I. Development of the Pancreas

A. Pancreatic development is influenced by both signaling and transcription factors
   1. Hedgehog proteins—signaling molecules that both stimulate and inhibit pancreatic growth
   2. Other factors influencing development—pancreatic duct primary cilia, fibroblast growth factor, transforming growth factor-β, vascular endothelial growth factor and homeobox transcription factor

B. At 4–5 weeks’ gestation, distinct dorsal and ventral pancreatic buds arise from the endoderm of the caudal foregut (the primordial proximal duodenum)
   1. The dorsal bud is larger than and slightly cranial to the ventral bud
   2. Each bud communicates with the foregut through a duct

C. Rotation of the duodenum causes the ventral pancreatic bud to rotate clockwise to the left of the duodenum, and brings it posterior and inferior to the dorsal pancreatic bud

D. During the 7th week of gestation, the two buds fuse to form the pancreas
   1. The ventral pancreatic bud forms the inferior part of the head of the pancreas and the uncinate process
   2. The dorsal pancreatic bud forms the superior part of the head, the body, and the tail of the pancreas

E. During the 8th week of gestation, the ductal systems of the two buds anastomose
   1. The longer dorsal duct drains into the proximal part of the ventral duct to form the main pancreatic duct (duct of Wirsung), which enters the duodenum at the major duodenal papilla (ampulla of Vater)
   2. If the proximal portion of the dorsal duct remains, it forms an accessory duct (duct of Santorini) that opens into a minor accessory papilla located about 2 cm above the main duct
      a. The accessory duct opens into a minor papilla in 33% of people and ends blindly in 8% of people, while about half of individuals do not have one

F. At about 8 weeks’ of gestation, groups of endocrine cells (islets) originating from ductal epithelium are identifiable
   1. From 10–14 weeks’ gestation, the islets form clumps and detach from the ducts

G. At about 12 weeks’ gestation, exocrine cells appear along the pancreatic ducts
   1. Exocrine pancreatic development continues after birth with maturation of specific digestive enzymes, including pancreatic amylase and lipase

II. Anatomy

A. Arterial supply
   1. Pancreatic head—supplied by the superior pancreaticoduodenal artery (a branch of the gastroduodenal artery), and the inferior pancreaticoduodenal artery (a branch of the superior mesenteric artery)
   2. Remainder of pancreas is supplied by the pancreatic branches of the splenic artery

B. Venous drainage
   1. Head of the pancreas is drained by superior mesenteric and portal veins
   2. Body and neck of pancreas are drained by splenic vein

C. Innervation
   1. Acini, islets and ducts innervated by the vagus nerve
   2. Blood vessels innervated by sympathetic nervous system
D. Endocrine cells
   1. These cells are distributed within the islets of Langerhans
   2. There are 4 four types:
      a. A cells: produce glucagon
      b. B cells: produce insulin
      c. D cells: secrete somatostatin
      d. F cells: secrete pancreatic polypeptide
   3. These hormones enter systemic circulation via pancreatic blood flow

E. Exocrine cells
   1. The exocrine pancreas consists of lobules that contain acini and ductal system
      a. Each acinus contains ~6–8 pyramidal cells, with their apical poles facing a lumen that empties into an intercalated duct
      b. Intercalated ducts fuse to form intralobular ducts that drain into interlobular ducts
      c. Interlobular ducts empty into the main pancreatic duct which enters the duodenum
   2. The acinus synthesizes, stores and releases pancreatic enzymes
      a. The basal region of the acinar cell contains the nucleus and endoplasmic reticulum where proteins are synthesized
      b. Enzymes are packaged in secretory (zymogen) granules in the Golgi complex
      c. Secretory granules are stored in the apical region of the cell
      d. Acinar basolateral membrane has multiple receptors for secretagogues (e.g., cholecystokinin) and neurotransmitters (e.g., acetylcholine and vasoactive intestinal peptide)

F. Duct cells
   1. Centroacinar (proximal ductular) cells that empty into the acinar lumen and pancreatic duct cells both modify pancreatic juice by secretion of water and bicarbonate

III. Physiology

A. The adult human pancreas delivers ~2.5 L of fluid to the duodenum daily
   1. The fluid is composed of digestive enzymes, bicarbonate to ensure an optimal pH for enzyme activity, and water
   2. At rest, pancreatic secretion rate is 0.2 mL/min, with bicarbonate concentration equal to that of plasma
   3. After stimulation, secretion rate increases to ~4 mL/min, and bicarbonate concentration increases to a maximum of 140 mEq/L, creating a pH of ~8.2 in pancreatic fluid

B. Regulation of pancreatic secretion
   1. Hormones that stimulate pancreatic fluid secretion
      a. Secretin
         1) Major mediator of hydrogen ion-stimulated bicarbonate and water secretion
         2) Released by S-type enteroendocrine cells in the proximal small intestine in the presence of duodenal acidification (pH threshold 4.5), bile, and the products of protein and fat digestion
      b. Cholecystokinin
         1) Major mediator of meal-stimulated enzyme secretion
         2) Secreted primarily by intestinal I cells in response to the products of protein and fat digestion
   2. Interdigestive pancreatic secretion
      a. There is a cyclic secretion of pancreatic juice that closely follows the pattern of the migrating myoelectric complex in the intestine
      b. Interdigestive secretion is important in the digestion of residual food, cellular debris and pathogens in the duodenum
      c. Regulation occurs via motilin, pancreatic polypeptide and the autonomic nervous system
3. Postprandial pancreatic secretion
   a. Cephalic phase: vagus nerve mediates pancreatic secretion at the sight, smell, taste and thought of food
   b. Gastric phase: distension of the stomach produces vasovagal cholinergic reflex that causes increased pancreatic secretion
   c. Intestinal phase: chyme in the duodenum leads to pancreatic secretion via secretin, cholecystokinin and the vagus nerve

4. Hormones that inhibit pancreatic secretion
   a. Pancreatic polypeptide: released from the islets of Langerhans in response to food and duodenal acidification
   b. Peptide YY: released in response to fat in the distal ileum and colon
   c. Somatostatin: produced in mucosa of stomach and duodenum and in islets of Langerhans. Released in response to fat and amino acids in the intestinal tract

C. Pancreatic exocrine function (see section on Exocrine Function)

**Recommended Reading**


I. Exocrine Pancreatic Development

A. The pancreas forms during the 4th week of gestation, developing from the endodermal lining of the duodenum as ventral and dorsal outpouchings. By Week 6 of gestation, the dorsal aspect develops a nodular pattern resembling the basic acinar pancreatic anatomy, while the ventral aspect develops a connection with the early common bile duct. The ventral and dorsal elements fuse at Week 7 of gestation, and the main pancreatic duct attaches to the common bile duct (which forms from the fusion of the common bile duct, pancreatic duct and the ventral pancreas).

B. Hedgehog proteins (signaling molecules) regulate pancreatic morphogenesis by promoting cellular proliferation and differentiation. Indian hedgehog protein appears to be the sole hedgehog protein involved in pancreatic growth. Pancreatic acini are present by the 3rd month of gestation. Zymogen granules appear by the 12th week of gestation. By the 20th week of gestation, zymogens identical to those in adult pancreas are observed. Infants have exocrine pancreatic function similar to adults at term, although zymogen size and enzyme content may differ.

II. Tests for Exocrine Pancreatic Insufficiency

A. 72-hour fecal fat collection is the gold standard indirect measure of lipolytic enzyme activity
   1. Requires accurate estimate of dietary fat intake for 72 hours
   2. Requires complete collection of stool for 72 hours
   3. Total fats are extracted from stool and weighed
   4. Total fat excreted as fraction of fat intake calculated
   5. Normal fat excretion is <7% of intake in children over 2 years. May be higher in young children, especially those infants younger than 6 months of age
   6. Very accurate measure of lipase activity, but difficult because of poor compliance with stool collection and diet record

B. Stool trypsin/chymotrypsin measures proteolytic activity in stool
   1. Indirect measure of pancreatic proteolytic enzyme secretion
   2. Trypsin in stool is prone to bacterial degradation, producing false low values (poor sensitivity)

C. Breath hydrogen excretion
   1. Using starch as substrate, an increase in breath hydrogen excretion of 20 ppm over baseline after oral administration roughly indicates insufficiency of pancreatic amylase activity
   2. Positive tests occur in patients with small bowel bacterial overgrowth and monosaccharide transport defects who may be inaccurately diagnosed with pancreatic exocrine insufficiency

D. Serum immunoreactive trypsinogen measures trypsin precursor in serum
   1. In true exocrine pancreatic insufficiency, serum immunoreactive trypsinogen will be very low
   2. In newborns with cystic fibrosis, serum IRT is elevated because of obstruction of pancreatic ducts and regurgitation of IRT into bloodstream
   3. In newborns with cystic fibrosis and distal intestinal obstruction at birth (meconium ileus), IRT is usually low because of extensive prenatal destruction of pancreatic acini
E. Secretin/CCK infusion test is the gold standard direct measurement of pancreatic exocrine enzyme secretion
   1. IV infusion of secretin and/or cholecystokinin is followed by aspiration of duodenal contents (biliary and pancreatic secretions) by nasoduodenal tube for 15 minutes to 1 hour
   2. Aspirated pancreatic secretions tested for pH, bicarbonate concentration and lipase, amylase and proteolytic activity
   3. Test is expensive and invasive
   4. Test accuracy is increased by simultaneous perfusion of the duodenum with a nonabsorbed marker, so that total volume of secretion following stimulation can be determined

F. Fecal elastase measures amount of pancreatic neutrophil elastase in stool
   1. Low fecal elastase concentration indicates pancreatic exocrine insufficiency
   2. Test is easy to perform
   3. Patients with pancreatic sufficient Shwachman-Diamond syndrome may have falsely low fecal elastase
   4. Patients with short bowel syndrome have falsely low fecal elastase
   5. Falsely low results occur in patients with large volume diarrhea due to dilution

III. Diagnoses Associated With Exocrine Pancreatic Insufficiency
A. Acquired pancreatic exocrine insufficiency may occur as a complication of chronic pancreatitis. Causes of chronic pancreatitis include:
   1. Trauma, after endoscopic retrograde cholangiopancreatogram (ERCP)
   2. Medication use (eg, isoniazid)
   3. Infections (eg, ascariasis)
   4. Biliary disease
   5. Pancreas divisum
   6. Metabolic causes (eg, hypercalcemia, hypertriglyceridemia, malnutrition)
   7. Associated with systemic diseases (hemolytic uremic syndrome or Kawasaki disease)

B. Cystic fibrosis is the most common inherited cause of exocrine pancreatic insufficiency (approximately 1 in 2,000 live births)
   1. Dysfunction of the cystic fibrosis transmembrane conductance regulatory protein (CFTR)
   2. Most common CFTR gene mutation is ΔF508
   3. Measuring exocrine pancreatic function is not the recommended means of making a diagnosis of cystic fibrosis. Knowing the extent of exocrine insufficiency may assist in management. Recommended diagnostic tests include:
      a. Sweat chloride
      b. Nasal mucosal potential difference
      c. Cystic fibrosis gene (CFTR) mutation analysis

C. Second most common cause of pancreatic insufficiency is Shwachman-Diamond syndrome (1 in 75,000 live births)—exocrine pancreatic insufficiency, bone marrow abnormalities, metaphyseal dysostosis, growth retardation and immune dysfunction (see section on Shwachman-Diamond Syndrome)

D. Other causes of pancreatic exocrine insufficiency
   1. Hereditary pancreatitis (autosomal dominant) typically presents in 2nd decade of life, associated with pancreatic malignancy. Can be seen with PRSS1 mutation or SPINK1 mutation affecting cationic trypsinogen gene
   2. Pearson's bone marrow syndrome: pancreatic exocrine insufficiency, sideroblastic anemia, bone marrow vacuolization
   3. Congenital rubella due to cell loss, possibly from molecular mimicry/immune destruction
   4. Pancreatic agenesis/hypoplasia: 10 cases reported
   5. Isolated pancreatic enzyme defects: very rare (lipase deficiency, colipase deficiency, enterokinase deficiency)
   6. Johanson-Blizzard syndrome: pancreatic exocrine insufficiency, failure to thrive, deafness, hypothyroidism, microcephaly, abnormal hair pattern, nasal cartilage hypoplasia, small or absent permanent teeth
**Recommended References**


7C. Congenital Anomalies of the Pancreas

Maria E. Perez, DO
Cheryl Gariepy, MD

I. Pancreatic Divisum
A. Most common congenital anomaly of the pancreas
B. Failure of fusion of the dorsal and ventral pancreatic buds off the foregut (typically Weeks 7–8 of gestation) causes formation of two separate drainage systems
   1. Head of the pancreas is drained through the major papilla
   2. Neck and tail of the pancreas (majority of the pancreatic tissue) is drained through the minor papilla
C. Clinical significance is controversial
   1. Normal variant vs possible cause of recurrent pancreatitis
   2. Possible cause of recurrent pancreatitis
      a. High volume of pancreatic secretions through the smaller papilla allows activated pancreatic enzymes to inflame the papilla, leading to stasis, stenosis and pancreatitis
D. Diagnosis — ERCP and MRCP
E. Treatment — Endoscopic enlargement of the minor papilla, sphincteroplasty, stent placement

II. Ectopic Pancreas
A. Also known as pancreatic rest
B. Pancreatic tissue with no vascular or physical continuity with the pancreas
C. Most common locations: prepyloric stomach, duodenum, Meckel diverticulum
D. Clinical signs/symptoms:
   1. Usually causes no symptoms
   2. May be the source of abdominal pain, dyspepsia, GI bleed, pyloric obstruction
   3. Ectopic pancreatitis is rare, but it has been documented in the adult and pediatric population
E. Diagnosis — usually an incidental finding on upper GI series or upper endoscopy; appears as a round, slightly raised, smooth, submucosal mass with a central umbilication
F. Treatment — usually requires no treatment. Surgical resection only if the rest is thought to be causing serious symptoms

III. Annular Pancreas
A. Ventral portion of the pancreas encircles the second portion of the duodenum and fuses with the dorsal aspect of the developing pancreas
B. Most common presentation is neonatal duodenal obstruction
C. 75% associated with other congenital anomalies
   1. Anomalies of the GI tract are most common, including malrotation; duodenal web, atresia or stenosis; TE fistula, imperforate anus and Hirschsprung disease
   2. Congenital heart disease
   3. Increased incidence in trisomy 21
D. Clinical signs/symptoms
   1. Infancy: UGI obstruction, vomiting (may or may not be bilious), pancreatitis
   2. Adolescents/adults: duodenal obstruction, chronic pancreatitis
E. Diagnosis
   1. Double bubble on plain abdominal x-ray
   2. MRCP/ERCP provide best view
F. Treatment — surgical bypass of lesion with duodenoduodenostomy

Recommended Reading
7D. Acute Pancreatitis

Maria E. Perez, DO
Cheryl E. Gariepy, MD

I. Incidence
The incidence of acute pancreatitis in children has increased in the past decade as a result of increased physician awareness of pathophysiology and improved diagnostic methods. In adults, alcohol use and gallstones account for most cases. In children, there are multiple etiologies and many cases remain idiopathic. Management is supportive, and most patients recover without complications.

II. Three Phases in Pathophysiology of Pancreatitis
   A. An event triggers pancreatic injury
   B. Acinar cell injury occurs through the activation of digestive enzymes, such as trypsinogen
   C. Cell injury produces a local inflammatory response with the release of inflammatory mediators

III. Etiology
   A. Systemic illnesses associated with pancreatitis
      1. Hemolytic uremic syndrome
      2. Systemic lupus
      3. Inflammatory bowel disease
      4. Sickle cell disease
      5. Kawasaki disease
      6. Shock/hypoperfusion injury
      7. Cystic fibrosis
   B. Biliary disease—cholelithiasis, choledochal cyst, biliary sludge
   C. Trauma—motor vehicle accidents or bike handle injuries
   D. Medications
      1. Valproic acid and L-asparaginase are drugs most commonly associated with pancreatitis at therapeutic doses
      2. Azathioprine, mercaptopurine, mesalamine and metronidazole have also been associated with acute pancreatitis
   E. Anatomic—pancreas divisum, annular pancreas
   F. Obstruction—duodenal ulcer, tumor of the papilla, duodenal Crohn disease
   G. Infections—below are major pathogens
      1. Mycoplasma
      2. Coxsackie virus
      3. Mumps virus
      4. Varicella, HSV, CMV
      5. Rubeola
      6. Hepatitis A & B
      7. Influenza A & B
      8. HIV
   H. Genetic—PRSS1 mutations, CFTR mutations, SPINK-1 mutations
   I. Metabolic—hypercalcemia, hyperlipidemia, malnutrition
   J. Toxins—acetaminophen overdose, organophosphates, alcohol, spider venom, heroin, amphetamines

IV. Clinical Manifestations/Diagnosis
   A. Diagnosis of acute pancreatitis requires at least two of the following three criteria:
      1. Abdominal pain consistent with pancreatitis
      2. Elevation of serum amylase and/or lipase of at least three times the upper limit of normal
      3. Radiographic evidence of pancreatitis (ultrasound, CT scan, etc)
B. Indicators of disease severity at presentation: age <7 years, lower body weight, elevated WBC, and LDH >2,000 associated with more severe disease

C. Predictors of severe disease at 48 hours
1. Low serum calcium
2. Low serum albumin
3. Elevated BUN
4. High fluid requirements

D. Signs and symptoms of acute pancreatitis are listed in Table 1. These vary based on the age of the child at presentation
1. Turner sign—bluish discoloration of the flank
2. Cullen sign—bluish discoloration of the periumbilical region
3. Turner and Cullen signs indicate hemorrhagic pancreatitis and are late signs in the clinical course of pancreatitis

<table>
<thead>
<tr>
<th>Table 1. Signs and Symptoms</th>
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<tr>
<td>Common</td>
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<tr>
<td><strong>Symptoms</strong></td>
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<tr>
<td>Abdominal pain</td>
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<tr>
<td>Irritability (infants)</td>
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<tr>
<td>Nausea</td>
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<td>Vomiting</td>
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<td>Anorexia</td>
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<td>Abdominal tenderness</td>
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<td>Abdominal distension</td>
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<td>Evidence of dehydration</td>
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<td></td>
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<tr>
<td><strong>Signs</strong></td>
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E. Laboratory Findings
1. Serum amylase
   a. 33%–45% from the pancreas, remainder from the salivary glands
   b. Increases in 2–12 hours and remains increased 3–5 days
   c. Can be elevated in other conditions such as diabetic ketoacidosis, renal failure, burns, mumps, anorexia and bulimia
2. Serum lipase
   a. Increases in 4–8 hours and remains increased 8–14 days
   b. More sensitive indicator of pancreatic injury than amylase
3. Other evaluation to determine underlying etiology
   a. Elevated transaminases and GGT suggest possible underlying biliary obstruction
   b. Electrolytes may reveal an elevated calcium level
   c. Elevated triglycerides suggest an underlying hyperlipidemia
   d. Genetic testing for PRSS1, CFTR, SPINK-1 mutations if there is a significant family history or patient history of recurrent pancreatitis

F. Imaging
1. Ultrasound
   a. Very good initial test
   b. Available, inexpensive, no radiation exposure
   c. High sensitivity for gallstones
   d. Limited by obesity and bowel gas
2. CT scan with IV and enteral contrast
   a. Not necessary in most cases of acute pancreatitis
   b. Helpful in patients with a prolonged course because it can identify possible etiologies and/or complications
   c. Radiation exposure is a drawback
3. Magnetic resonance cholangiopancreatography (MRCP)
   a. Helpful in patients with recurrent episodes of acute pancreatitis
   b. Can reveal anatomic abnormalities and obstructive etiologies, such as pancreatic divisum, gallstones and choledochal cyst
   c. Requires anesthesia in younger children
4. Endoscopic retrograde cholangiopancreatography (ERCP)
   a. Limited role in initial evaluation of acute pancreatitis
   b. Most helpful for interventional procedure (stone removal, stent placement, etc)
5. Esophagogastroduodenoscopy (EGD)
   a. Not routine in the evaluation of acute pancreatitis
   b. May reveal duodenal ulcer, tumor of the papilla or duodenal Crohn disease
6. Endoscopic ultrasound
   a. Not in widespread use yet
   b. Helpful for gallstones and microlithiasis
   c. Limited data in children

V. Treatment/Management

A. Fluid Management
   1. Early aggressive fluid resuscitation improves outcome and prevents severe disease in animal and human studies, by maintaining cardiovascular stability and decreasing the incidence of pancreatic necrosis

B. Pain Control
   1. Parenteral narcotics are preferred
   2. All opiates increase sphincter of Oddi pressure, but this action does not affect outcome or clinical course

C. Nutrition
   1. Pancreatic rest (nothing by mouth) is standard in treatment of acute pancreatitis, but no clear evidence supports this practice
   2. Early enteral nutrition is recommended
      a. Associated with lower infection risk, reduced surgical interventions and shorter hospital stay
      b. Jejunal feeds may be helpful, since there is less stimulation of the exocrine pancreas
      c. No evidence-based guidelines in children. Adult studies suggest oral nutrition be resumed when pain and nausea resolve in mild cases. In severe pancreatitis, enteral nutrition within the first 48 hours has been associated with a better outcome
   3. No evidence that clear liquid or a low-fat diet improves outcome

VI. Complications/Outcomes

A. Most cases resolve in 7–10 days without complications
B. 13%–20% of children have prolonged courses with complications
C. Mortality rate ranges from 2%–10%, and in children is typically associated with systemic illness
D. Peripancreatic fluid collections and pseudocyst
   1. Most common complication in children (13%–16% of cases)
   2. Trauma often associated with pancreatic pseudocyst formation in children
   3. Suspect pseudocyst if acute episode is not resolving, abdominal mass develops or pancreatitis recurs
   4. Ultrasound or CT scan aid in diagnosis (Figure 1)
   5. Pseudocyst can be managed conservatively. Some require surgical drainage (endoscopic or surgical, often into the stomach) and long-term antibiotics
E. Other local complications
   1. Fat necrosis
   2. Pancreatic necrosis, pancreatic abscess
   3. Abscess extension to adjacent organs
F. Systemic complications
   1. Electrolyte abnormalities
   2. Sepsis
   3. Pleural effusions
   4. Acute renal failure
   5. Coagulopathy
   6. Shock

**Figure 1.** Pseudocyst (between white arrows) near the distal body and tail of the pancreas. Figure adapted from Lowe ME. Pancreatitis. In: Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*. 4th ed. Philadelphia, PA: Elsevier Saunders; 2011: Chapter 82.

**Recommended Reading**


7E. Chronic Pancreatitis

I. Chronic pancreatitis
Chronic pancreatitis is the continuous destruction of the pancreatic gland with irreversible scarring of acinar and ductal cells. Each exacerbation leads to additional damage. Fortunately, the pancreas has significant reserves and is able to function with as little as 10% of the gland functioning. The etiology of chronic pancreatitis can be divided into obstructive (ductal anomalies, strictures, trauma and autoimmune), calcific (hereditary, hyperlipidemia and hypercalcemia) and idiopathic.

II. Genetic causes of chronic pancreatitis
A. Hereditary pancreatitis (PRSS1)
1. Most common genetic cause of chronic pancreatitis
2. Mutation in cationic trypsinogen gene (serine protease 1) located on chromosome 7q35, autosomal dominant
3. R112H is the most prevalent mutation followed by N291
4. Recurrent bouts of pancreatitis starting at 10–20 years of age
5. Family history usually positive for recurrent pancreatitis
6. Long-term risk of diabetes and pancreatic adenocarcinoma
B. SPINK-1 gene produces pancreatic trypsin inhibitor
1. Mutations cause uninhibited activation of trypsin in pancreatic ducts
2. Mutations may be autosomal dominant, autosomal recessive or multigenic
3. Family history usually absent
C. Cystic fibrosis transmembrane conductance regulator gene (CFTR)
1. Heterozygous mutations of this autosomal recessive gene found in 20%–40% of patients with chronic pancreatitis
a. Gene expressed in pancreatic ductal tissue of Type 1 is cystic fibrosis with a CFTRsev/CFTRsev
b. Type 2 is atypical cystic fibrosis with a CFTRsev/CFTRm-v
c. Type 3 is CFTRsev or CFTRm-v plus a second pancreatitis modifier or susceptibility gene in a polygenetic condition
d. Type 4 is CFTRsev or CFTRm-v plus a strong environmental risk factor, such as alcohol

III. Causes of chronic obstructive pancreatitis
A. Pancreas divisum
1. 25 % of patients with pancreatic divisum develop obstructive pancreatitis
2. Diagnosed by MRCP or ERCP (see Figure 1)
3. Optimum therapy not established
   a. Endoscopic sphincterotomy or surgical sphincteroplasty
   b. Stent of minor papilla
B. Idiopathic fibrosing pancreatitis
1. Very rare
2. Presents with obstructive jaundice or abdominal pain and pancreatitis
3. Diffuse pancreatic fibrosis ± inflammation
4. Can be associated with PRSS1, SPINK-1 and CFTR 5T
C. Abdominal trauma may cause obstructive pancreatitis if there is duct damage and stricture formation
D. Congenital anomalies associated with chronic pancreatitis: choledochal cyst, pancreatic ductal duplication, anomalous pancreaticobiliary ductal union
E. Autoimmune pancreatitis
   1. Primary: isolated pancreatic involvement may require biopsy diagnosis
   2. Associated with lupus erythematosus, autoimmune hepatitis, Sjögren disease
   3. Histology shows ductal and periductal infiltration by lymphocytes, plasma cells and granulocytes with irregular narrowing of pancreatic duct and pancreatic enlargement
   4. Associated increase in IgG4 (most commonly in adults)
   5. Responsive to steroids

IV. Other causes of chronic pancreatitis
   A. Hypertriglyceridermia syndromes
      1. Type I hyperlipidemia—30% develop pancreatitis
      2. Type IV—15% of patients develop pancreatitis
      3. Type V—30%–40% of patients develop pancreatitis
      4. Common features include triglyceride levels >1,000 mg/dL
   B. Tropical chronic pancreatitis
      1. Disease with young onset
      2. Occurs in tropics
      3. Associated with large intraductal calculi, steatorrhea and diabetes
   C. Hypercalcemia
   D. Organic acidemia

V. Clinical presentation of chronic pancreatitis
   A. Repeated bouts of pancreatitis
   B. Acute and chronic abdominal pain
   C. Chronic abdominal pain may improve in longstanding disease due to loss of pancreatic tissue
   D. Some patients present with diabetes, exocrine pancreatic insufficiency and obstructive jaundice without obvious pain

VI. Diagnostic testing
   A. Elevated serum amylase and lipase almost always present during acute episodes but may not be dramatic as disease progresses
   B. Biochemical markers of protein and fat malabsorption occur late in disease due to exocrine insufficiency
   C. Pancreatic stimulation test helpful to evaluate exocrine function (see section on Pancreatic Function Testing)
   D. Fecal elastase (see section Pancreatic Function Testing) is a noninvasive method to document pancreatic exocrine insufficiency
   E. Functional MRCP obtained after intravenous secretin improves definition of pancreatic duct anatomy
   F. Other imaging studies to clarify duct structure, cysts, masses, ductal stricture or dilation
      1. Endoscopic ultrasound—head of pancreas
      2. Abdominal CT
      3. MRCP
   G. Genetic testing to clarify causation (see above)

VII. Treatment
   A. Treat acute episodes – (see section on Acute Pancreatitis)
   B. Acute and chronic pain management
   C. Nutrition
      1. Low-fat diet, although evidence is lacking
      2. Nasoduodenal feeds
   D. Surgical therapies
      1. Puestow procedure—pancreas and main pancreatic duct are sectioned longitudinally and oversewn with a segment of jejunum to directly drain pancreatic secretions into bowel
      2. Partial pancreatectomy may relieve pain
      3. Complete pancreatectomy with islet cell transplantation in recalcitrant disease
      4. Celiac sympathectomy in recalcitrant disease with pain
Figure 1. Typical pancreatic divisum. Small ventral duct (arrows) drains via major papilla. Larger dorsal duct (open arrows) drains via minor papilla. Adapted from Yu J, Turner MA, Fulcher AS, Halvorsen RA. AJR. 2006;187:1544-1553. Reprinted with permission from the American Journal of Roentgenology.

Recommended Reading


7F. Shwachman-Diamond Syndrome

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Cheryl E. Gariepy, MD

I. Overview/ Epidemiology
A. Autosomal recessive condition characterized by the triad of exocrine pancreatic insufficiency, bone marrow dysfunction and skeletal abnormalities
B. Prevalence is 1:50,000
   1. SDS is the 2nd most common inherited cause of pancreatic insufficiency after cystic fibrosis
   2. SDS is the 3rd most common inherited bone marrow failure syndrome
C. Variable clinical presentation with gastrointestinal and hematologic abnormalities in almost all patients
D. Median survival for all patients is 35 years. Severe bacterial infection and leukemia are the major causes of morbidity and death

II. Pathogenesis
A. Biallelic mutations in the SBDS gene on chromosome 7 occur in 90% of cases. The remaining 10% have the clinical picture of SDS but no identified mutations
B. The SBDS gene product seems to participate in ribosome biogenesis, RNA processing, stabilizing the mitotic spindle and neutrophil chemotaxis
C. Mutation causes failure of normal development of pancreatic acinar tissue in utero with fatty replacement of acini
D. Bone marrow abnormalities
   1. Abnormal myeloid clones in bone marrow with mutations of chromosome 7 (eg, monosomy) and dysmyelogenesis
   2. Leukemia or aplastic anemia are long-term complications
   3. Impaired neutrophil function
E. Skeletal abnormalities
   1. No correlation between genotype and skeletal phenotype
   2. Delayed secondary ossification
   3. Variable widening, thickening, and irregularity of the metaphyses and growth plates
   4. Generalized osteopenia

III. Comparison of Pancreatic Function in CF and SDS
A. Sweat chloride
   1. Normal sweat chloride concentration in SDS
   2. Elevated sweat chloride in CF
B. Histology
   1. Normal ductal elements in SDS. Fatty replacement of the acinar tissue
   2. Duct obstruction, fibrosis and ectasia in CF
C. Pancreatic enzyme output
   1. Increased pancreatic volume and enzyme output in SDS patients over time with normal fat absorption in approximately 50% of patients by 4 years of age
   2. No increased risk of pancreatitis in SDS
   3. Enzyme output in CF is dependent on genotype, whereas in patients with SDS it is NOT dependent on genotype
IV. Laboratory Diagnosis of SDS

A. Low pancreatic secretion of lipase, amylase and trypsin in response to secretin and CCK stimulation
B. Low serum immunoreactive trypsinogen and low serum isoamylase in children <3 years of age
C. Serum immunoreactive trypsinogen and fat absorption may normalize in older children/adults.
D. Low serum isoamylase levels and starch malabsorption persist to adulthood
E. Cyclic or persistent neutropenia. Additional cytopenias may also be present. Anemia has been reported in 42%–66% of patients, and thrombocytopenia has been reported in 24%–60%
F. Imaging
   1. Abdominal CT scan or ultrasound shows a fatty pancreas of normal size
   2. Skeletal x-ray findings include clinodactyly, syndactyly, genu and cubitus valgus, tooth enamel defects, metaphyseal dysostosis

V. Clinical Manifestations

A. Diarrhea, steatorrhea, failure to thrive
B. Hematology
   1. Recurrent neutropenia is most common abnormality (>90%)
   2. Impaired neutrophil chemotaxis
   3. Pancytopenia (in approximately 10%–25%) carries the worst prognosis
   4. 1/3 of patients with severe chronic neutropenia develop myelodysplastic syndrome (MDS)
   5. 10%–25% of patients with severe chronic neutropenia develop acute myeloid leukemia (AML)
C. Skeletal abnormalities
   1. Progressive metaphyseal dysostosis in approximately 45% of patients
   2. Thoracic cage abnormalities in approximately 1/3 of patients
   3. Short stature, usually remaining at less than the 5th percentile for life
   4. May be at higher risk for slipped capital femoral epiphysis (SCFE)
D. Others
   1. Dental caries, enamel abnormalities, delayed dentition
   2. Hepatomegaly and elevated transaminases are common in infancy and usually resolve by 5 years of age. Histologic abnormalities may include microvesicular and macrovesicular steatosis, perportal and portal inflammation, bridging fibrosis and glycogenosis
   3. Learning difficulties including weaknesses in higher-order language skills, perceptual skills and perceptual reasoning are more common in patients with SDS compared to both healthy controls and patients with CF
   4. Behavioral issues and social problems are also more common in patients with SDS compared to healthy siblings, healthy unrelated controls and patients with CF

VI. Treatment/Management

A. Oral pancreatic enzyme supplementation. Steatorrhea typically resolves in approximately 50% of patients by 4 years of age. Fecal fat measurement should be repeated to determine the need for continued supplementation
B. Fat-soluble vitamin supplementation
C. Serial CBC (at least every 4–6 months)
D. Bone marrow biopsy (every 1–3 years)
E. Transfusions as needed
F. Timely evaluation of fever and neutropenia, including physical exam, cultures and prophylactic antibiotics
G. Granulocyte colony-stimulating factor (G-CSF) for those patients with ANC <500 and with repeated infections. The French Neutropenia Registry has documented an 80% response with G-CSF, but there has been no association between G-CSF use and the subsequent risk of AML
H. Bone marrow transplant is the only curative therapy for bone marrow failure
VII. Differential Diagnosis

A. Cystic fibrosis: sweat chloride and genetic testing will differentiate. In addition, high immunoreactive trypsinogen in most infants with CF

B. Johanson-Blizzard syndrome
   1. Exocrine pancreatic insufficiency
   2. Multiple congenital abnormalities: deafness, imperforate anus, urogenital malformations, dental anomalies
   3. Endocrine abnormalities: hypothyroidism, GH deficiency, diabetes, panhypopituitarism
   4. Typical facies: nasal hypoplasia with beak-shaped appearance, small misshapen teeth, sparse hair

C. Pearson Marrow-Pancreas syndrome
   1. Rare mitochondrial disorder
   2. Exocrine pancreatic insufficiency
   3. Bone marrow involvement
      a. Profound sideroblastic anemia
   4. Lactic acidosis is very common
   5. Early death is very common

D. Jeune syndrome
   1. Rare autosomal-recessive disorder
   2. Exocrine pancreatic insufficiency
   3. Respiratory difficulties, asphyxiating thoracic dystrophy

Recommended Reading


I. Description
Cystic fibrosis is the most common lethal genetic disease in Caucasians. Cystic fibrosis affects many organ systems, including the gastrointestinal tract (meconium ileus, distal intestinal obstruction syndrome), hepatobiliary system (neonatal cholestasis, steatosis, biliary cirrhosis, biliary sludge) and pancreas (exocrine dysfunction).

II. Carrier Rate/Inheritance/Diagnosis
A. Autosomal recessive with carrier rate in Caucasians of 1 in 25
B. Disease prevalence
   1. Caucasians 1 in 2,500
   2. African Americans 1 in 15,000
   3. Asians 1 in 31,000
C. Of more than 1,500 mutations now described, ΔF508 accounts for 66%
   1. Deletion of the three nucleotides comprising the codon for phenylalanine at position 508
D. Most cases of CF are diagnosed by newborn screen with high values of immunoreactive trypsinogen (IRT)
   1. False positive (high) IRT may be produced by:
      a. hypoxia, respiratory or physiologic stress
      b. low Apgar scores, organ damage
      c. trisomies 13, 18, 21
      d. renal dysfunction
      e. hypoglycemia
      f. contamination of filter paper
      g. carrier status
      h. early specimen collection
   2. False negative (low) IRT results seen in:
      a. CF genetic variant with normal pancreatic function
      b. Older affected infant with pancreatic insufficiency
      c. Meconium ileus (severe pancreatic insufficiency)
E. Gold standard of CF testing remains sweat chloride.
   1. Normal <40 mmol/L
   2. Abnormal ≥60 mmol/L
   3. Borderline readings between 40–60 require repeat sweat chloride test, CFTR mutation analysis or nasal potential difference to confirm diagnosis
   4. False positive sweat chloride test caused by
      a. Anorexia nervosa, Addison disease, nephrogenic diabetes insipidus and hypothyroidism
   5. False negative sweat chloride test caused by
      a. Edema

III. CFTR: Structure and Function (See Figure 1)
A. Localized in the epithelial cells of the airway, pancreatic and hepatic ducts, intestine, sweat gland and vas deferens
B. CFTR opens channels in the cell membrane which transport chloride ions out of the cells
C. Six classes of mutations with increasing severity
   1. Mutations of lower class (I-IV) involve mutation, with effect closer to the transcription and processing phase of the CFTR protein with complete loss of function
      a. More serious complications of the lower classes include pancreatic insufficiency (PI), meconium ileus and hepatic complications
   2. Mutations of higher class (V-VI) have reduced function once CFTR reaches the surface membrane (see Figure 1)
IV. Meconium Ileus (see section on Miscellaneous Cystic Fibrosis)
   A. One of the earliest manifestations of cystic fibrosis occurs in 15% of CF neonates
   B. 50% of cases resolve without complication
      1. Gastrografin enema can be both diagnostic and therapeutic
      2. In cases unresponsive to gastrografin enema, T-tube ileostomy with instillation of
         n-acetylcysteine, gastrografin or surgical decompression is possible
   C. Complications of meconium ileus (MI)
      1. Meconium peritonitis from in utero perforation, gangrene, volvulus and atresia often
         require surgical intervention
      2. CF patients with meconium ileus have ↑ neonatal mortality, ↑ incidence of distal
         intestinal obstructive syndrome (DIOS) and ↑ incidence of surgical complications
      3. Relationship between MI and later CF liver disease is unclear
   D. Overall survival rate, nutritional status and pulmonary function of CF patients with and without
      MI are similar

V. Hepatic complications of cystic fibrosis
   A. Prevalence of significant liver disease in CF children estimated at 13%–25%
   B. 30% of CF children have hepatomegaly
   C. Mechanism of hepatobiliary disease:
      1. CFTR mutations lead to defective CFTR function in the biliary tree
      2. Focal biliary obstruction by viscous secretions leads to focal periportal inflammation and
         biliary cirrhosis
      3. Portal inflammation causes decreased bile flow, increased toxic (deconjugated) bile and
         increased bile precipitation
      4. Long-term outcome may be multilobular cirrhosis, hepatosplenomegaly, portal
         hypertension and hypersplenism
      5. More severe liver disease may be modulated by other genetic and/or environmental
         factors
   D. Prolonged neonatal cholestasis occurs in 35% of CF neonates
      1. The hepatic prognosis is favorable, with only a small percentage progressing to cirrhosis
      2. There is no therapy that will alter the course of progression to cirrhosis in CF
      3. Ursodiol has been shown to improve bile flow and biochemical parameters of liver injury
         in CF

Figure 1. CFTR structure and function.
E. Hepatic steatosis is common in CF patients of all ages
   1. It is a reflection of malnutrition and/or deficiency of essential fatty acids, carnitine or choline
   2. In older children, the development of diabetes can also contribute to steatosis
   3. Ultrasonography and computed tomography show increased hepatic fat
   4. Steatosis does not progress to serious focal biliary cirrhosis
F. Focal biliary cirrhosis
   1. Usually presents in teen years or later
   2. CF patients are generally asymptomatic until late in the disease course
   3. Hepatomegaly or splenomegaly can be present along with elevated serum transaminases
   4. Elevated serum bilirubin usually a late finding
   5. CF patients with high transaminases for 3–6 months should have Doppler US to assess hepatic blood flow and possible esophageal varices
   6. MRCP can be used for checking biliary tree and gallbladder
   7. Liver biopsy is another option
   8. Treatment includes ursodiol and nutritional improvement
G. Portal hypertension
   1. Pace of progression is unpredictable
   2. The incidence of portal HTN and variceal bleeding in CF patients is <5%
H. Cholelithiasis and biliary sludging
   1. Incidence ranging from 1%–10% of CF patients
   2. CF patients usually have radiolucent gallstones rich in calcium bilirubinate and proteins; therefore, ursodiol does not help dissolve the stones
   3. Symptomatic patients require cholecystectomy with intraoperative cholangiogram to assess intrahepatic biliary tree
I. Microgallbladder is found in 20% of CF patients
   1. It is a relatively benign condition
   2. Bile duct stenosis requiring dilation occurs in <1% of CF patients
J. Liver transplantation
   1. Almost all patients with cystic fibrosis have some evidence of liver disease, but only 3%–7% develop the degree of cirrhosis that progresses to end-stage liver disease
   2. In 2002 Milkiewicz reported that among CF patients requiring liver transplant, the average age was 13 years. Recommendation is that liver transplant be performed before lung transplant if both are needed
H. CF patients have an increased risk of malignancies including esophagus, stomach, small and large intestine, rectum, liver, biliary tract and pancreas. Greatest risk for malignancy is 20–29 years of age

VI. Nutritional Complications
A. Pancreatic insufficiency (PI)
   1. Exocrine pancreatic insufficiency occurs in 60% of infants and in 90% by 1 year of age
   2. Protein-calorie malnutrition due to maldigestion and increased energy requirements occurs in untreated patients
   3. An acute Marasmic-Kwashiorkor-like presentation can occur with growth failure, anemia, hypoproteinemia, edema and ascites
B. Fat-soluble vitamin deficiencies occur in up to 50% CF infants by 2 months of age
   1. Even when supplemented with standard ADEK, there can still be a deficiency, especially vitamin E
C. Electrolyte abnormalities
   1. NaCl loss can occur with increased sweating (environmental, fever)
   2. Salt supplementation at 2–4 mmol/kg/day
   3. Most common presentation is hypochloremic alkalosis and dehydration
   4. Very low urinary sodium is a good indicator that salt supplementation is needed
VII. Pancreatic Exocrine Function Association With Genotypes/Abnormalities

A. CFTR genotypes are more closely related to the severity of pancreatic exocrine dysfunction than they are to the severity of lung disease
B. Fecal fat excretion is more accurate than fecal elastase or serum IRT for classifying the extent of pancreatic exocrine insufficiency
C. The most accurate test of pancreatic exocrine function is direct pancreatic stimulation with exogenous hormones (i.e., cholecystokinin or secretin) (see section on Pancreatic Function)
D. Pancreatic insufficiency occurs when <10% of normal pancreatic exocrine function remains

Recommended Reading


