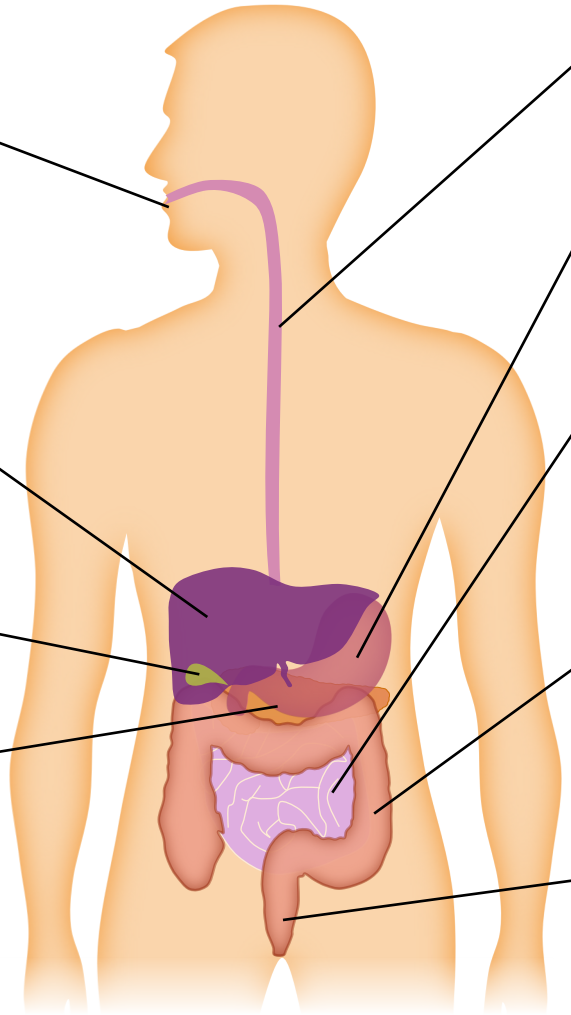
Cystic Fibrosis and GI Manifestations

Objectives

- Explain the role of cystic fibrosis transmembrane conductance regulator (CFTR) in the gastrointestinal (GI) tract
  - Normal GI function
  - Pathophysiology of GI changes in cystic fibrosis (CF)
- Discuss the clinical signs and symptoms of CF in the GI tract
- Review the natural history of CF-related GI disorders
- Discuss GI cancers in patients with CF

VERTEX

Main Functions of GI Tract: Digestion, Absorption, and Waste Excretion[1,2]



Mouth and salivary glands
- Mechanical breakdown of food
- Secretion of enzymes that initiate carbohydrate breakdown

Accessory GI organs

Liver
- Production of bile, which emulsifies fats
- Protein synthesis
- Detoxification

Gall bladder
- Storage of bile
- Secretion of bile into small intestine

Pancreas (exocrine)
- Production and secretion of enzymes and bicarbonate ions into small intestine

Esophagus
- Movement of food from mouth to stomach

Stomach
- Secretion of acids for digestion
- Mixing of food and secretions

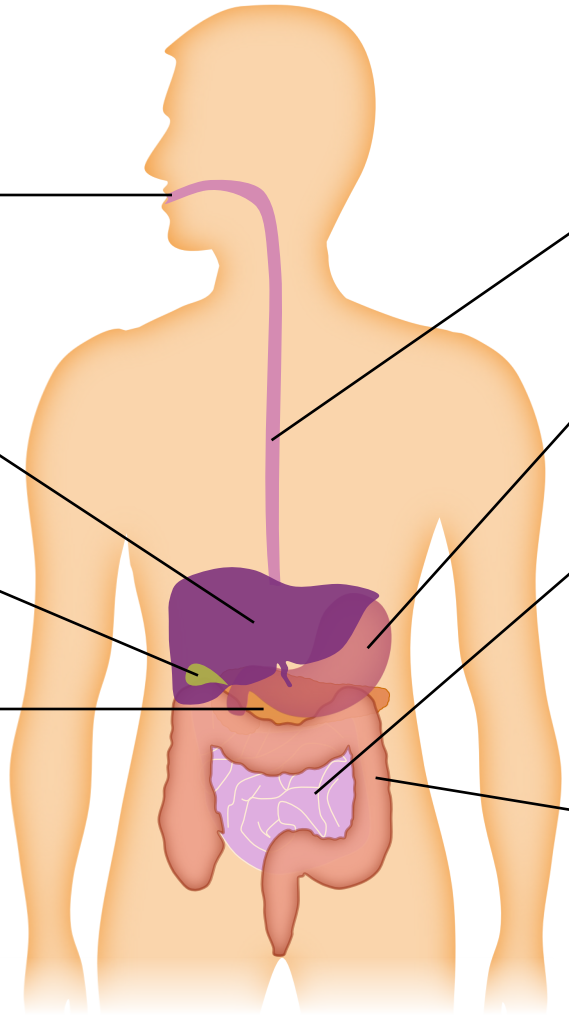
Small intestine
- Digestion of proteins, fats, and carbohydrates
- Absorption of nutrients and fluids
- Movement of contents to the large intestine

Large intestine
- Absorption of fluids
- Formation, storage, and mobilization of stool to the rectum

Rectum and anus
- Brief storage of stool
- Regulates waste elimination

1. National Institutes of Health. The Digestive System and How It Works. https://www.niddk.nih.gov/health-information/digestive-diseases/digestive-system-how-it-works. Accessed April 2020. 2. PubMed Health. National Library of Medicine, National Institutes of Health. How does the liver work? https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0072577. Accessed April 2020.

CFTR Is Expressed Throughout Most of the GI Tract



Salivary glands
- Submandibular and parotid duct cells[1]

Liver
- Bile duct epithelial cells[4]

Gall bladder
- Lumenal epithelial cells[3]

Pancreas
- Duct cells[3]
- Insulin secreting β-cells[5]

Esophagus
- Submucosal gland duct cells[2]

Stomach
- Low level diffuse staining in gastric mucosa[3]

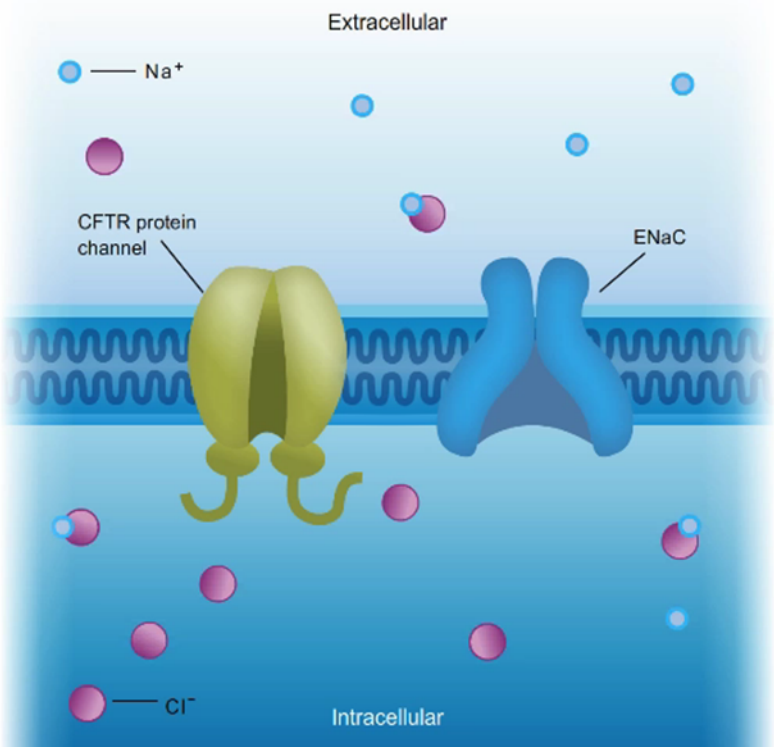
Small intestine
- Epithelial cells, multiple types[3]
- High levels in duodenum, decreasing toward large intestine[3]

Large intestine
- Epithelial cells, highest levels at base of crypts[3]

1. Zinn VZ et al. *Eur J Oral Sci.* 2015(3);123:140-148. 2. Abdulnour-Nakhoul S et al. *Am J Physiol Regul Integr Comp Physiol*. 2011;301(1):R83-R96.
3. Strong TV et al. *J Clin Investig*. 1994;93(1):347-354. 4. Cohn JA et al. *Gastroenterology*. 1993;105(6):1857-1864. 5. Guo JH et al. *Nat Commun.* 2014;5:4420.

CFTR Channels Regulate Fluid and Electrolyte Balance in Epithelial Tissues

CFTR channels act in tandem with ENaC to regulate fluid and electrolyte balance[1,2]

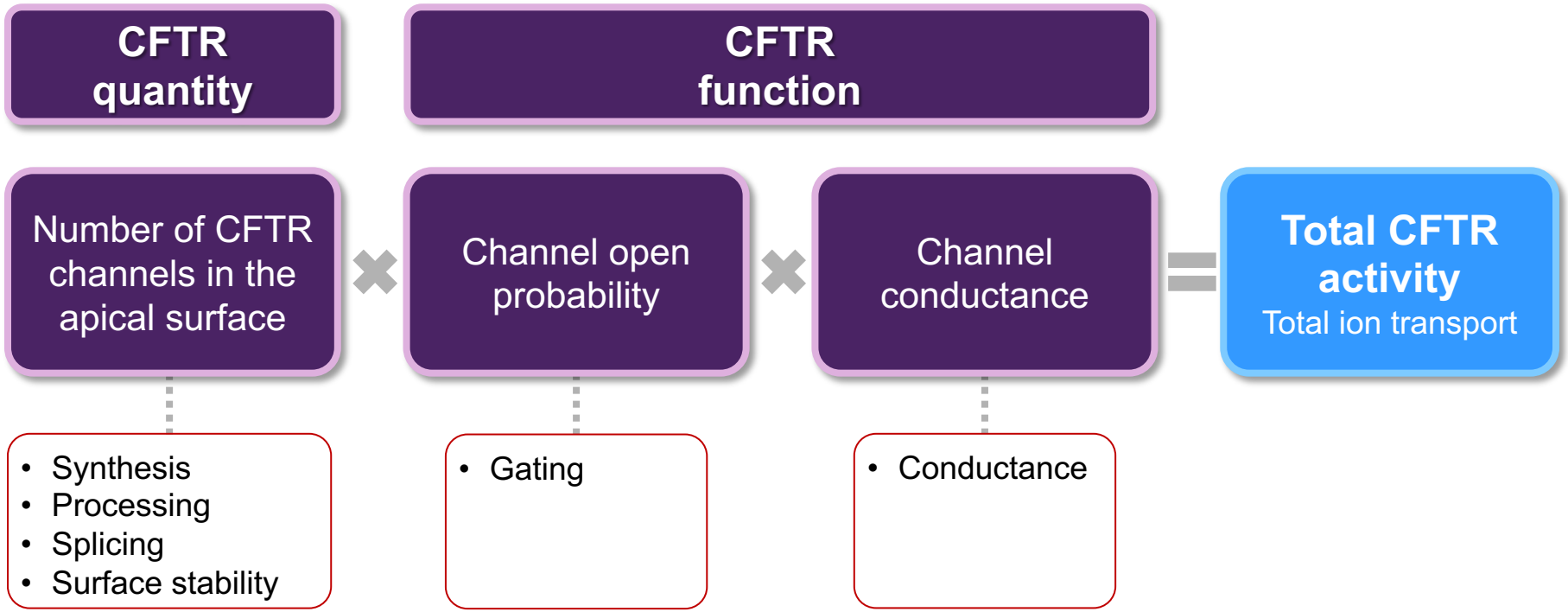


CFTR gene mutations can result in CFTR protein channel abnormalities—the underlying defect of CF disease[3]

ENaC, epithelial sodium channel.

1. MacDonald KD et al. *Paediatr Drugs.* 2007;9(1):1-10. 2. Goralski JL et al. *Curr Opin Pharmacol.* 2010;10(3):294-299. 3. Rowe SM et al. *N Engl J Med.* 2005;352(19):1992-2001.

Total CFTR Activity Is Determined by the Quantity and Function of CFTR Channels at the Cell Surface[1,2]

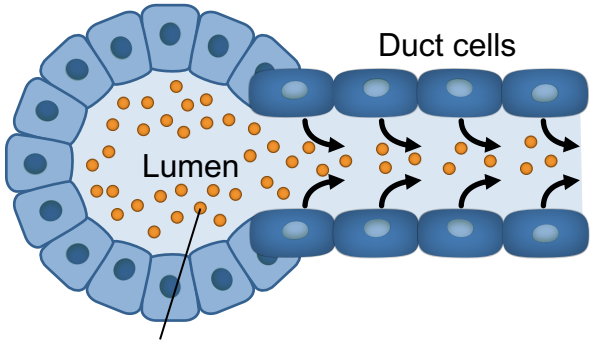


1. Zielenski J. *Respiration.* 2000;67(2):117-133. 2. Boyle MP, De Boeck K. *Lancet Respir Med.* 2013;1(2):158-163.

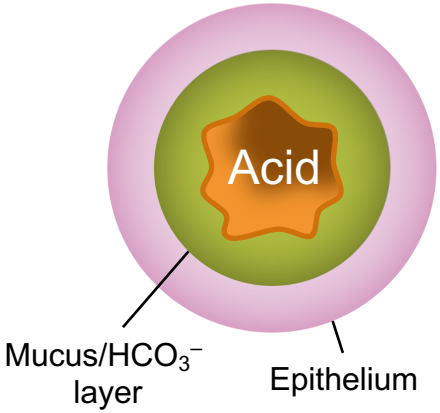
CFTR Facilitates Secretion, Protects Epithelium, and Neutralizes pH in the GI Tract

CFTR
Cl^- and HCO_3^- Transporter

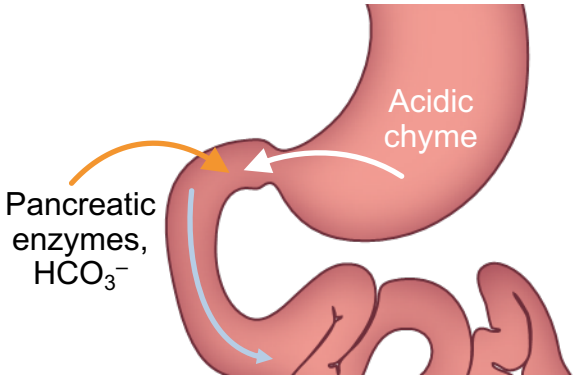
GI secretory functions
(eg, in salivary glands, pancreas)[1,2]



Epithelial protection
(eg, in esophagus, stomach, duodenum)[3-5]



pH neutralization
(eg, in duodenum)[6]



Duodenal pH neutralized

1. Wilschanski M, Durie PR. *Gut*. 2007;56(8):1153-1163. 2. Frizzell RA, Hanrahan JW. *Cold Spring Harb Perspect Med*. 2012;2(6):a009563. 3. Garcia MA et al. *J Clin Invest*. 2009;119(9):2613-2622. 4. Chen EY et al. *Am J Physiol Lung Cell Mol Physiol*. 2010;299(4):L542-L549. 5. Abdulnour-Nakhoul S et al. *Am J Physiol Regul Integr Comp Physiol*. 2011;301(1):R83-R96. 6. Pandol SJ. *The Exocrine Pancreas*. San Rafael (CA): Morgan & Claypool Life Sciences; 2010.

Pathophysiology of CF in the GI Tract

CFTR Gene Mutations Give Rise to CFTR Protein Channel Defects That Reduce Cl^- and Other Ion Transport

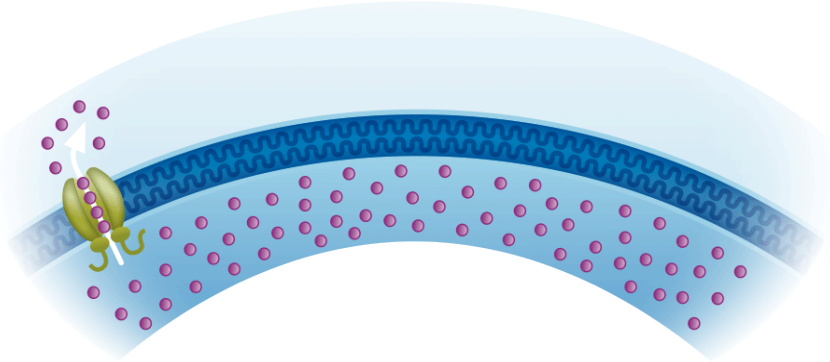
CFTR quantity

Number of CFTR channels in the apical surface

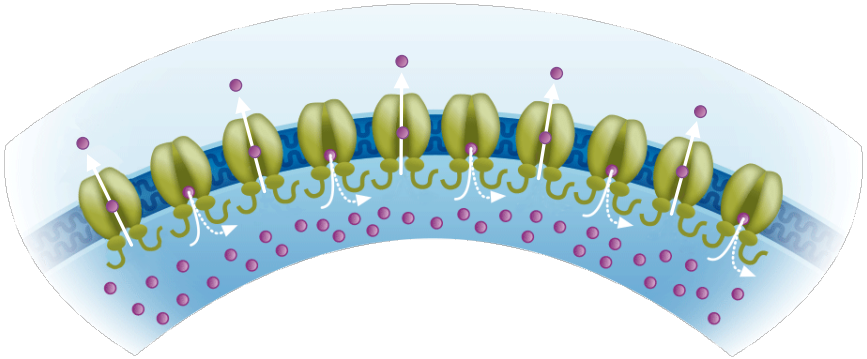
CFTR function

Channel open probability ✖ Channel conductance

Mutations that reduce the **QUANTITY** of functional CFTR proteins that reach the apical cell surface



Mutations that reduce the **FUNCTION** of CFTR proteins at the apical cell surface

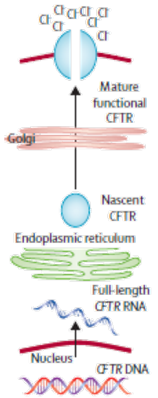
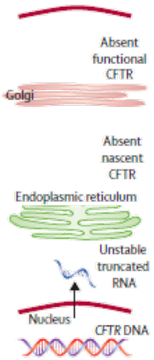
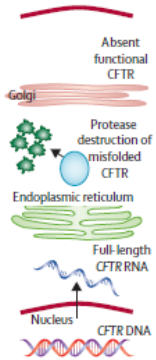
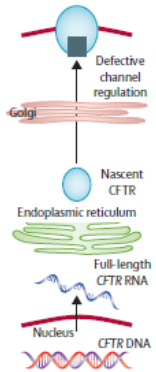
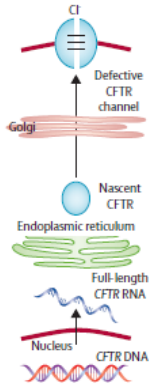
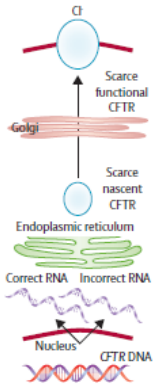
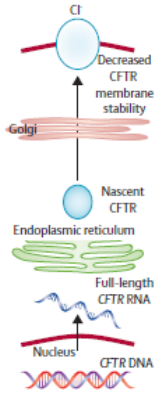


- CFTR channels conduct bicarbonate in addition to chloride ions

MacDonald KD et al. *Paediatr Drugs.* 2007;9(1):1-10.

VERTEX

CFTR Mutations Have Traditionally Been Classified I-VI Based on the Types of Molecular Defects

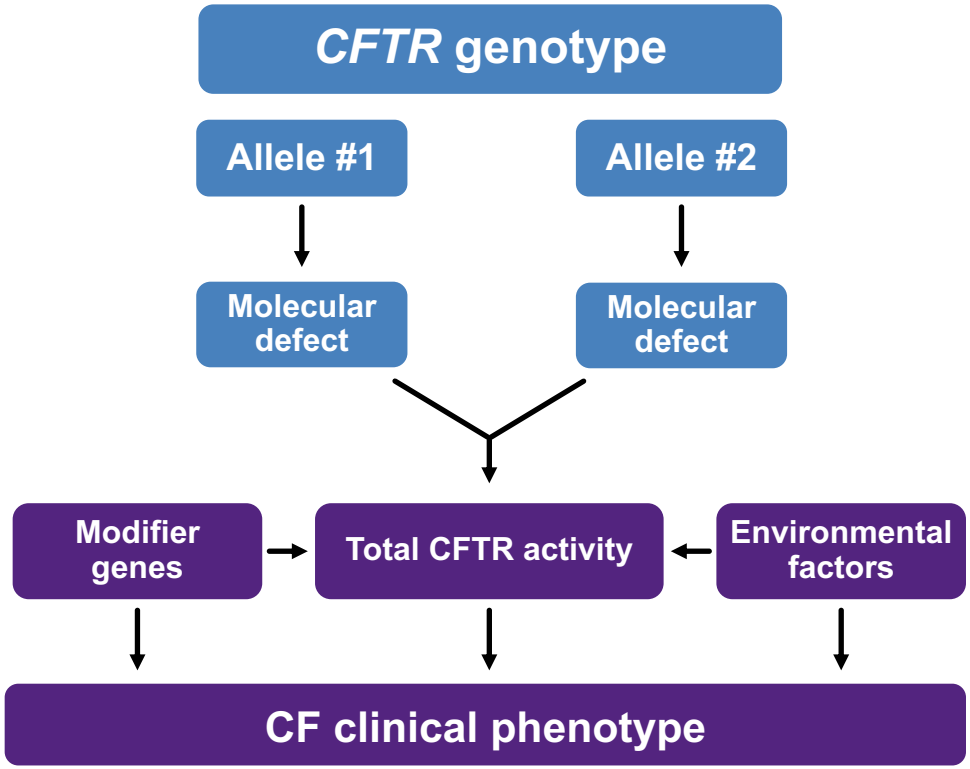
Normal	I	II	III	IV	V	VI
						
CFTR defect	No synthesis	Processing/ trafficking defect	Gating defect	Conductance defect	Reduced synthesis	Surface stability defect
Type of mutations	Nonsense, frameshift, canonical splice	Missense, amino acid deletion	Missense, amino acid change	Missense, amino acid change	Missense, non-canonical splice	Missense, amino acid change

Reprinted from *The Lancet Respiratory Medicine*, 1(2), Boyle MP, De Boeck K, A new era in the treatment of cystic fibrosis: correction of the underlying CFTR defect, 158-163, 2013, with permission from Elsevier.
Boyle MP, De Boeck K. *Lancet Respir Med*. 2013;1(2):158-163.

VERTEX

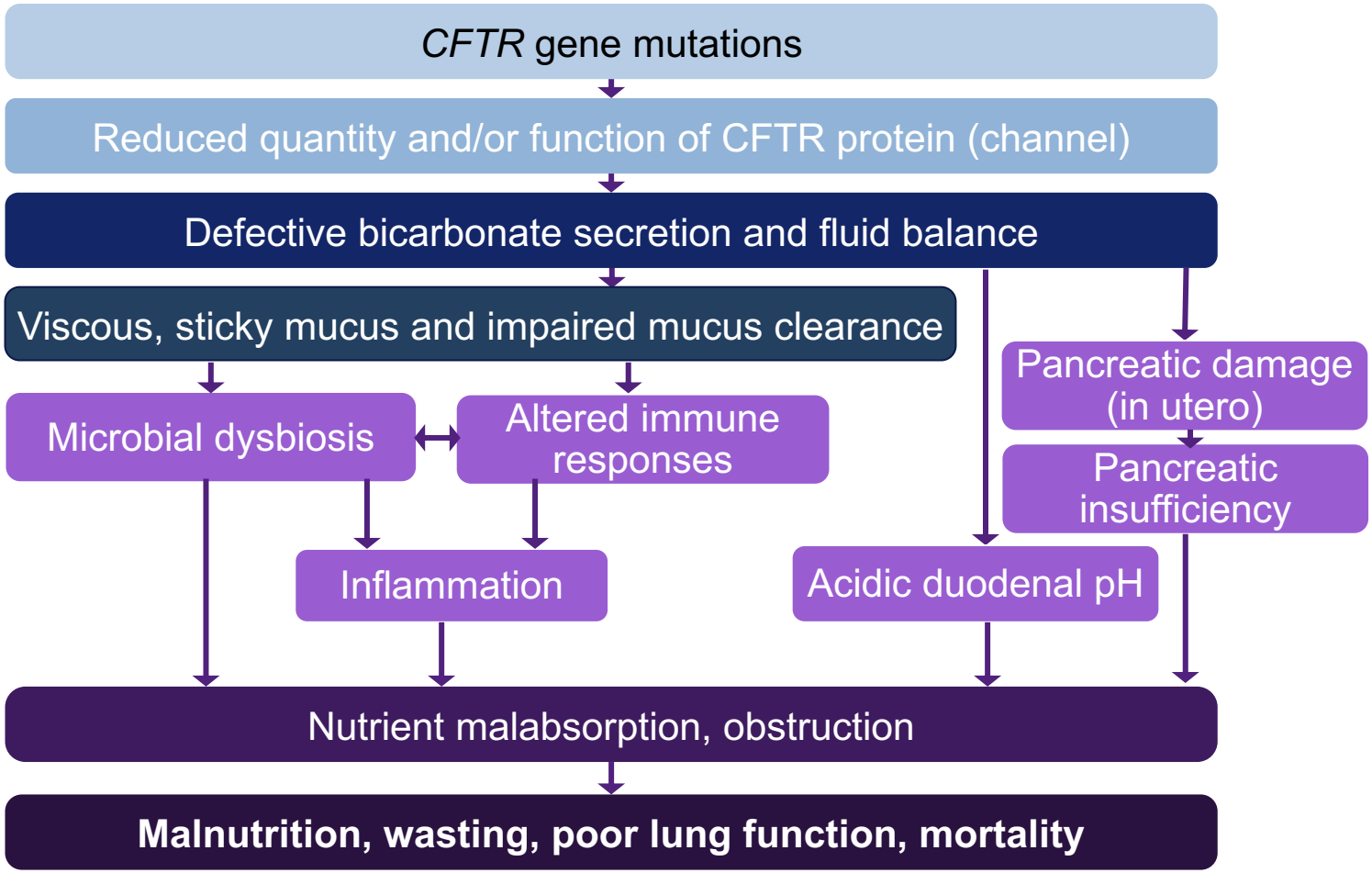
Clinical Phenotype Is Influenced by Multiple Factors

- ***CFTR* genotype and the resulting amount of total CFTR activity[1,2]**
  - Generally, 2 mutations with little or no CFTR activity are associated with a more classic phenotype. The presence of a complex allele may also contribute to reduction in CFTR activity
- **Modifier genes[3]**
  - Many genes have been identified that affect organ function and impact disease manifestations (eg, *SLC26A9*, *SLC9A3*, and *SLC6A14*)
- **Environmental factors[4]**
  - Exposure to cigarette smoke and other toxins; pulmonary bacterial colonization and infection may affect phenotype and longevity



de Gracia J et al. *Thorax*. 2005;60(7):558-563. 2. Castellani C et al. *J Cyst Fibros*. 2008;7(3):179-196. 3. Cutting GR et al. *Nat Rev Genet*. 2015;16(1):45-56. 4. Cutting GR. *Annu Rev Genomics Hum Genet*. 2005;6:237-260.

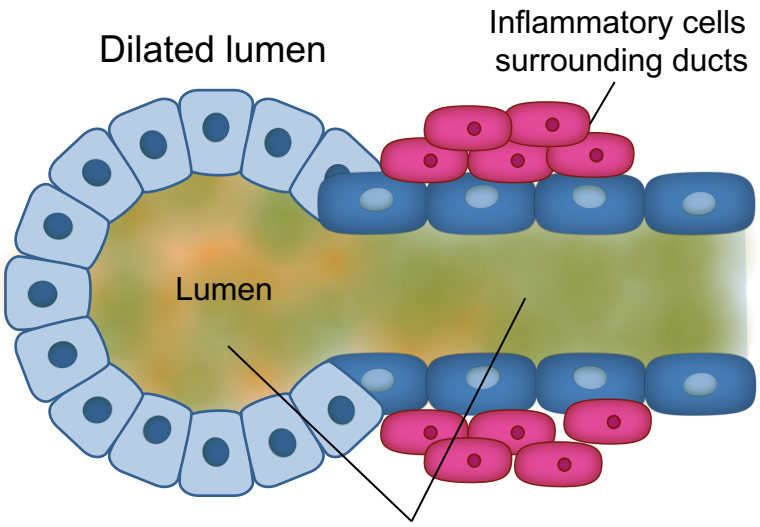
Cascade of CF GI Manifestations May Lead to Malnutrition, Poor Lung Function, and Mortality



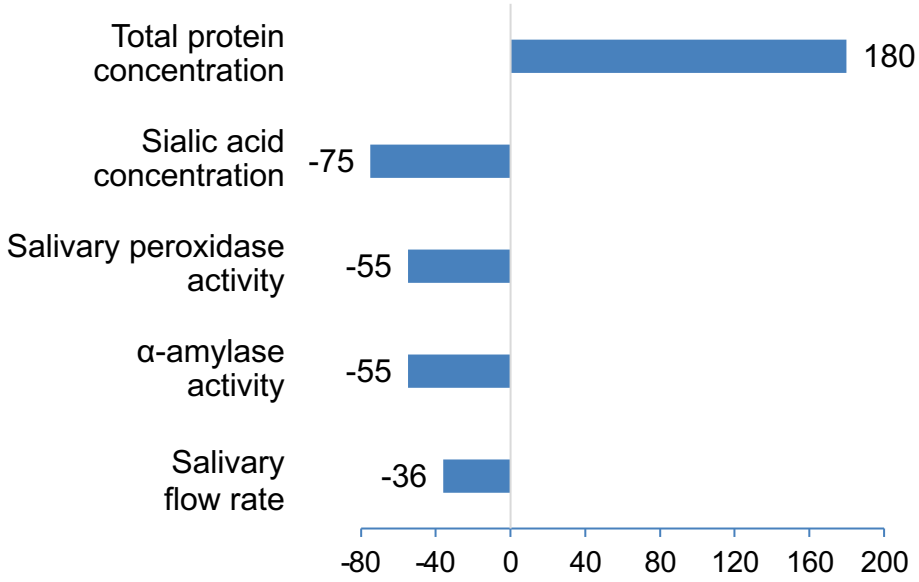
De Lisle RC, Borowitz D. *Cold Spring Harb Perspect Med.* 2013;3(9):a009753.

CFTR Defects Lead to Loss of Secretory Acini in the Salivary Glands and Altered Salivary Parameters

Progressive loss of serous acini in a mouse model[1]



Salivary parameters in children with CF vs controls[2]



CF group n=21; control group n=28
Mean (SD) age: 9 (2) years

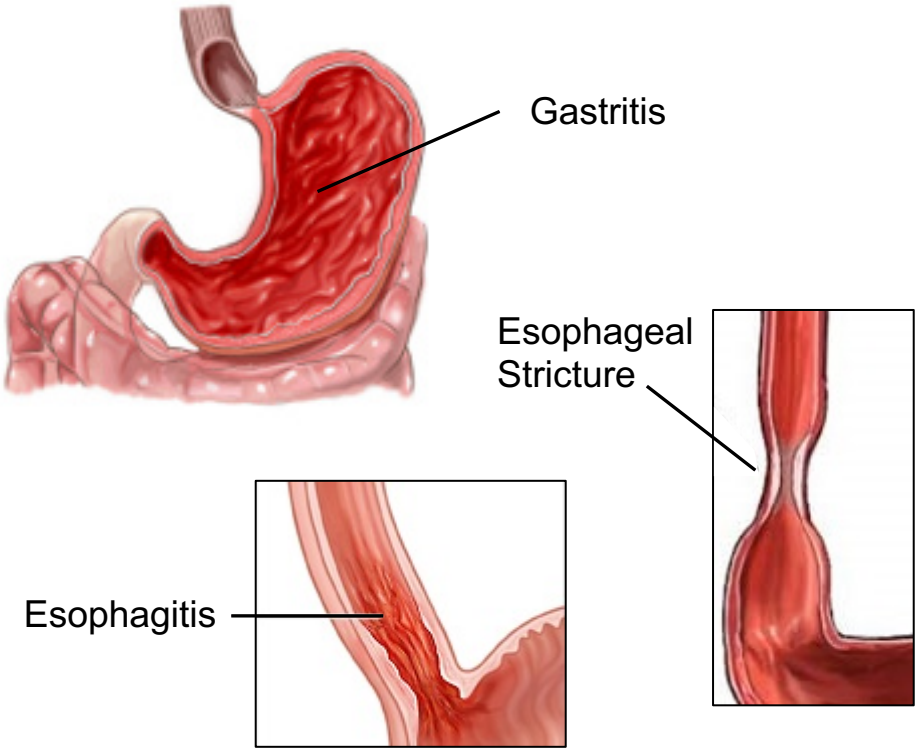
Clinical implications

- Decreased oral antimicrobial activity (α-amylase, peroxidase), antioxidant activity (peroxidase), and glycoprotein barrier (sialic acid) increase susceptibility to oral diseases, caries, and periodontal disease[2]

1. Durie PR et al. *Am J Pathol.* 2004;164(4):1481-1493. 2. da Silva Modesto KB et al. *Arch Oral Biol.* 2015;60(11):1650-1654.

CFTR Defects Contribute to the Upper GI Tract Manifestations of CF

CFTR-related upper GI consequences of CF[1]

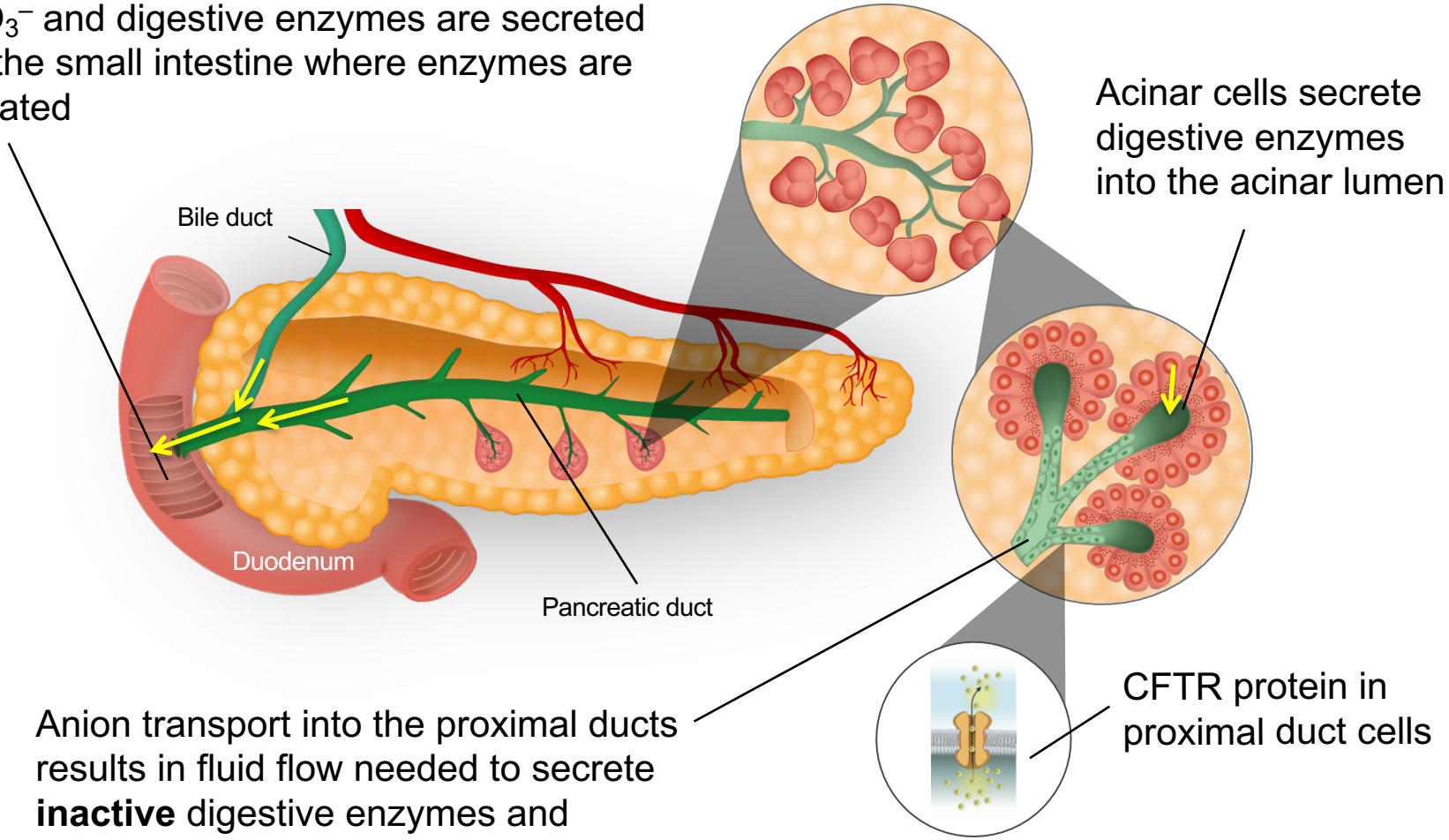


- Evidence includes
  - CFTR expression in the esophagus and stomach[2,3]
  - Role of HCO_3^- secretion from esophageal and gastric glands[2,4]
  - Role of esophageal and gastric mucus to protect from acid related tissue injury[2,5]

1. Wilschanski M, Durie PR. *Gut.* 2007;56(8):1153-1163. 2. Abdulnour-Nakhoul S et al. *Am J Physiol Regul Integr Comp Physiol.* 2011;301(1):R83-R96. 3. Strong TV et al. *J Clin Invest.* 1994;93(1):347-354. 4. Elberle JA et al. *Front Physiol.* 2013;4:1-10. 5. Garcia MA et al. *J Clin Invest.* 2009;119(9):2613-2622.

Pancreatic CFTR Secretes HCO_3^- and Digestive Enzymes into the Small Intestine[1,2]

HCO_3^- and digestive enzymes are secreted into the small intestine where enzymes are activated



Anion transport into the proximal ducts results in fluid flow needed to secrete **inactive** digestive enzymes and HCO_3^- to neutralize acids

1. Pandol SJ. *The Exocrine Pancreas*. San Rafael (CA): Morgan & Claypool Life Sciences; 2010. 2. Wilschanski M, Durie PR. *Gut*. 2007;56(8):1153-1163.

CFTR Defects Lead to Loss of HCO_3^- and Enzyme Secretion, and Pancreatic Insufficiency

Defective CFTR leads to deficient luminal HCO_3^- secretion, which leads to increased viscosity and precipitation of secreted proteins resisting flow of digestive enzymes and fluids into the small intestine[1]

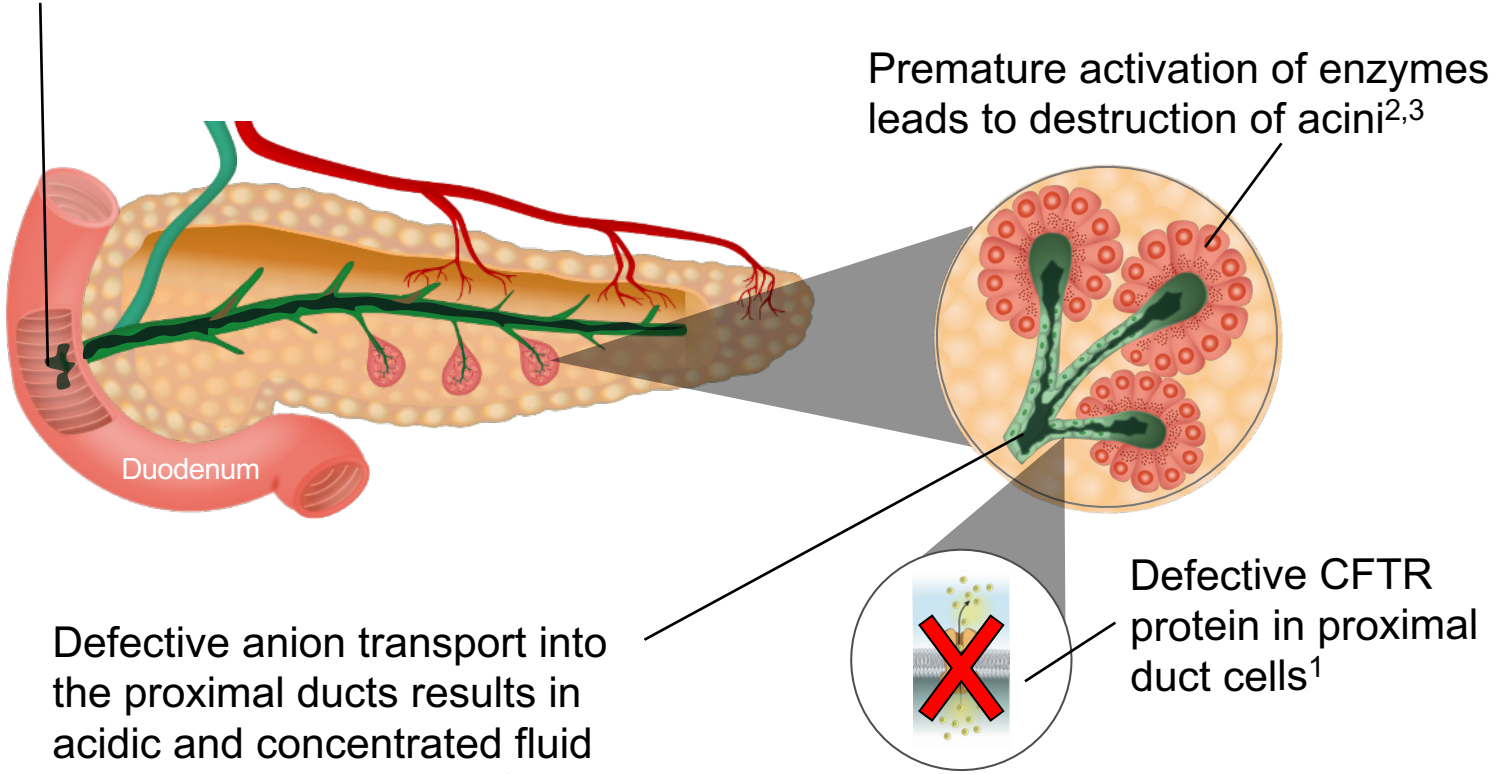


Figure adapted from Pandol SJ. *The Exocrine Pancreas*. San Rafael (CA): Morgan & Claypool Life Sciences; 2010.

1. Wilschanski M, Durie PR. *Gut.* 2007;56(8):1153-1163. 2. Abu-El-Haija M et al. *Am J Pathol.* 2012;181(2):499-507. 3. Sendler M et al. *Gut.* 2013;62(3):430-439.

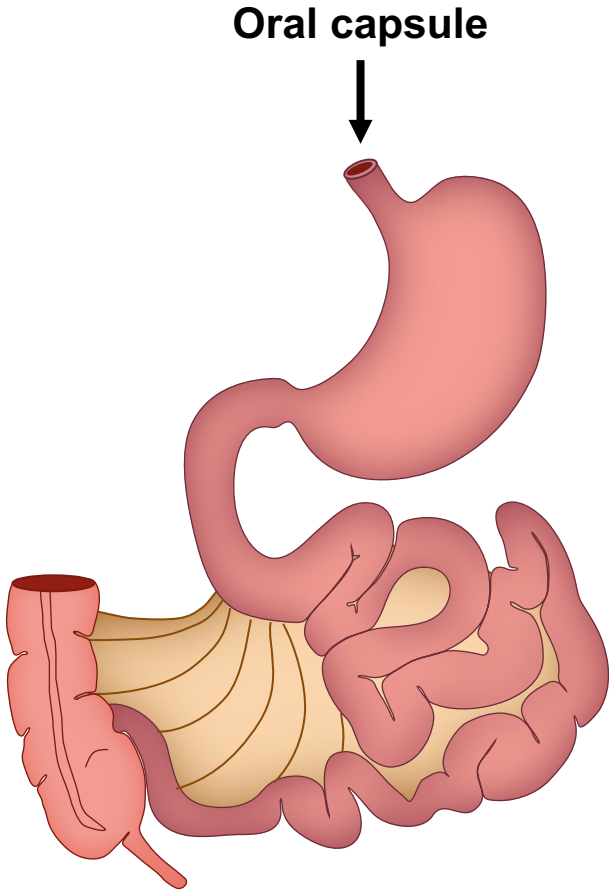
Wireless Motility Capsule Measures pH and Transit Time in Patients With CF

- Transit time can be determined based on temperature and pH landmarks of the stomach, small intestine, and colon
- GI pH assessment reveals deficient neutralization of the acidic milieu in the duodenum, correlating to decreased HCO_3^- secretion in CF

Wireless motility capsule

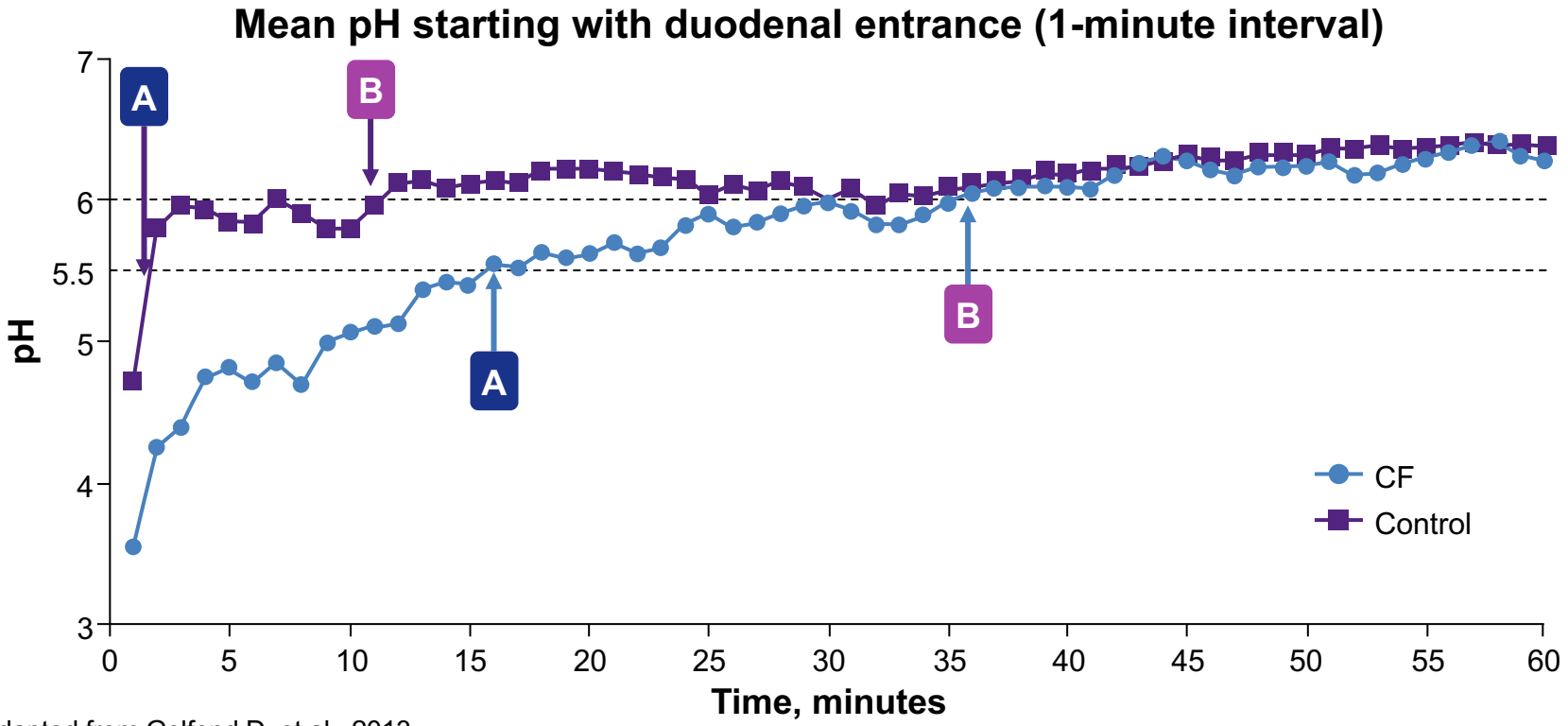
Image courtesy of Daniel Gelfond, MD

Wireless motility capsule



Bodewes FA et al. *J Cyst Fibros*. 2015;14(2):169-177.

Patients With CF Have Delayed Neutralization of Duodenal pH Measured by Wireless Motility Capsule

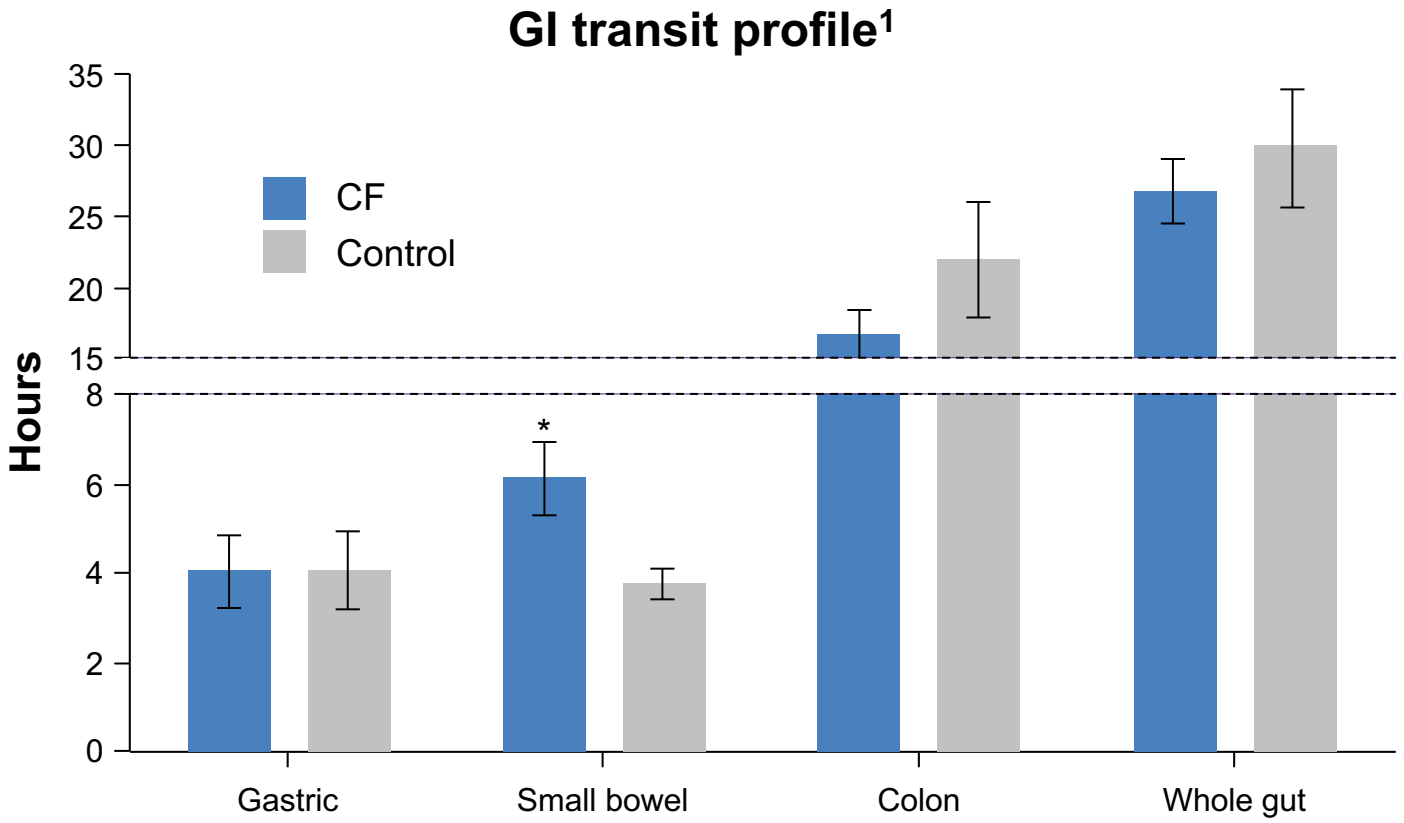


Adapted from Gelfond D, et al., 2013.

- Significant differences between groups in time to maintain pH >5.5 A and pH >6.0 B (P<0.001)
- Inadequate acid neutralization likely contributes to the nutritional deficiencies and various GI symptoms prevalent in patients with CF

Reprinted from *Digestive Diseases and Sciences*, Intestinal pH and gastrointestinal transit profiles in cystic fibrosis patients measured by wireless motility capsule, 58, 2013, 2275-2281, Gelfond D et al, with permission of Springer.
Gelfond D et al. *Dig Dis Sci*. 2013;58(8):2275-2281.

Small Bowel Transit Time Is Increased in Patients With CF With Pancreatic Insufficiency vs Healthy Controls



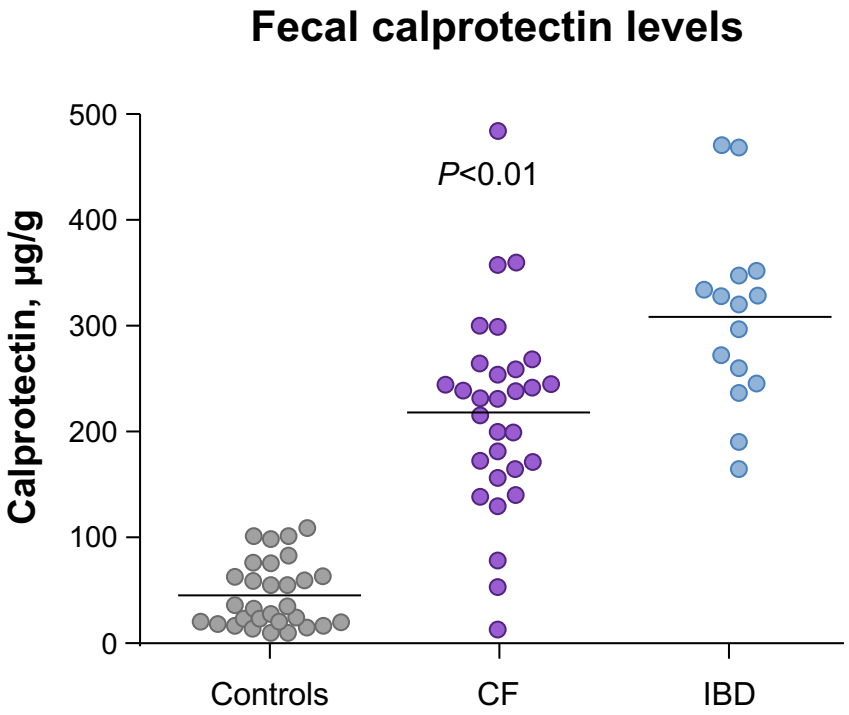
- Delayed small bowel transit observed in this and other studies in patients with CF taking pancreatic enzyme supplementation[1-3]

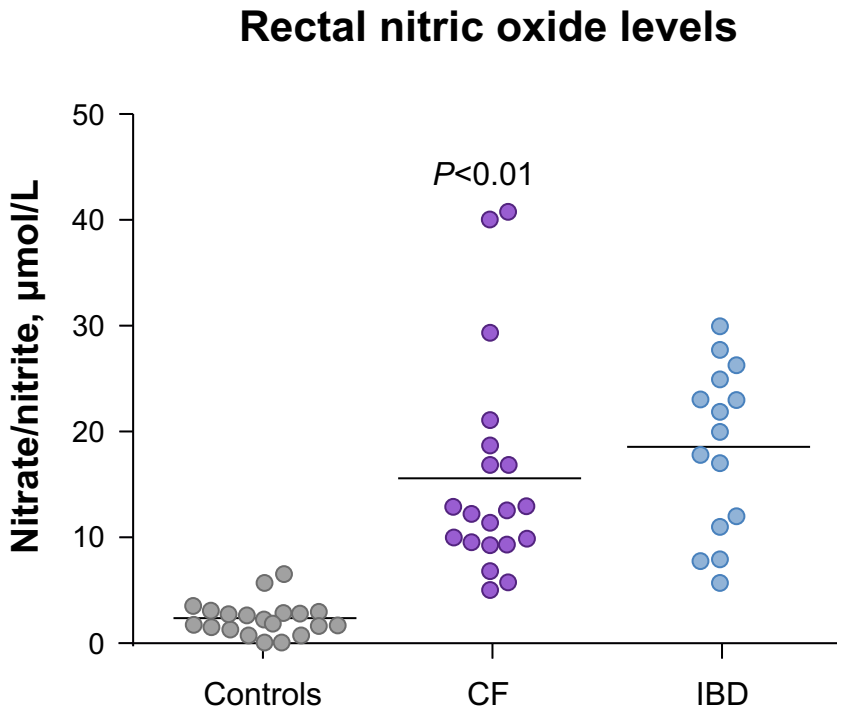
*P=0.004.

Reprinted from *Digestive Diseases and Sciences*, Intestinal pH and gastrointestinal transit profiles in cystic fibrosis patients measured by wireless motility capsule, 58, 2013, 2275-2281, Gelfond D et al, with permission of Springer.

1. Gelfond D et al. *Dig Dis Sci*. 2013;58(8):2275-2281. 2. Hedsund C et al. *Scand J Gastroenterol*. 2012;47(8-9):920-926. 3. Rovner AJ et al. *J Pediatr Gastroenterol Nutr*. 2013;57(1):81-84.

Markers of GI Inflammation Are Elevated in Patients With CF

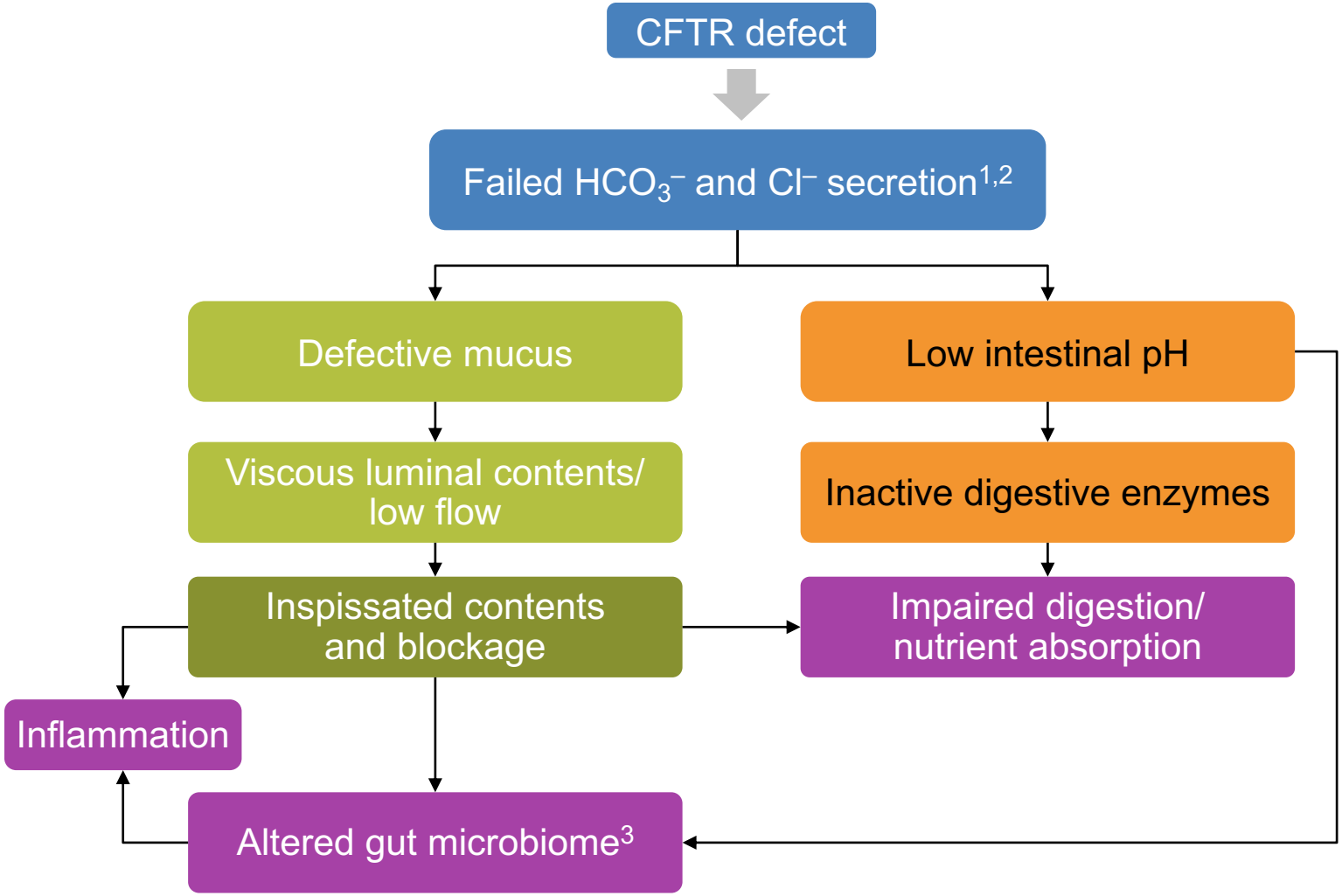




- Children with CF had a significantly higher incidence of intestinal inflammation vs controls as determined by levels of fecal calprotectin and rectal nitric oxide
- Incidence of intestinal inflammation was higher in children with CF and children with inflammatory bowel disease compared with controls

IBD, inflammatory bowel disease.
Reprinted from Bruzzese E et al, Intestinal inflammation is a frequent feature of cystic fibrosis and is reduced by probiotic administration. © 2004 Blackwell Publishing Ltd, *Aliment Pharmacol Ther* 20, 813–819.
Bruzzese E et al. *Aliment Pharmacol Ther.* 2004;20(7):813-819.

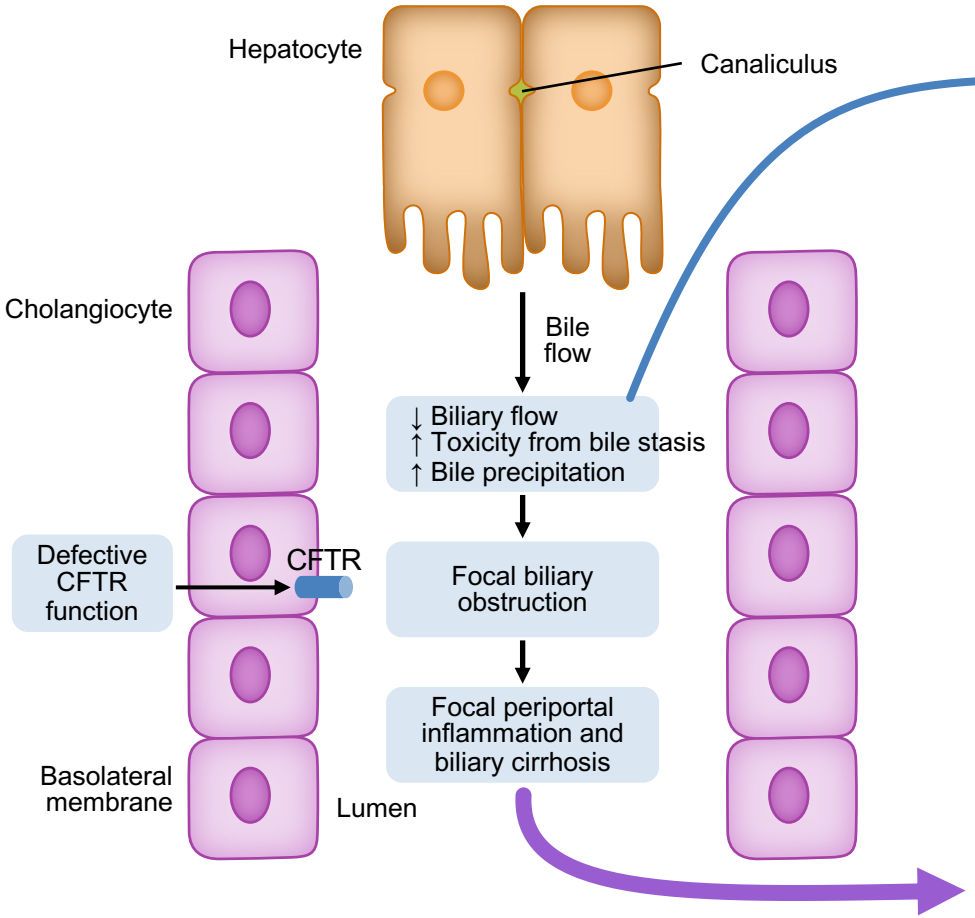
CFTR Deficits Lead to Thick, Inspissated Mucus, Acidic pH, Impaired Digestion, and Dysbiosis in the Intestines



1. Borowitz D. *Pediatr Pulmonol*. 2015;50(Suppl 40):S24-S30. 2. Ooi CY, Durie PR. *Nat Rev Gastroenterol Hepatol*. 2016;13(3):175-185. 3. Schippa S et al. *PLoS One*. 2013;8(4):e61176.

CFTR Defects Lead to Hepatobiliary Disease and Manifestations in the GI Tract

CFTR defects may lead to liver disease[1]



↓ bile flow, ↓ bile pH, and ↑ bile precipitation may contribute to[2]

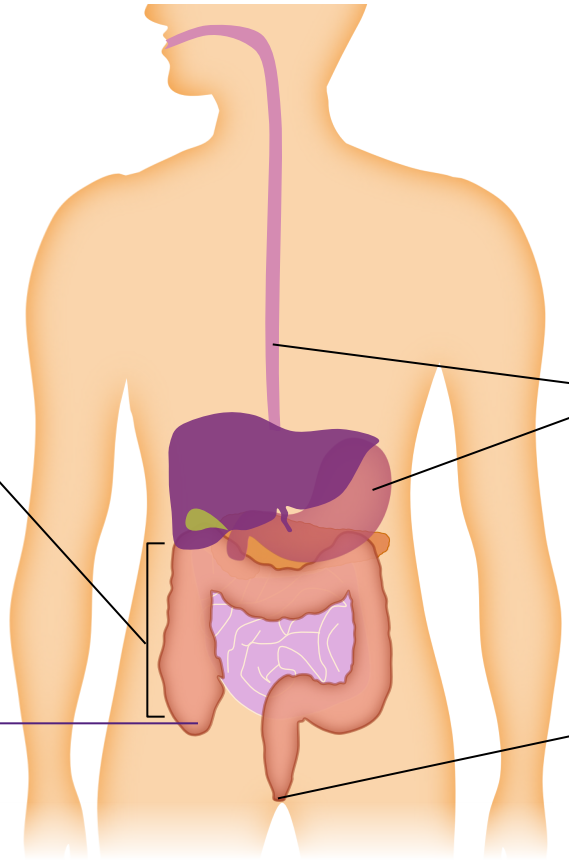
- Low pH in the small intestine
- Fat malabsorption

Intestinal inflammation and ulceration, pathogenic bacterial overgrowth, and ↑ permeability may lead to liver disease[3]

Reprinted by permission from Macmillan Publishers Ltd: Ooi CY, Durie PR. *Nat Rev Gastroenterol Hepatol*. 2016;13(3):175-185. © 2016.
1. Ooi CY, Durie PR. *Nat Rev Gastroenterol Hepatol*. 2016;13(3):175-185. 2. Li L, Somerset S. *Dig Liver Dis*. 2014;46(10):865-874. 3. Flass T et al. *PLoS One*. 2015;10(2):e0116967.

GI Clinical Signs and Symptoms in CF

There Are Multiple Clinical Manifestations of CF in the GI Tract



SIBO[1]
Intussusception[1]

GERD[1]
Esophagitis, strictures[2]
Gastritis[2]
Peptic ulcer disease[3]

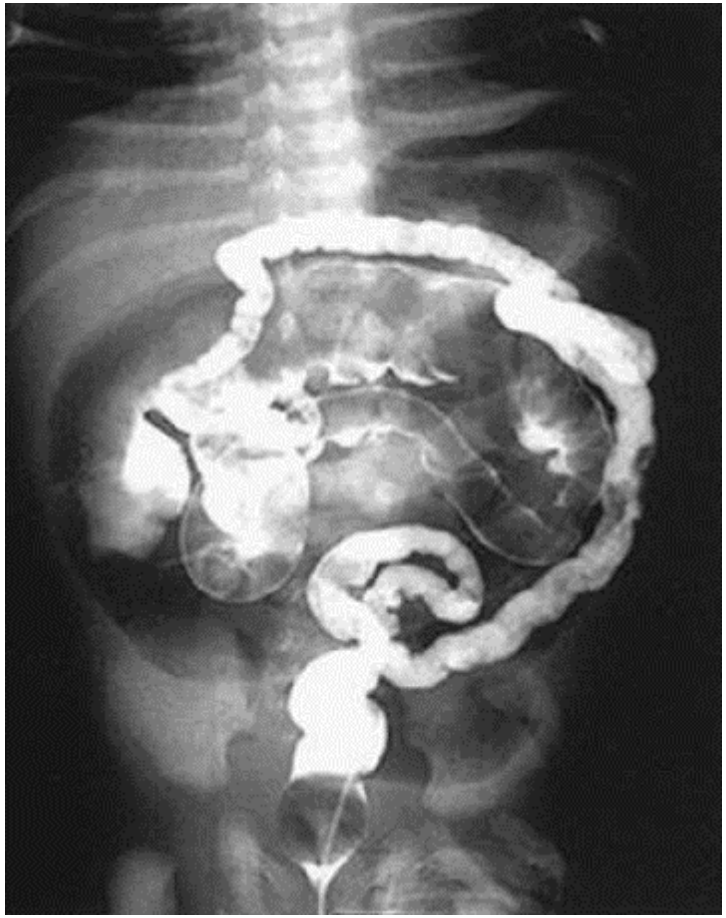
DIOS[2]
Meconium ileus[2]

Constipation/obstipation[1]
Rectal prolapse[1]

DIOS, distal intestinal obstruction syndrome; GERD, gastroesophageal reflux disease; SIBO, small intestine bacterial overgrowth.

1. Ooi CY, Durie PR. *Nat Rev Gastroenterol Hepatol*. 2016;13(3):175-185. 2. Wilschanski M, Durie PR. *Gut*. 2007;56(8):1153-1163. 3. Kelly T, Buxbaum J. *Dig Dis Sci*. 2015;60(7):1903-1913.

Meconium Ileus May Present as Simple or Complex



Neonatal bowel obstruction by inspissated mucus and meconium in the distal small bowel

Simple: Failure to pass meconium by 48 hours without other complications

Complex: Has 1 or more of the following complications

1. Intestinal atresia
2. Microcolon due to failed passage of luminal contents
3. Necrosis
4. Perforation (may occur with meconium peritonitis or pseudocyst)

Image shows meconium ileus in CF infant.
Reprinted from De Lisle RC, Borowitz D. *Cold Spring Harb Perspect Med.* 2013;3(9):a009753. Copyright holder is Cold Spring Harbor Laboratory Press.
Kelly T, Buxbaum J. *Dig Dis Sci*. 2015;60(7):1903-1913.

Meconium Ileus Is Most Common With Class I-III Mutations, and Is Typically Fatal if Untreated

Risk Factors

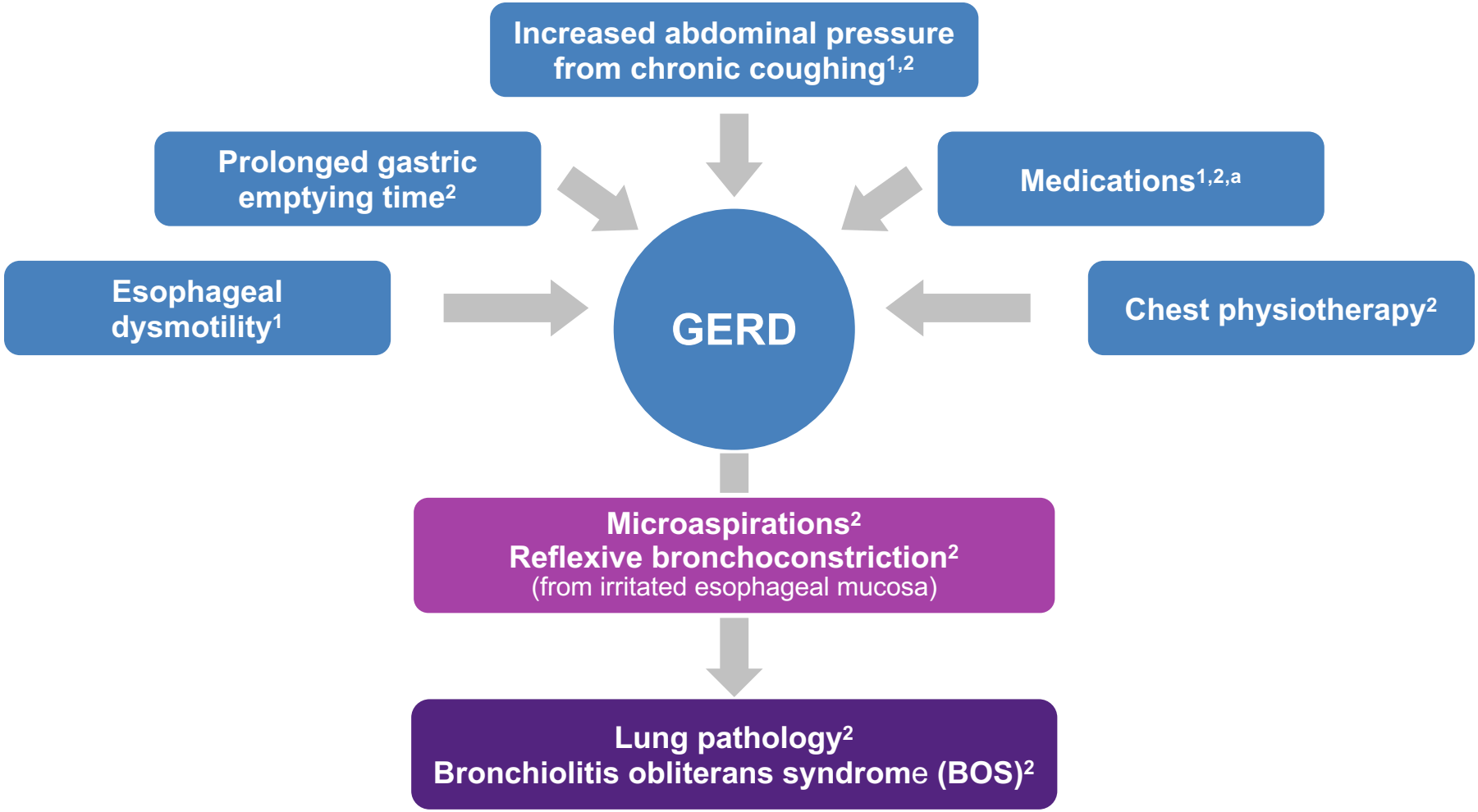
- More prevalent with class I, II, or III mutations on both alleles[1]
- Genome-wide association studies account for ~17% of the phenotypic variability,[2] suggesting non-CFTR factors (candidate modifier genes: *MSRA*, *ADIPOR2*, *SLC4A4*, *SLC6A14*, *SLC26A9*)[3]

Management[4]

- Hyperosmolar enemas, nasogastric decompression, antibiotics, and intravenous hydration
- Surgical approaches are applied if these fail
- Management is aggressive; meconium ileus is typically fatal if untreated

1. Wilschanski M, Durie PR. *Gut*. 2007;56(8):1153-1163. 2. Gelfond D, Borowitz D. *Clin Gastroenterol Hepatol*. 2013;11(4):333-342. 3. Knowles MR, Drumm M. *Cold Spring Harb Perspect Med*. 2012;2(12):a009548. 4. Kelly T, Buxbaum J. *Dig Dis Sci*. 2015;60(7):1903-1913.

GERD Has Multiple Causes and Is Associated With Worsening Lung Pathology in CF



[a]Including, but not limited to, aminophylline, antibiotics, bronchodilators, progesterone, alpha-adrenergics, opioid analgesics, and calcium channel blockers that reduce lower sphincter pressure.[1,2]

1. Lavelle LP et al. *Radiographics*. 2015;35(3):680-695. 2. Kelly T, Buxbaum J. *Dig Dis Sci*. 2015;60(7):1903-1913.

GERD Symptoms, Risk Factors, and Management

Symptoms

- Heartburn
- Acid brash
- Dysphagia
- Dyspepsia

Reported in 21% to 63% of patients with GERD[1,2]

Risk Factors

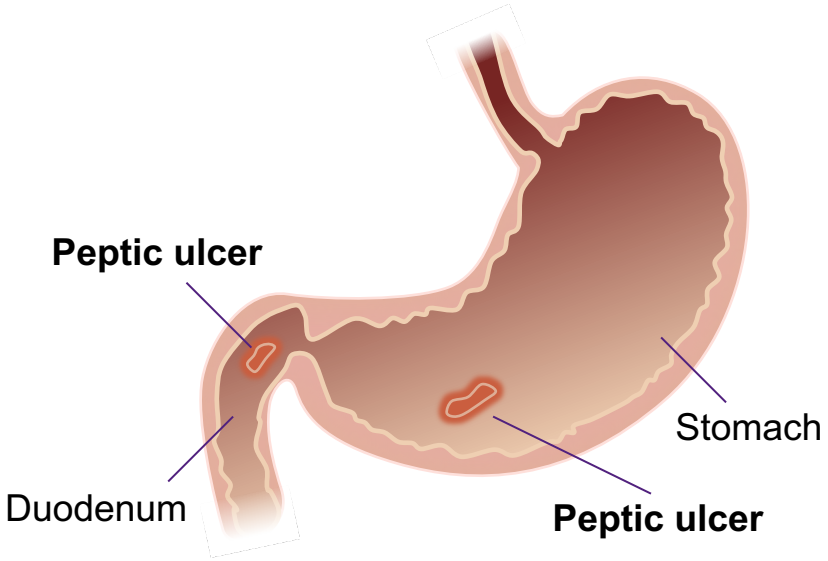
- Lung disease[3]
- Transplantation[3]
  - 50% have GERD post-transplant; of which 25% have nonacidic GERD
- BOS?[3]

Symptom Management[3,4]

- Acidic GERD: Proton pump inhibitors or H_2 receptor antagonists
- Non-acidic GERD: May require surgical fundoplication
- Acid suppression does not decrease aspiration of gastric contents or treat BOS
- Fundoplication is often used for uncontrolled GERD[5] or post-transplant

1. Sabati AA et al. *J Cyst Fibros*. 2010;9(5):365-370. 2. Scott RB et al. *J Pediatr*. 1985;106(2):223-227. 3. Kelly T, Buxbaum J. *Dig Dis Sci*. 2015;60(7):1903-1913. 4. Mousa HM, Woodley FW. *Curr Gastroenterol Rep*. 2012;14(3):226-235. 5. Sheikh SI et al. *Pediatr Pulmonol*. 2013;48(6):556-562.

Peptic Ulcer Disease Related to Excess Acidity May Occur in Patients With CF



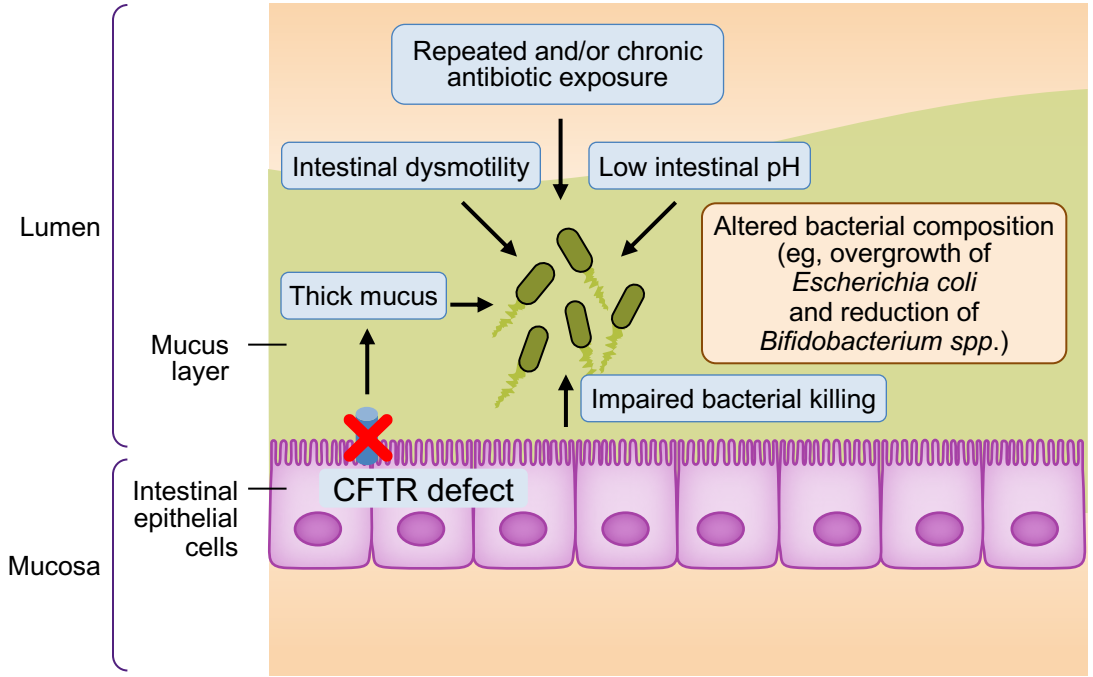
- Cause: Gastric hypersecretion and decreased HCO_3^- production[1-3]
- Duodenal ulcers reported in 10% of patients with CF at autopsy[1-3]
  - Most studies were done prior to the proton pump inhibitor era[3]

1. Agrons GA et al. *Radiographics*. 1996;16(4):871-893. 2. Constantine S et al. *Australas Radiol*. 2004;48(4):450-458. 3. Kelly T, Buxbaum J. *Dig Dis Sci*. 2015;60(7):1903-1913.

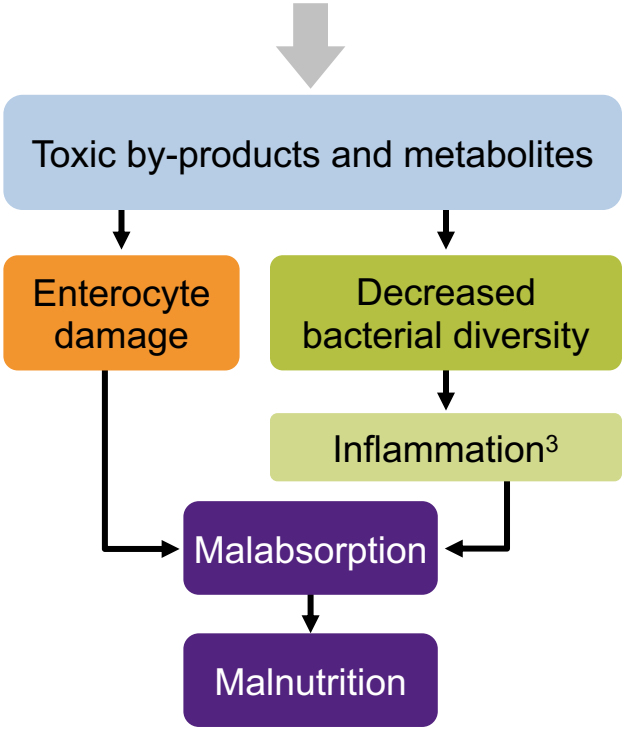
SIBO Is Common and Multifactorial in Patients With CF

- Occurs in 30% to 55% of patients with CF[1]
- Symptoms: Abdominal pain/distension and diarrhea[1]

Pathophysiology of SIBO[2]

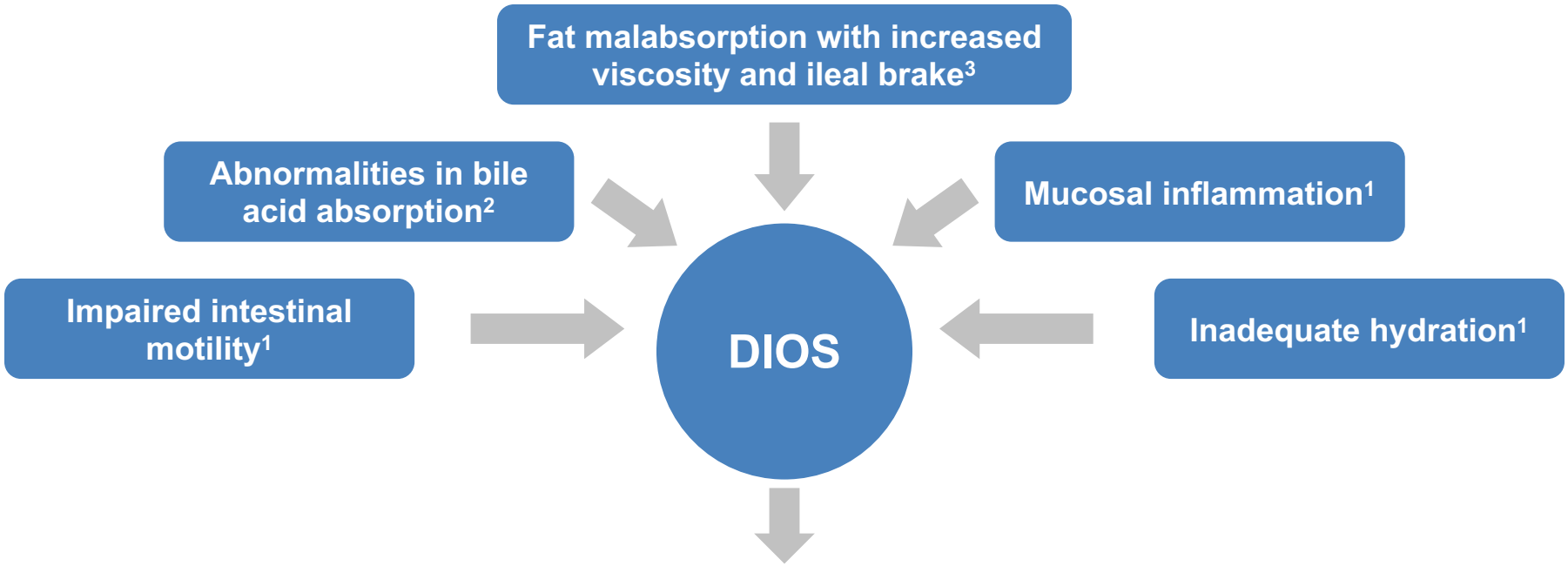


Consequences of SIBO[1]



Reprinted by permission from Macmillan Publishers Ltd: Ooi CY, Durie PR. *Nat Rev Gastroenterol Hepatol*. 2016;13(3):175-185. © 2016.
1. Gelfond D, Borowitz D. *Clin Gastroenterol Hepatol*. 2013;11(4):333-342. 2. Ooi CY, Durie PR. *Nat Rev Gastroenterol Hepatol*. 2016;13(3):175-185. 3. De Lisle RC, Borowitz D. *Cold Spring Harb Perspect Med*. 2013;3(9):a009753.

DIOS Has Multiple Contributing Factors



- Complete or incomplete fecal obstruction of the ileocecum[1]
  - Mass is strongly attached to the crypts and villi so it is difficult to remove
- Signs and symptoms[1]: Abdominal pain and cramping, distension, and a palpable mass in the right lower quadrant of the abdomen

1. Gelfond D, Borowitz D. *Clin Gastroenterol Hepatol.* 2013;11(4):333-342. 2. Colombo C et al. *J Cyst Fibros.* 2011;10(Suppl 2):S24-S28. 3. Brown NJ et al. *Gut.* 1990;31(10):1126-1129.

DIOS Has Multiple Risk Factors and Requires Early Aggressive Management

Risk Factors

- Mutation class I-III
- Pancreatic insufficiency
- Dehydration
- History of meconium ileus
- Prior episodes of DIOS
- Organ transplantation
- CF-related diabetes

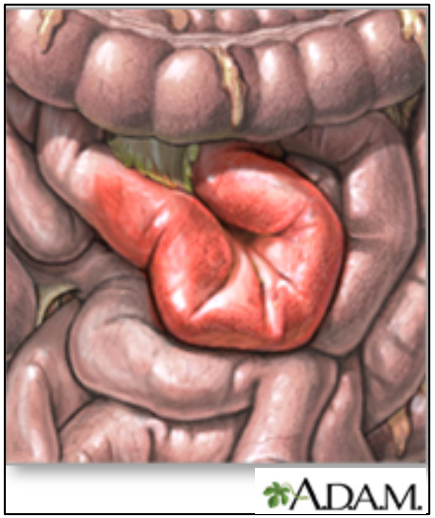
Symptom Management

- Severe DIOS: Hospitalization with IV rehydration and nasogastric aspiration
- Gastrografin given by enema (radio opaque) to perform retrograde lavage with hydrostatic pressure, but may cause serious complications related to fluid shift
  - Diatrizoate placed in the cecum has been described as an alternative approach
- Preventative measures: Maintenance laxative therapy and adequate hydration

Colombo C et al. *J Cyst Fibros*. 2011;10(Suppl 2):S24-S28.

Intussusception

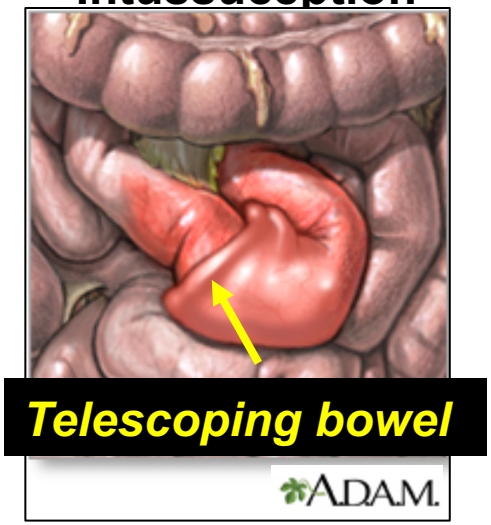
Normal bowel



Pathophysiology[1]

- Thickened secretions
- Altered motility
- Altered bowel thickness
- Appendiceal dilatation

Intussuception

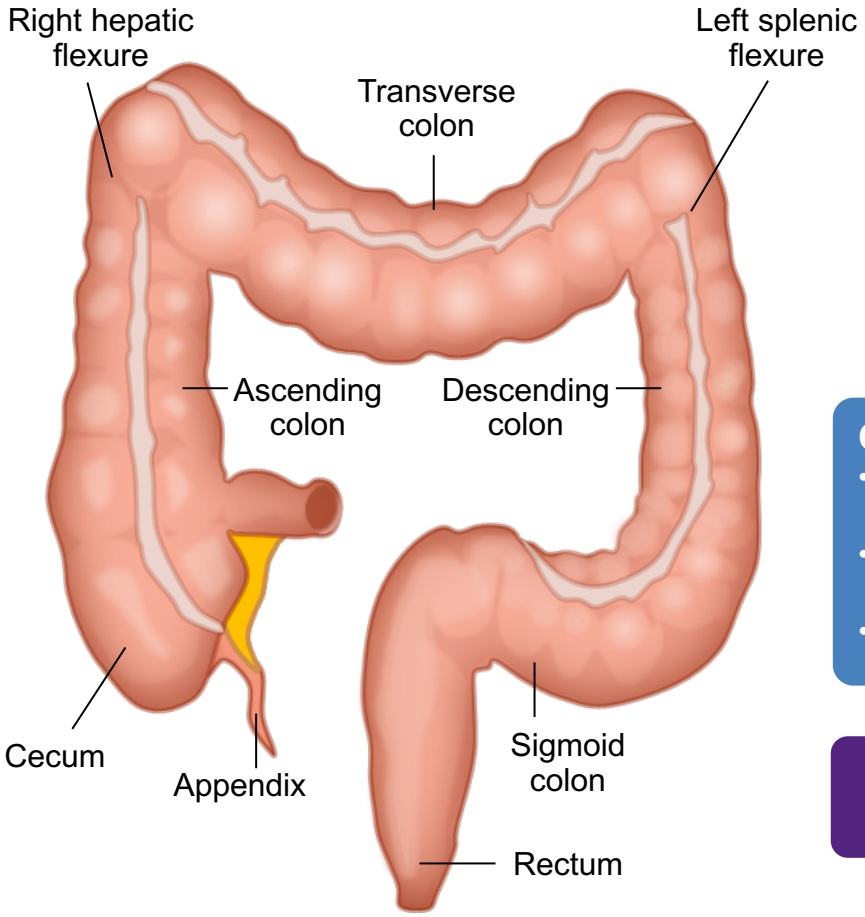


Presentation and Symptoms

- 10- to 20-fold greater incidence in patients with CF compared with general population, with 25% of cases occurring with small bowel obstruction[2]
- In adults, can be confused with DIOS, and often resolves spontaneously[3]
- Symptoms: Colicky abdominal pain, vomiting, a palpable mass, rectal bleeding[4]

1. Nash EF et al. *Dig Dis Sci*. 2011;56(12):3695-3700. 2. Wilschanski M, Durie PR. *Gut*. 2007;56(8):1153-1163. 3. Kelly T, Buxbaum J. *Dig Dis Sci*. 2015;60(7):1903 1913. 4. Lavelle LP et al. *Radiographics*. 2015;35(3):680-695.

Constipation/Obstipation* Must Be Differentially Diagnosed From DIOS in CF



- Viscous intestinal contents[1]
- Dysmotility[2]
- Decreased water secretion caused by CFTR defect[2]

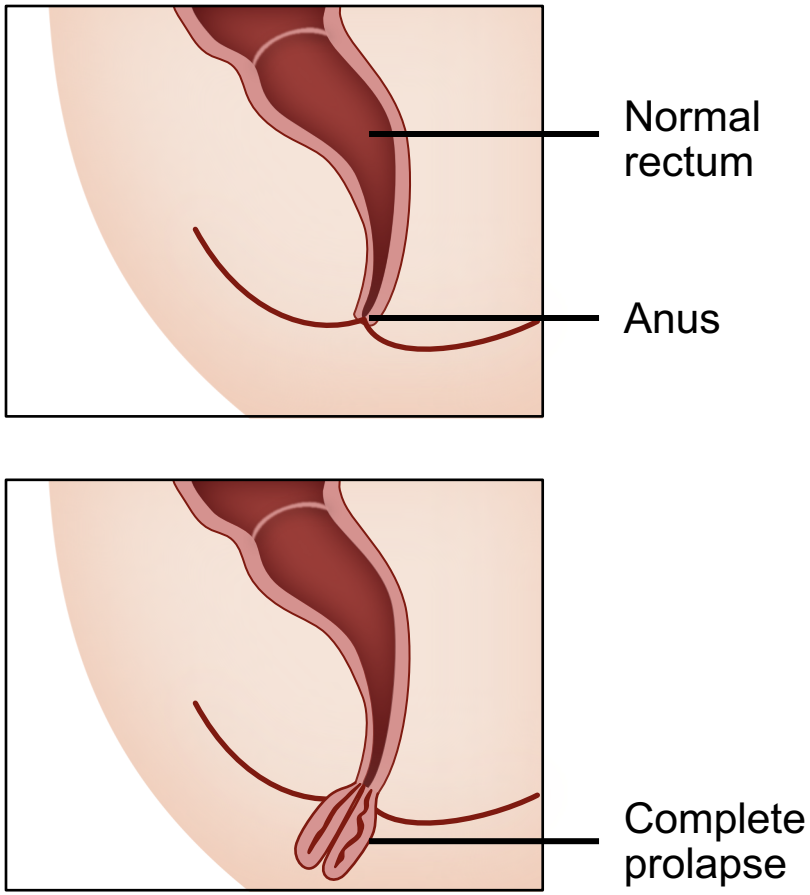
Constipation
- Gradual fecal impaction of the total colon[3]
- Starts at the sigmoid and extends proximally[2]
- Milder, longer lasting[2]

DIOS
- Starts at the terminal ileum and extends distally[2]
- Acute onset[3]

Can occur concurrently or independently[2]
Similar management with laxatives[1-3]

1. Nash EF et al. *Dig Dis Sci*. 2011;56(12):3695-3700. 2. Wilschanski M, Durie PR. *Gut*. 2007;56(8):1153-1163. 3 Kelly T, Buxbaum J. *Dig Dis Sci*. 2015;60(7):1903 1913. 4. Lavelle LP et al. *Radiographics*. 2015;35(3):680-695.

Coughing and Constipation May Lead to Rectal Prolapse in CF



Related to intra-abdominal pressure from coughing and intense straining due to constipation

May cause bleeding and be difficult and painful to reduce

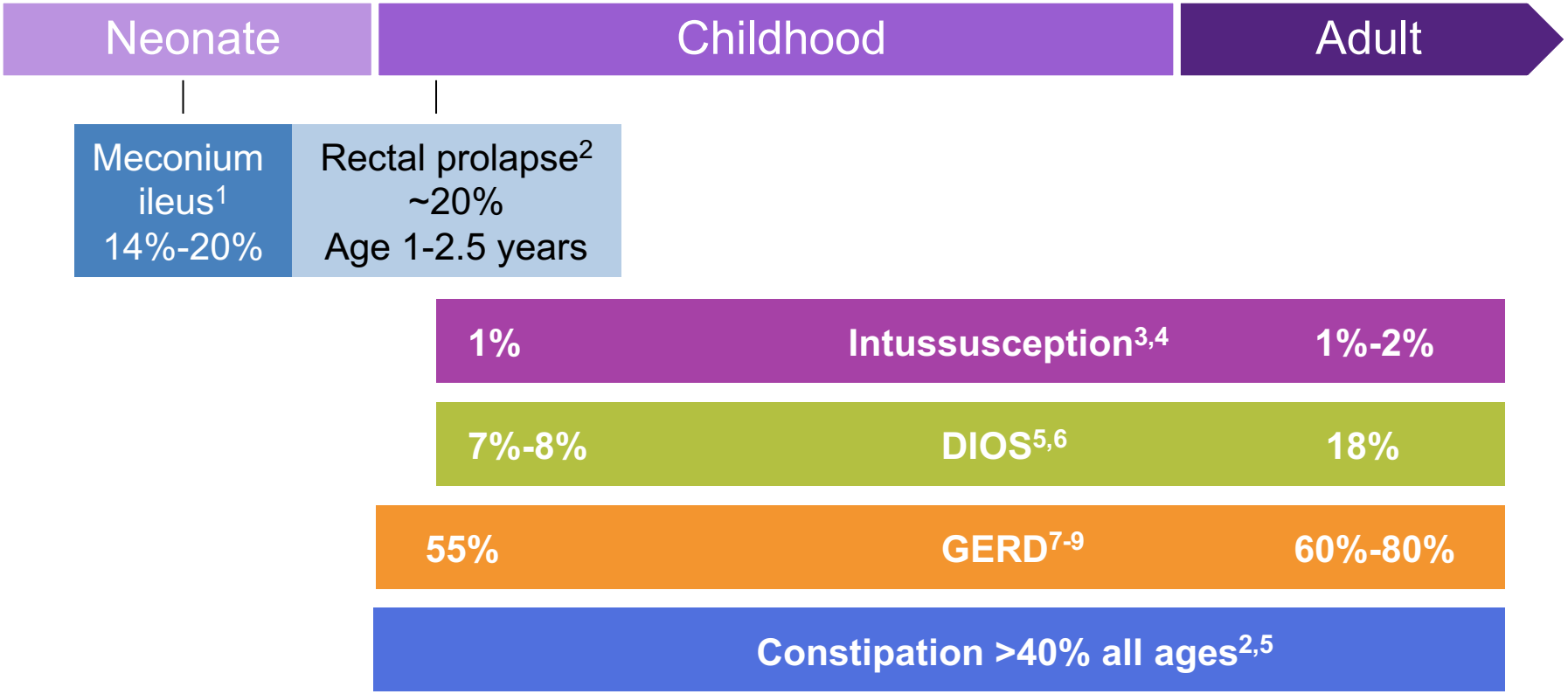
Typically managed conservatively in patients with CF

Kelly T, Buxbaum J. *Dig Dis Sci.* 2015;60(7):1903-1913.

VERTEX

Natural History of GI Manifestations in CF

CF GI Manifestations Are Prevalent Throughout the Patient's Life

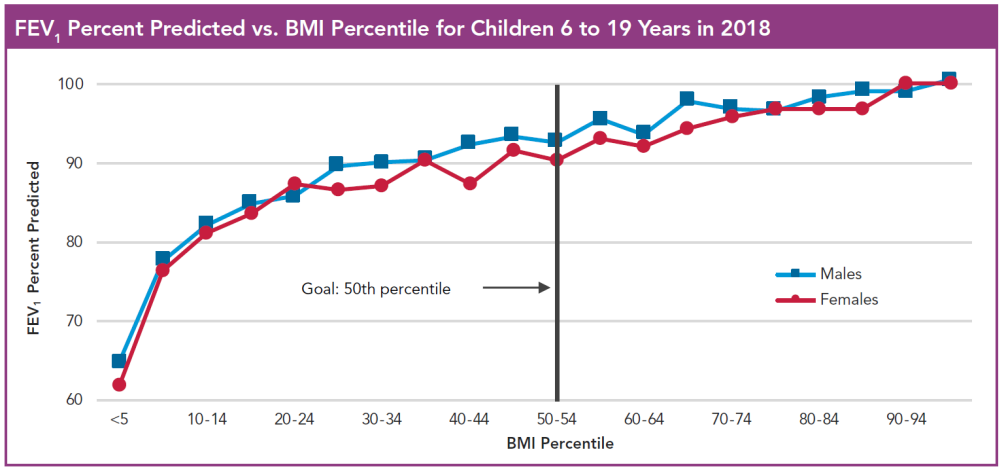


- Pancreatic insufficiency is present in 70% of infants at screening and develops in another 25% before age 3 years[2]

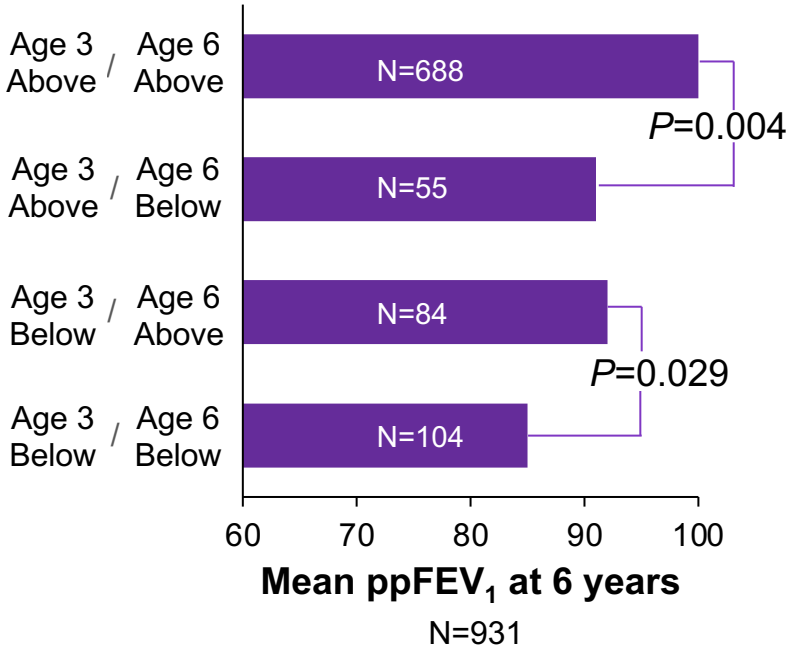
1. Ooi CY, Durie PR. *Nat Rev Gastroenterol Hepatol*. 2016;13(3):175-185. 2. Kelly T, Buxbaum J. *Dig Dis Sci.* 2015;60(7):1903-1913. 3. Wilschanski M, Durie PR. *Gut.* 2007;56(8):1153-1163. 4. Holsclaw DS et al. *Pediatrics*. 1971;48(1):51-58. 5. van der Doef HP et al. *Curr Gastroenterol Rep*. 2011;13(3):265-270. 6. Dray X et al. *Clin Gastroenterol Hepatol*. 2004;2(6):498-503. 7. Brodzicki J et al. *Med Sci Monit*. 2002;8(7):CR529-CR537. 8. DiMango E et al. *BMC Pulm Med.* 2014;14:21. 9. Ledson MJ et al. *J R Soc Med*. 1998;91(1):7-9.

Growth and Nutritional Status Associated With Pulmonary Function in Patients With CF

Higher BMI is associated with better FEV_1 in children with CF aged 6 to 19 years (US Data)[1]



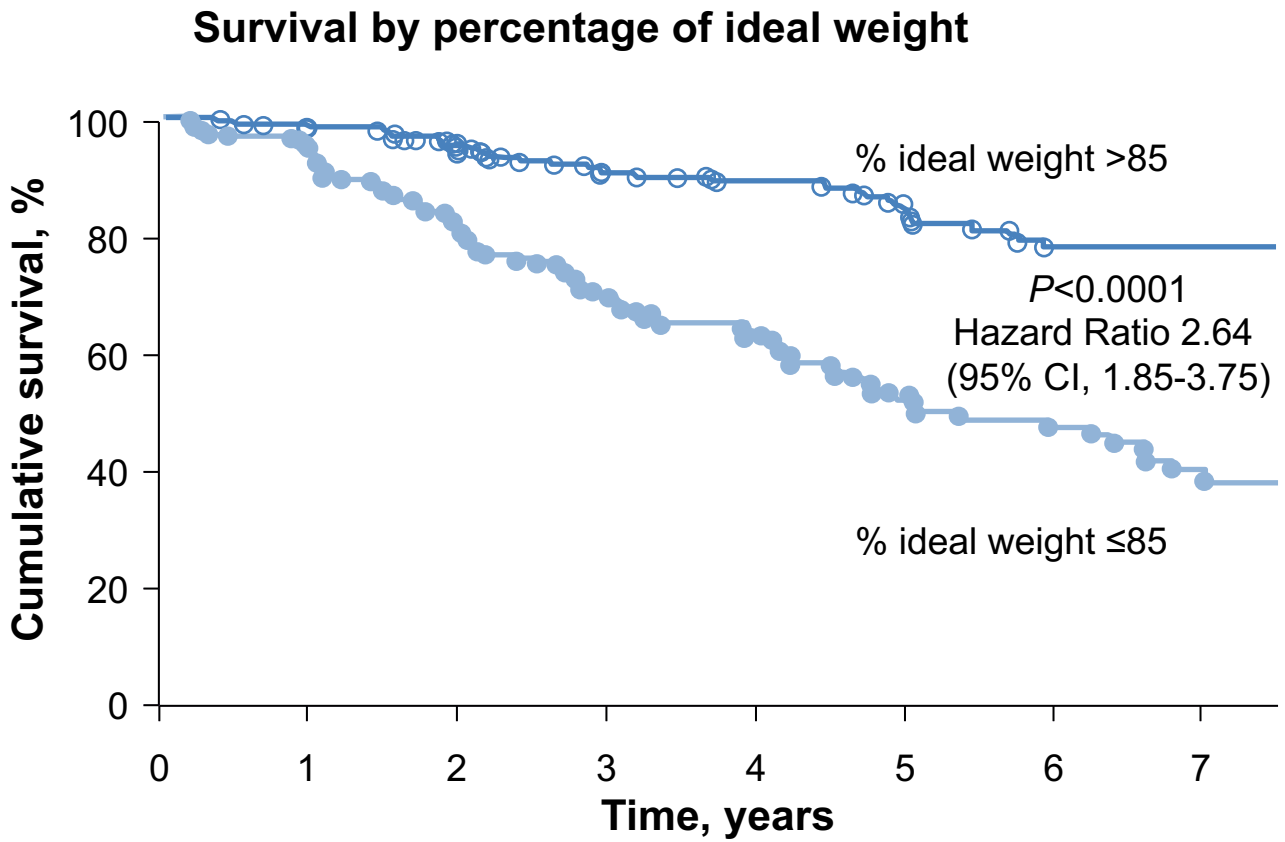
WFA >10th percentile at age 3 years and 6 years associated with better FEV_1 at age 6 years in CF[2]



BMI, body mass index; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; WFA, weight for age.

1. Cystic Fibrosis Foundation (CFF) Patient Registry. 2018 Annual Data Report. Bethesda, MD: CFF; 2019. 2. Konstan M et al. *J Pediatr.* 2003;142(6):624-630.

Low Body Weight Is a Predictor of Mortality in CF



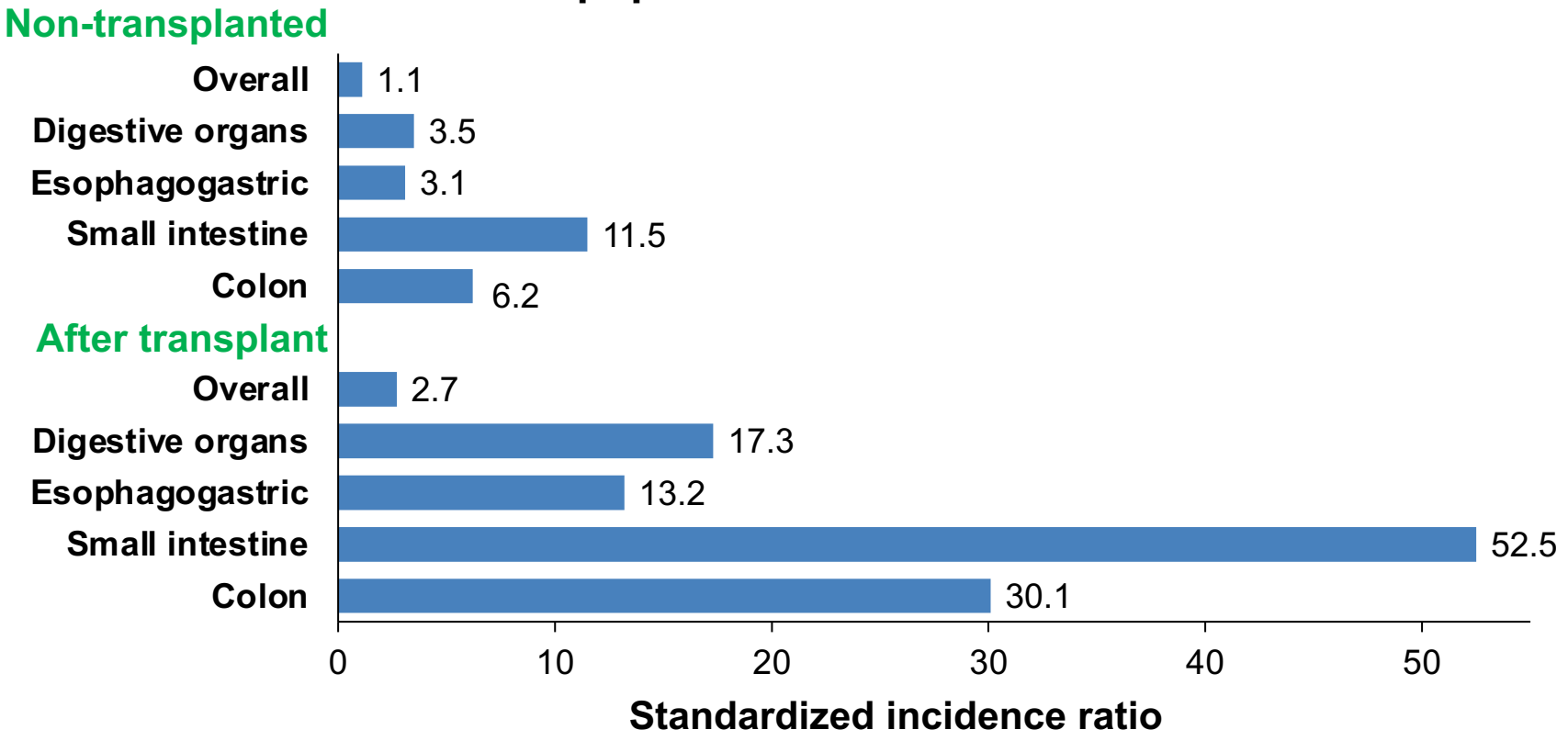
Patients at risk:				
% ideal weight >85	364	211	135	53
% ideal weight ≤85	220	108	57	17

Reproduced from *Thorax*, Sharma R et al, 56, 746-750, © 2001 with permission from BMJ Publishing Group Ltd.
Sharma R et al. *Thorax*. 2001;56(10):746-750.

CF and GI Cancer

Patients With CF With or Without Lung Transplant Have Increased Risk of GI Cancers

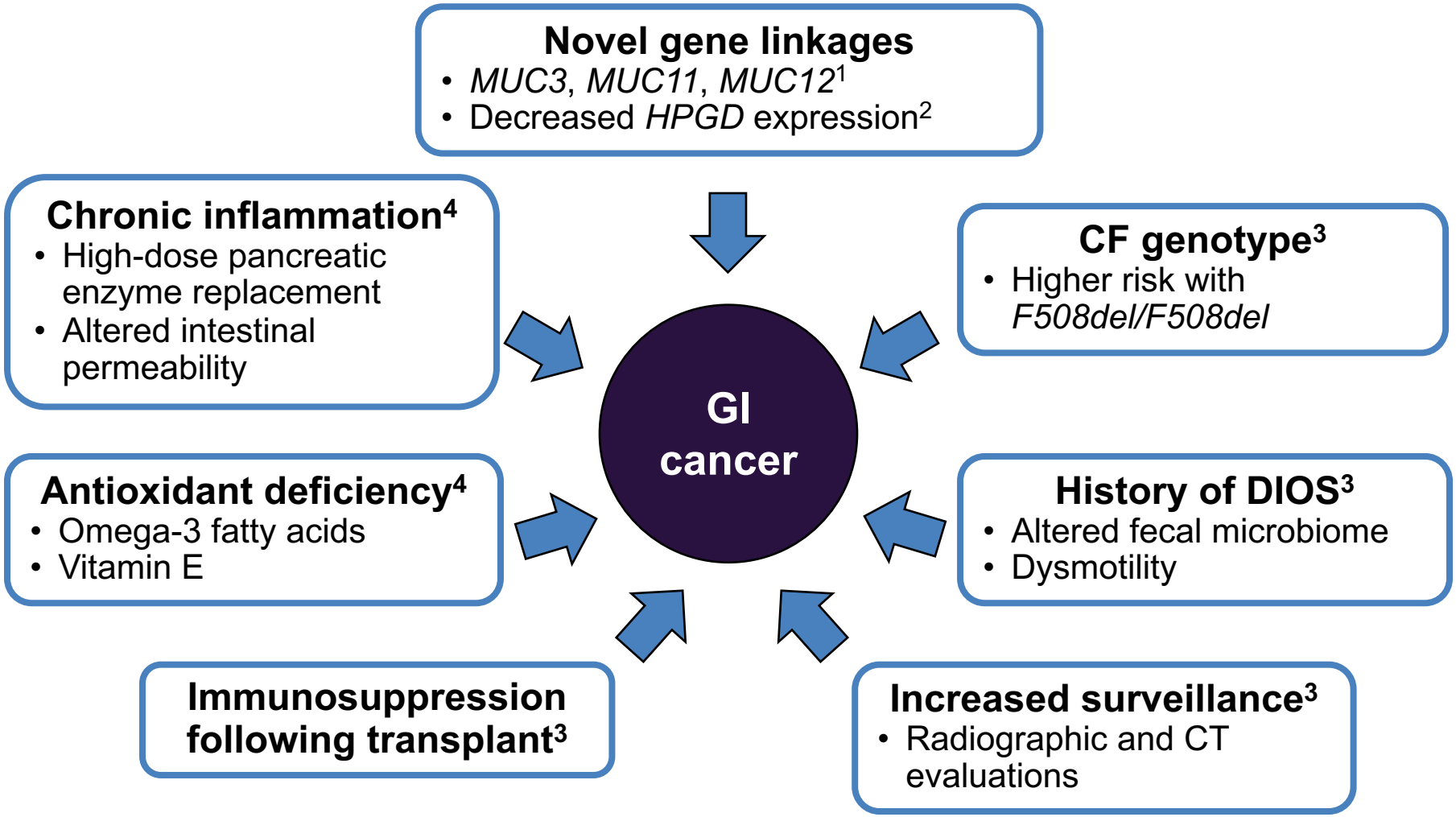
Incidence ratio of GI cancers in patients with CF compared with the general US population: 1990 to 2009



- Incidence ratio 1 indicates the same incidence in CF and general populations
- Incidence ratio >1 indicates higher incidence in CF population

Maisonneuve P et al. *J Natl Cancer Inst*. 2013;105(2):122-129.

Factors Underlying Elevated Risk of GI Cancer in CF Are Unknown, But Candidates Have Been Identified



CT, computed tomography.

1. Hernandez-Jimenez I et al. *J Cyst Fibros*. 2008;7(5):343-346. 2. De Lisle RC, Borowitz D. *Cold Spring Harb Perspect Med.* 2013;3(9):a009753. 3. Maisonneuve P et al. *J Natl Cancer Inst*. 2013;105(2):122-129. 4. Alexander CL et al. *J Cyst Fibros*. 2008;7(1):1-6.

Summary

- GI manifestations in CF occur early and continue throughout the life of a patient with CF
- GI manifestations have become an increasingly recognized cause of morbidity in patients with CF, in part because of improved life expectancy
- With the increasing aging population of patients with CF, the risk of cancer increases

Interactive Question 1

Where is CFTR found in the GI tract?

A. Submandibular and parotid duct cells
B. Esophageal submucosal gland duct cells
C. Gastric mucosa of stomach
D. Epithelial cells of small intestine
E. All of the above

Interactive Question 1

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E. All of the above

Interactive Question 2

What is the earliest GI complication observed in patients with CF?

A. GERD
B. Meconium ileus
C. DIOS
D. Rectal prolapse
E. Intussusception

Interactive Question 2

What is the earliest GI complication observed in patients with CF?

A. GERD
B. Meconium ileus
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Interactive Question 3

The incidence of colon cancer in patients with CF compared with the general population is

A. Higher
B. Lower
C. The same

Interactive Question 3

The incidence of colon cancer in patients with CF compared with the general population is

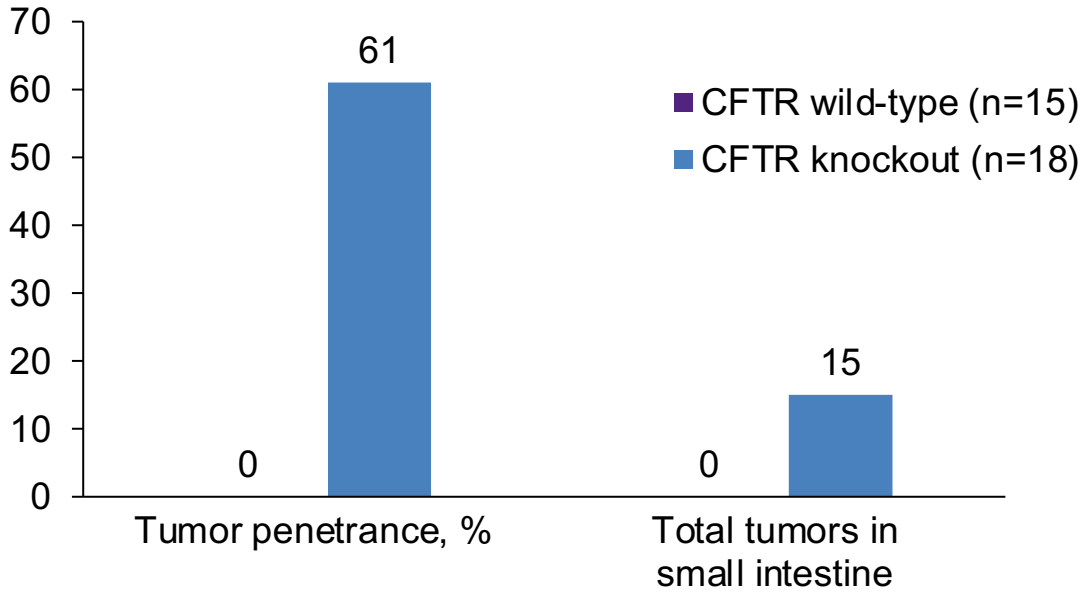
A. Higher
B. Lower
C. The same

More Information

CFTR May Be a Tumor Suppressor Based on Data in Animal Models

- Mice with digestive tract–specific CFTR knockout had higher rate of GI tumor formation than wild-type mice

Intestinal tumors occurring in mouse models over 1 year



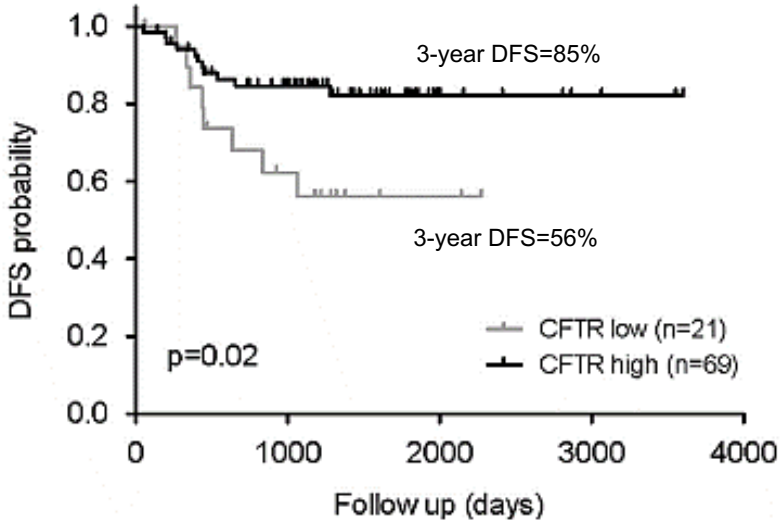
Than BL et al. *Oncogene*. 2016;35(32):4179-4187.

CFTR May Be a Tumor Suppressor Based on Data in Humans

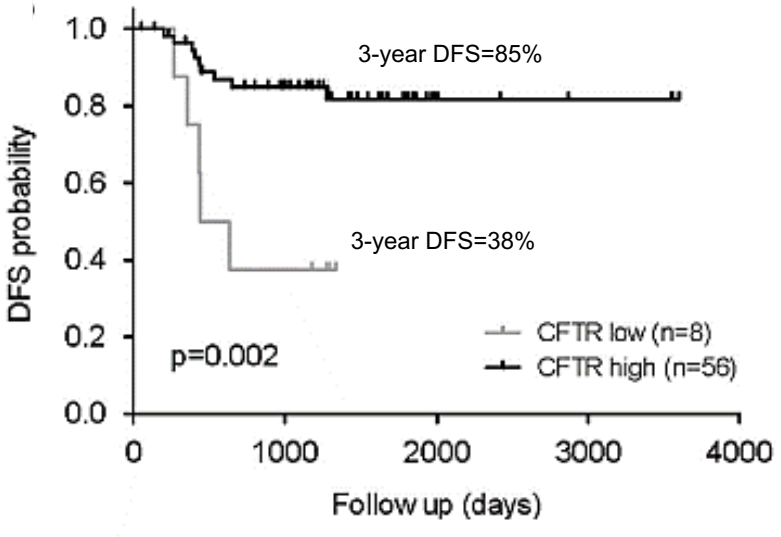
- Low CFTR expression is associated with poor 3-year disease-free survival (DFS) in patients with colorectal cancer
  - Even more pronounced in patients with high risk of recurrence

DFS in patients with surgically-resected colorectal cancer based on CFTR expression levels

Total population



High-risk population



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