty infiltration of the liver, in some cases despite apparently adequate nutrition.
- At autopsy, hepatic congestion secondary to cor pulmonale is frequently observed.
- The gallbladder may be hypoplastic and filled with mucoid material and often contains stones.
- Atresia of the cystic duct and stenosis of the distal common bile duct have been observed.

- Glands of the uterine cervix are distended with mucus, copious amounts of which collect in the cervical canal.
- In >95% of males, the body and tail of the epididymis, the vas deferens, and the seminal vesicles are obliterated or atretic, resulting in male infertility.

CLINICAL MANIFESTATIONS

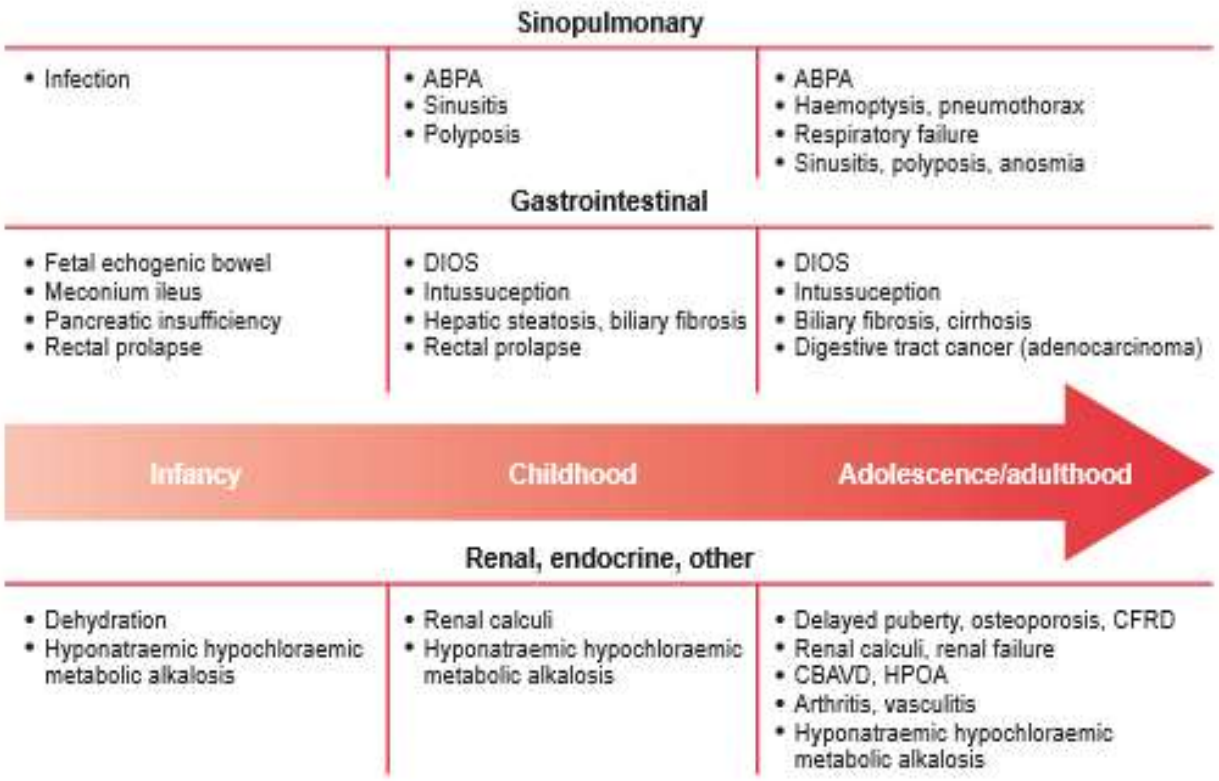
- The earliest symptom is usually cough that may begin with a viral respiratory tract infection but then persists unless treated with antibiotics.

- With treatment, the generally realized goal is for patients to remain asymptomatic throughout childhood, except for the periodic development of cough, chest congestion, sputum production, and/or wheezing that define a pulmonary exacerbation

- The rate of progression of lung disease is the chief determinant of morbidity and mortality.
- As lung disease slowly progresses, chronic cough, sputum production, exercise intolerance, shortness of breath, and failure to thrive are noted.
- Cor pulmonale, respiratory failure, and death eventually supervene unless lung transplantation is accomplished; this has become increasingly uncommon in childhood.
- Infection with certain strains of B. cepacia and other multidrug-resistant organisms may be associated with particularly rapid pulmonary deterioration and death.

- Eventual physical findings include increased anteroposterior diameter of the chest, generalized hyperresonance, scattered or localized coarse crackles, and digital clubbing.
- Expiratory wheezes may be heard, a manifestation of airway inflammation and edema that may or may not be associated with bronchodilator responsiveness.
- Cyanosis is a late sign.
- Common pulmonary complications include atelectasis, hemoptysis, pneumothorax, and cor pulmonale; these usually appear in late adolescence or beyond.

- Even though the paranasal sinuses are virtually always opacified radiographically, acute sinusitis is infrequent.
- Nasal obstruction and rhinorrhea are common, caused by inflamed, swollen mucous membranes or, in some cases, nasal polyposis.
- Nasal polyps are most troublesome between 5 and 20 yr of age.


Sinopulmonary
• Infection
• ABPA
• Sinusitis
• Polyposis
• ABPA
• Haemoptysis, pneumothorax
• Respiratory failure
• Sinusitis, polyposis, anosmia
Gastrointestinal
• Fetal echogenic bowel
• Meconium ileus
• Pancreatic insufficiency
• Rectal prolapse
• DIOS
• Intussuception
• Hepatic steatosis, biliary fibrosis
• Rectal prolapse
• DIOS
• Intussuception
• Biliary fibrosis, cirrhosis
• Digestive tract cancer (adenocarcinoma)
Infancy
Childhood
Adolescence/adulthood
Renal, endocrine, other
• Dehydration
• Hyponatraemic hypochloraemic metabolic alkalosis
• Renal calculi
• Hyponatraemic hypochloraemic metabolic alkalosis
• Delayed puberty, osteoporosis, CFRD
• Renal calculi, renal failure
• CBAVD, HPOA
• Arthritis, vasculitis
• Hyponatraemic hypochloraemic metabolic alkalosis

- Intestinal Tract In 15–20% of newborn infants with CF, the ileum is completely obstructed by meconium (meconium ileus).
- Abdominal distention, emesis, and failure to pass meconium appear in the first 24-48 hr of life and often requires surgical intervention.
- 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 as the presence of peritoneal or scrotal calcifications.
- Ileal obstruction with fecal material (distal intestinal obstruction syndrome [DIOS]) occurs in older children, causing cramping abdominal pain, abdominal distention, and obstruction that can be treated with medical approaches to bowel evacuation.

- More than 85% of children with CF have exocrine pancreatic insufficiency, causing protein and fat malabsorption.
- Symptoms, if untreated, include frequent, bulky, greasy stools and failure to gain weight even when food intake appears to be large.
- A protuberant abdomen, decreased muscle mass, poor growth, and delayed maturation are classic and rarely seen physical signs.

- Supplementation with fat-soluble vitamin preparations has made deficiencies of vitamin A, E, and K unusual, but vitamin D deficiency continues to be prevalent and, although rickets is rare, osteoporosis is common, especially in older patients and those with more severe lung disease.

- Historically a relatively common event, rectal prolapse occurs much less frequently as the result of earlier diagnosis and initiation of pancreatic enzyme replacement therapy.

- Biliary Tract Infants may occasionally present with neonatal jaundice suggestive of biliary obstruction.
- Evidence for liver dysfunction is most often detected in the first 15 yr of life and can be found in up to 30% of individuals.
- Biliary cirrhosis becomes symptomatic in only 5–7% of patients.
- Manifestations can include icterus, ascites, hematemesis from esophageal varices, and evidence of hypersplenism.
- Biliary colic secondary to cholelithiasis may occur in the 2nd decade or later.
- Liver disease occurs independent of genotype but is associated with meconium ileus and pancreatic insufficiency.

- Cystic Fibrosis–Related Diabetes and Pancreatitis Endocrine pancreatic insufficiency tends to develop in the 2nd decade and beyond and is more common in patients with a family history of type II diabetes mellitus.
- It most commonly begins with postprandial hyperglycemia and may or may not be accompanied by weight loss or flattening weight gain.
- Fasting hyperglycemia and elevated hemoglobin A1c are later manifestations.
- 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 occasionally in individuals who have residual exocrine pancreatic function and may be the sole manifestation of homozygotic CFTR mutations.

- Genitourinary Tract Virtually all males are azoospermic because of failure of development of wolffian duct structures, but sexual function is generally unimpaired.
- The female fertility rate is diminished, especially in women who have poor nutrition or advanced lung disease.
- Pregnancy is generally tolerated well by women with good pulmonary function but may accelerate pulmonary progression in those with advanced lung problems and may lead to glucose intolerance.

- Urinary incontinence associated with cough occurs in 18–47% of female children and adolescents

- Sweat Glands 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 may present with hypochloremic alkalosis.
- Hyponatremia is a risk particularly in warm climates.
- Frequently, parents notice salt frosting of the skin or a salty taste when they kiss the child.
- A few genotypes are associated with normal sweat chloride values.

DIAGNOSIS AND ASSESSMENT

- The diagnosis of CF has been based on a positive quantitative sweat test (Cl^- ≥ 60 mEq/L) in conjunction with one or more of the following features:
  - identification of 2 CFTR mutations
  - typical chronic obstructive pulmonary disease
  - documented exocrine pancreatic insufficiency
  - a positive family history.

- With newborn screening, diagnosis is often made prior to obvious clinical manifestations such as failure to thrive and chronic cough.

Sweat Testing

- The sweat test, which involves using pilocarpine iontophoresis to collect sweat and performing chemical analysis of its chloride content, is the standard approach to diagnosis of CF.
- Infants with a positive newborn screen for CF should have the sweat chloride testing performed after 36-wk corrected gestational age and at a weight greater than 2 kg and at age greater than 10 days to increase the likelihood of sufficient sweat collection for an accurate study.
- Positive results should be confirmed; for a negative result, the test should be repeated if suspicion of the diagnosis remains.
- More than 60 mmol/L of chloride in sweat is diagnostic of CF when one or more other criteria are present.
- In individuals with a positive newborn screen, a sweat chloride level less than 30 mmol/L indicates that CF is unlikely.
- Borderline (or intermediate) values of 30-59 mmol/L have been reported in patients of all ages who have CF with atypical involvement and require further testing.

Table 432.3	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 (CF transmembrane regulator) dysfunction:

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

Table 432.4	Conditions Associated With False-Positive and False-Negative Sweat Test Results
WITH FALSE-POSITIVE RESULTS	
Eczema (atopic dermatitis)	
Ectodermal dysplasia	
Malnutrition/failure to thrive/deprivation	
Anorexia nervosa	
Congenital adrenal hyperplasia	
Adrenal insufficiency	
Glucose-6-phosphatase deficiency	
Mauriac syndrome	
Fucosidosis	
Familial hypoparathyroidism	
Hypothyroidism	
Nephrogenic diabetes insipidus	
Pseudohypoaldosteronism	
Klinefelter syndrome	
Familial cholestasis syndrome	
Autonomic dysfunction	
Prostaglandin E infusions	
Munchausen syndrome by proxy	
WITH FALSE-NEGATIVE RESULTS	
Dilution	
Malnutrition	
Edema	
Insufficient sweat quantity	
Hyponatremia	
Cystic fibrosis transmembrane conductance regulator mutations with preserved sweat duct function	

DNA Test

- DNA Testing Several commercial laboratories test for 30-96 of the most common CFTR mutations.
- This testing identifies ≥90% of individuals who carry 2 CF mutations.

- Other Diagnostic Tests The finding of increased potential differences across nasal epithelium (nasal potential difference) that is the increased voltage response to topical amiloride application, followed by the absence of a voltage response to a ß-adrenergic agonist, has been used to confirm the diagnosis of CF in patients with equivocal or frankly normal sweat chloride values.
- This testing is primarily used in research applications and has never undergone extensive validation as a clinical tool.

Pancreatic Function

- The diagnosis of pancreatic malabsorption can be made by the quantification of elastase-1 activity in a fresh stool sample by an enzyme-linked immunosorbent assay specific for human elastase.
- The quantification of fat malabsorption with a 72-hr stool collection is rarely necessary in the clinical setting.

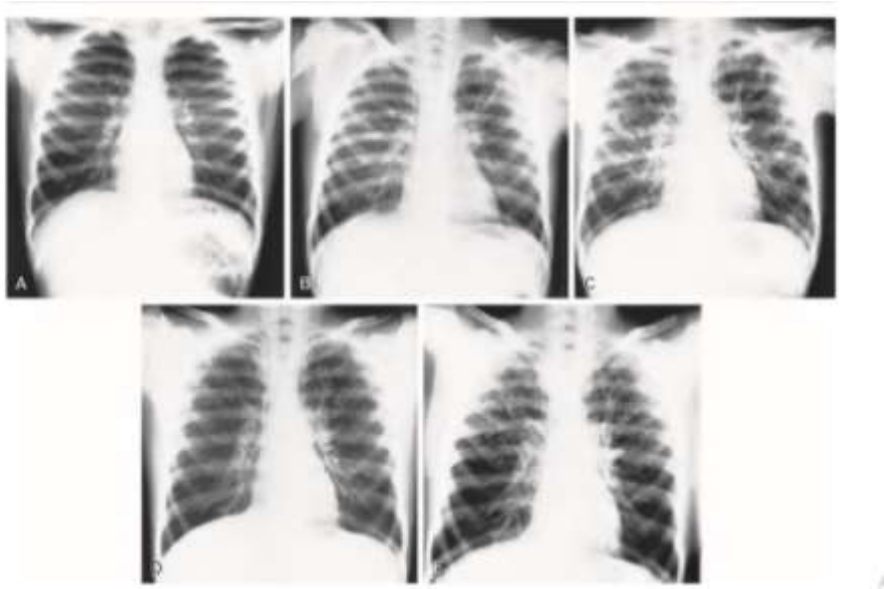
- CF-related diabetes affects approximately 20% of adolescents and 40–50% of adults, and clinical guidelines recommend yearly oral glucose tolerance testing (OGTT) after age 10.
- OGTT may sometimes be clinically indicated at an earlier age.
- Spot testing of blood and urine glucose levels and glycosylated hemoglobin levels are not sufficiently sensitive

- Radiology Hyperinflation of lungs occurs early and is often accompanied by nonspecific peribronchial thickening .
- Bronchial thickening and plugging and ring shadows suggesting bronchiectasis usually appear first in the upper lobes.
- Nodular densities, patchy atelectasis, and confluent infiltrate follow.
- Hilar lymph nodes may be prominent.
- With advanced disease, impressive hyperinflation with markedly depressed diaphragms, anterior bowing of the sternum, and a narrow cardiac shadow are noted

- Cyst formation, extensive bronchiectasis, dilated pulmonary artery segments, and segmental or lobar atelectasis is often apparent with advanced disease.
- Most CF centers obtain chest radiographs (posteroanterior [PA] and lateral) at least annually.
- Standardized scoring of radiologic changes has been used to follow progression of lung disease.
- CT of the chest can detect heterogeneous hyperinflation and localized thickening of bronchial airway walls, mucous plugging, focal hyperinflation, and early bronchiectasis .
- CT abnormalities are commonly seen at a young age, even in asymptomatic children with normal lung function.

- Radiographs of paranasal sinuses reveal panopacification and, often, failure of frontal sinus development.
- CT provides better resolution of sinus changes if this information is required clinically.

- Fetal ultrasonography may show pancreatic changes indicative of CF and suggest ileal obstruction with meconium early in the second trimester, but this finding is not predictive of meconium ileus at birth



- Standard pulmonary function studies are usually obtained starting at about 4 yr of age and are routinely done by age 6.
- Forced expiratory volume in 1 sec (FEV1) is the measurement that has been shown to correlate most closely with mortality and shows a gradual decline averaging 2–3% per year throughout childhood.

Microbiologic Studies

- H. influenza and S. aureus are the most common organisms recovered in young children .
- Pseudomonas may be acquired early and is eventually an organism of key significance.
- P. aeruginosa appears to have a special propensity for the CF airway and over time characteristically develops a biofilm associated with a mucoid appearance in the microbiology lab and which correlates with more rapid progression of lung disease.
- Once P. aeruginosa develops a mucoid phenotype, it is extremely difficult to eradicate from the airway.

Newborn Screening

- Most algorithms use a combination of immunoreactive trypsinogen (IRT) results and limited DNA testing on blood spots; because not all mutations can be found using this approach, babies with an elevated IRT and a single detected mutation are considered a positive screen, and all positive screens are followed by a confirmatory sweat analysis.
- Newborn diagnoses can prevent early nutritional deficiencies and improve long-term growth and may improve cognitive function.
- Importantly, good nutritional status (50 percentile weight for length or 50 percentile body mass index) is associated with better lung function at 6 yr of age.