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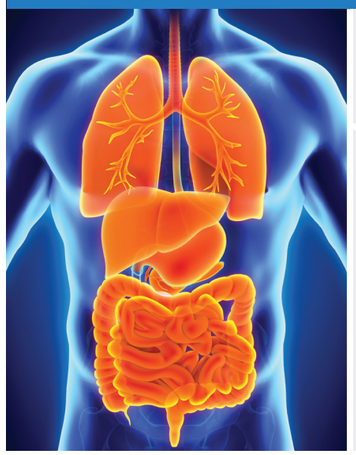
PROGRESSION OF CYSTIC FIBROSIS–RELATED ORGAN DAMAGE

	FETUS	INFANT (< 2 yrs)	CHILD (2–12 yrs)	ADOLESCENT (13–18 yrs)	YOUNG ADULT	OLDER ADULT
RESPIRATORY SYSTEM						
DISEASE FEATURES	Airway inflammation					
	↓ Tracheal size	Mucus stasis Airflow obstruction Bacterial infection and colonization Bronchiectasis				
	↓ Small airway distension					
			Parenchymal destruction			
POSSIBLE CLINICAL MANIFESTATIONS	Mucus hypersecretion in submucosal glands	Recurrent bacterial and viral infections Pulmonary exacerbations				
			Exercise limitation			
				Complications (eg, pneumothorax, hemoptysis, respiratory failure)		
GASTROINTESTINAL SYSTEM						
DISEASE FEATURES						
Intestines	Abnormal intestinal lining and mucus obstruction					
		Intestinal fat and fat-soluble vitamin malabsorption Bacterial overgrowth Inflammation and mucosal damage				
Liver		Cholestasis, biliary obstruction Hepatocyte and biliary tree injury Liver inflammation and fibrosis				
Pancreas	Pancreatic ductule obstruction					
		Pancreatic acinar cell destruction → ↓ HCO_3^-, ↓digestive enzyme secretion Pancreatic beta cell destruction → ↓ insulin production Pancreatic inflammation and fibrosis; replacement with adipose tissue				
POSSIBLE CLINICAL MANIFESTATIONS	Intestinal atresia Meconium ileus		Distal intestinal obstruction syndrome (DIOS) Small-intestine bacterial overgrowth			
		Hepatomegaly, hepatic steatosis, cholestasis Pancreatic insufficiency Nutritional/growth deficiencies				
			Cholecystitis, cholelithiasis Cirrhosis Pancreatitis CF-related diabetes			
						Colorectal and liver cancers

CFTR MODULATOR THERAPY FOR CYSTIC FIBROSIS*

MODULATOR	MECHANISM OF ACTION	AGE GROUP	CFTR MUTATIONS
IVACAFTOR	CFTR potentiator	≥ 1 year	**Ivacaftor is approved for patients aged ≥ 1 year who have 1 of the following mutations:** • **Gating Mutations** | G178R, G1244E, S549R, G551D, G1349D, S1251N, G551S, S549N, S1255P • **Residual Function Mutations** | A455E, E193K, R117C, A1067T, F1052V, R347H, D110E, F1074L, R352Q, D110H, G1069R, R1070Q D579G, K1060T, R1070W, D1152H, L206W, S945L, D1270N, P67L, S977F, E56K, R74W • **Splice Mutations** | 711+3A>G, 3272-26A>G, E831X, 2789+5G>A, 3849+10kbC>T • **Conduction Mutation** | R117H
LUMACAFTOR/IVACAFTOR	CFTR corrector (lumacaftor) plus a CFTR potentiator (ivacaftor)	≥ 2 years	**Lumacaftor/ivacaftor is approved for patients aged ≥ 2 years who have 2 copies of the F508del mutation, which is the most common CF mutation.** • **Protein Processing Mutation** | F508del
TEZACAFTOR/IVACAFTOR	CFTR corrector (tezacaftor) plus a CFTR potentiator (ivacaftor)	≥ 12 years	**Tezacaftor/ivacaftor is approved for patients aged ≥ 12 years who have 2 copies of the F508del mutation (a protein processing mutation) or who have at least a single copy of 1 of the following mutations:** • **Residual Function Mutations** | A455E, E56K, R74W, A1067T, E193K, R117C, D110E, F1052V, R347H, D110H, F1074L, R352Q, D579G K1060T, R1070W, D1152H, L206W, S945L, D1270N, P67L, S977F • **Splice Mutations** | 711+3A>G, 3272-26A>G, E831X, 2789+5G>A, 3849+10kbC>T

INTERVENTIONS THAT SLOW CF PROGRESSION OR IMPROVE ORGAN FUNCTION



Organ damage in CF starts in utero and progresses across the lifespan. The rate of progression depends on the CF genotype, environmental factors, and the timing of CF therapies. Guidelines on the diagnosis and treatment of CF are available from the Cystic Fibrosis Foundation at cff.org

- **Early diagnosis**
- **Early routine, multidisciplinary CF care**
  - Airway clearance measures
  - Mucus thinners
  - Appropriate antibiotic treatment
  - Anti-inflammatory medications
  - Pancreatic enzyme supplements
  - Nutritional supplements
  - Dietary modifications
  - Behavioral therapy and education
- **CFTR modulator therapy**

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References: Cystic Fibrosis Foundation clinical care guidelines, available at cff.org (accessed Sept 21, 2018). VanDevanter DR, et al. J Cystic Fibrosis. 2016;15:147-57. Grasemann H, Ratjen F. Lancet Respir Med. 2013;1:148-157. Meyerholz DK, et al. Am J Respir Crit Care Med. 2010;182:1251-61. Ramsey BW, et al. Am J Respir Crit Care Med. 2012;185:887-92. Ooi CY, Durie PR. Nat Rev Gastroenterol Hepatol. 2016;13:175-85. Li L, Somerset S. Dig Liver Dis. 2014;46:865-74. Sturgess JM. J Pediatr Gastroenterol Nutr. 1984;3:S55-S66.

* FDA prescribing information for ivacaftor, lumacaftor/ivacaftor, and tezacaftor/ivacaftor is available at fda.gov (accessed Sept 21, 2018).

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