3A. Normal Anatomy, Development, and Physiology

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I. Development

A. Primitive gut tube is formed by the incorporation of a portion of the yolk sac into the embryo during craniofacial and lateral folding
   1. Epithelial lining and glands are derived from endoderm
   2. Lamina propria, muscularis mucosa, submucosa, muscularis externa, and adventitia/serosa are derived from mesoderm
   3. Posterior luminal digestive structures and enteric nervous system are derived from the ectoderm
B. Epithelial lining proliferates rapidly, occluding the lumen. This process is later followed by recanalization
C. Primitive gut tube, which forms at 4 weeks, is divided into: foregut, midgut, and hindgut
   1. Caudal portion of the foregut—upper duodenum
      a. Blood supply—celiac artery
   2. Midgut—lower duodenum, jejunum, ileum, appendix, ascending colon, and proximal two-thirds of the transverse colon
      a. Blood supply: superior mesenteric artery (SMA)
      b. Midgut loop herniates through the primitive umbilical ring at 6 weeks' gestational age
      c. Midgut loop rotates counterclockwise 270° around the SMA as it returns to the abdominal cavity at 11 weeks’ gestational age
D. Differentiation
   1. Week 7: Primitive gut has a simple tubular form
   2. Week 9: Development of villi
   3. Week 12–14: Appearance of primitive crypts
   4. Week 13: Completed development of both circular and longitudinal muscle layers
   5. Week 16: Development of muscularis mucosa
   6. Week 20: Presence of well-developed villi and crypts, along with lamina propria and specialized connective tissue
E. Anomalies
   1. Duodenal/intestinal atresia or stenosis: Failure of recanalization
   2. Omphalocele: Failure of the midgut loop to return to the abdomen, covered with outer amniotic and inner peritoneal sac (see Gastrochisis and Omphalocele)
   3. Vitelline fistula: Persistence of the vitelline duct (meconium discharge from the umbilicus)
   4. Meckel’s diverticulum: Remnant of vitelline duct persists, forming a blind pouch on antimesenteric border of the ileum
      a. May contain ectopic gastric, thyroid, or endometrial tissue
   5. Malrotation: Midgut undergoes only partial rotation
   6. Non-rotation: Occurs in about 1 in 500 live births and has been described in 0.5% of autopsies
      a. Laxity of the umbilical ring, which allows reduction of the midgut without rotation during the 10th week of fetal development, is a likely cause of non-rotation

II. Molecular Mechanisms

A. Hox genes: Expressed in the mesoderm of the gut, play a role in gut patterning along the AP axis, including gross morphology, as well as epithelial differentiation
B. Hoxd13 and Hoxa13 play a role in the hindgut mesoderm-to-endoderm signaling and control final epithelial phenotype
C. In addition to Hox genes, at least two ParaHox transcription factor genes, Cdx2 and Pdx1, are critical for gut tube development

1. Cdx2 likely patterns the vertebrate gut by regulating Hox gene expression in the endoderm. During development, the homeobox gene Cdx2 exerts a homeotic function, providing the positional information necessary for correct specification of the midgut endoderm

2. The early patterning of the embryo determines the expression pattern of ParaHox, Hox, and other transcription factor genes in the endoderm and adjacent mesoderm. A complex interaction between these two tissues leads to the final pattern of the gut tube along the AP axis. Hedgehog, Bmp, Fgf, and Wnt signaling have all been implicated in various aspects of gut development

III. Anatomy

A. The length of the small intestine varies from 3–10 meters (10–33 feet). Average small intestine length is 6.5 meters (22 feet)

B. Small intestine is divided into duodenum, jejunum, and ileum

1. Duodenum: Approximately 25 cm in length. Extends from the pylorus to the duodenal-jejunal flexure (attachment of the ligament of Treitz)
   a. About 2.5 cm of the proximal duodenum are covered by the peritoneum; after that, it becomes a retroperitoneal organ
   b. There is no division between jejunum and ileum
   c. The diameter of the small bowel decreases from the proximal to distal end

C. Jejunum tends to have a thicker wall and bigger folds (valvulae conniventes)

1. Jejunum lies closer to the umbilical region, and ileum towards hypogastrium and pelvis

D. Blood supply

1. Arterial
   a. Branches of Superior Mesenteric Artery (SMA)
      1) Inferior pancreaticoduodenal artery: supplies pancreas and duodenum
      2) Jejunal and ileal branches of SMA: supply most of the small intestine
      3) Ileocolic artery: supplies terminal ileum, cecum, appendix, and proximal ascending colon

2. Venous
   a. Superior mesenteric vein joins the splenic vein to form the portal vein

E. Innervation

1. Autonomic nervous system is comprised of the extrinsic and intrinsic enteric nervous systems.
   a. Extrinsic nervous system
      1) Parasympathetic (vagal and pelvic nerves): excitatory on all GI functions
         a) Synapse in myenteric and submucosal plexus
      2) Sympathetic (fibers originate in the spinal cord T8-L2): inhibitory on all GI functions
   b. Intrinsic nervous system
      1) Myenteric plexus (Auerbach’s plexus) located between the circular and longitudinal muscular fibers, from which the nervous branches are distributed to the muscular coats of the intestine. Primarily controls the motility of the GI tract
      2) Submucosal (Meissner’s plexus) which lies in the submucous coat of the intestine; it also contains ganglia from which nerve fibers pass to the muscularis mucosae and to the mucous membrane. Primarily controls secretion and blood flow

IV. Immune System

A. The immune system of the small intestine is part of gut-associated lymphoid tissue (GALT).

It is comprised of:

1. Peyer’s patches: lymphoid follicles located mostly in the ileum and extending from mucosa to submucosa
2. Lamina propria lymphocytes: mostly IgA-secreting B cells scattered in the lamina propria
3. Intraepithelial lymphocytes: located beneath the tight junctions between the epithelial cells
4. M cells: located in Peyer’s patches and isolated lymphoid follicles, in dome-shaped areas overlying B cell follicles (follicle-associated epithelium)
   a. Function to pick up particles from the lumen and funnel them to hematopoietic cells in the lymphoid tissue on their basolateral side
   b. This allows antigens in the lumen to be sampled in a controlled manner and an appropriate immune response mounted
c. The defining characteristic of the M cell is its ability to pick up and transcytose particles from the gut lumen and deliver them to the lamina propria, where they are then processed by hematopoietic cells.

5. T cells can travel from Peyer patches to lamina propria and the epithelium.

6. Primary sites for the induction of intestinal T and B cell responses are Peyer's patches, colonic lymphoid follicles and MLNs.

7. Lamina propria (LP) and the intraepithelial cell (IEC) compartments are primarily effector sites.

8. IgA: principal class of antibody produced by gut lymphocytes.
   a. Comprises 60%–70% of about 3 g of antibodies produced daily in an adult.
   b. IgA is actively transported across epithelia (carried out by Fc receptor-poly Ig receptor located on the basal surface of the epithelial cells), then binds to and neutralizes microbes in the lumen and mucosal organs.

V. Normal Ion Transport

A. The intestinal epithelium acts as a physical barrier, separating the luminal environment and subepithelial tissues. This polarized barrier is primarily maintained by apical junctional complexes, including tight junctions and adherens junctions, which connect epithelial cells.

1. Tight junctions are made of complex interactions between up to 40 proteins, including the transmembrane proteins occludin, junctional adhesion molecule, and claudins.
   a. These proteins are anchored to the actin filaments and MLC of the perijunctional actinomyosin ring through cytosolic plaque proteins of the zonula occludens (ZO) family.

2. Adherens junctions lie basolateral to the tight junctions, and are formed by the interaction of the transmembrane protein E-cadherin with cytoplasmic proteins of the catenin family.
   a. Transport of electrolytes and water across the barrier occurs through cellular and paracellular pathways.

B. Sodium

1. Transport in the small intestine by:
   a. Na+ channels (passive): restricted diffusion through water-filled channels
   b. Concentration driven, increases the negative electric potential across the epithelial cell membrane.

2. Na+-glucose or Na+-amino acid cotransport: primarily proximal bowel.
   a. And electrically neutral (gradient dependent):
      1) Na+Cl- cotransport: primarily ileum
      2) Na+/H+ exchange: primarily proximal bowel
   b. Principle:
      1) Na+ pumped out of the cell against electrochemical gradient by Na+/K+ pump in the basolateral membrane.

C. Chloride

1. Cl- absorption occurs with Na+ absorption by:
   a. Passive diffusion through paracellular route
   b. Na+Cl- cotransport
   c. Cl-/HCO3- exchange–distal ileum.

D. Potassium


E. Water

1. Secondary to solute absorption
2. Iso-osmotic in the small intestine.

F. Secretion of water and electrolytes:

1. Secretory mechanisms are primarily located in the crypts
2. Cl- primary ion secreted. It is transported through chloride channels regulated by cAMP
3. Na+ passively follows Cl-, water follows Na+Cl- to maintain iso-osmotic conditions.

G. Iron

1. Absorbed as heme iron or free Fe2+ in the duodenum and jejunum
2. Heme iron is degraded in epithelial cells and free iron is released, which is bound to apoferritin, making a complex called ferritin.
   a. Some of the ferritin-bound iron can be utilized, but most gets lost with epithelial cell turnover.
3. Free iron in the blood is bound to transferrin (beta1 globulin) which transports it from the intestines to the liver and then bone marrow.
4. Iron is stored in the liver as ferritin
5. Organic acids (ascorbic or citric) reduce Fe3+ to Fe2+, which is absorbed more efficiently

H. Calcium
1. Calcium absorption through the brush border depends on 1,25 dihydroxyvitamin D3, which stimulates synthesis of calcium-binding protein
2. Calcium remains bound to the protein inside the cell
3. Exit at the basolateral membrane is dependent on Ca+ ATPase and Na+ Ca+ exchanger, both vitamin D3 dependent
4. Calcium absorption is regulated by serum calcium levels

I. GI Hormones

Table I. Review of Gastric Hormones

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Mode of Cell Signaling</th>
<th>Cell type</th>
<th>Location</th>
<th>Stimulus</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrin</td>
<td>hormone</td>
<td>G</td>
<td>Stomach</td>
<td>Peptide, amino acids, stomach distention, vagal (via GRP)</td>
<td>Increase in H+ secretion (inhibits gastrin secretion) Trophic effect on gastric mucosa</td>
</tr>
<tr>
<td>CCK</td>
<td>hormone</td>
<td>I</td>
<td>Duodenum, Jejunum</td>
<td>Peptides, amino acids, Fatty acids</td>
<td>Contraction of gall bladder Relaxation of sphincter of Oddi Pancreatic enzyme and HCO3 secretion Growth of exocrine pancreas/gallbladder Inhibits gastric emptying</td>
</tr>
<tr>
<td>Secretin</td>
<td>hormone</td>
<td>S</td>
<td>Duodenum</td>
<td>H+ in the duo-denum Fatty acids in duodenum</td>
<td>Pancreatic HCO3 secretion Biliary HCO3 secretion Inhibits gastric H+ secretion</td>
</tr>
<tr>
<td>GIP</td>
<td>hormone</td>
<td>GIP cells</td>
<td>Duodenum, Jejunum</td>
<td>Fatty acids Amino acids Oral glucose</td>
<td>Stimulates insulin secretion Inhibits gastric H+ secretion</td>
</tr>
<tr>
<td>Motilin</td>
<td>hormone</td>
<td>Mo</td>
<td>Small intestine</td>
<td></td>
<td>Motility</td>
</tr>
<tr>
<td>Histamine</td>
<td>paracrine</td>
<td>ECL</td>
<td>Stomach</td>
<td></td>
<td>Increases gastric H+ secretion Potentiates effects of gastrin and vagal stimulation</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>paracrine</td>
<td>D</td>
<td>Pancreas Stomach Small and large intestines</td>
<td>H+ in the lumen</td>
<td>Inhibits the release of all GI hormones Inhibits gastric H+ secretion</td>
</tr>
<tr>
<td>VIP</td>
<td>neurocrine</td>
<td>Neurons</td>
<td>Smooth muscle and mucosa</td>
<td></td>
<td>Relaxation of GI smooth muscles, possibly also vasodilation Stimulates pancreatic HCO3 secretion Inhibits gastric H+ Stimulates intestinal secretion</td>
</tr>
<tr>
<td>GRP (bombesin)</td>
<td>neurocrine</td>
<td>Vagus nerve</td>
<td>Gastric mucosa</td>
<td></td>
<td>Stimulates gastrin release from G cells</td>
</tr>
</tbody>
</table>
Recommended Reading


I. Small Bowel Histology

A. Overview
1. Mucosa composed of three components: epithelium, lamina propria, and muscularis mucosa
2. Surface epithelium and lamina propria form intraluminal projections, called villi, which cover entire luminal surface of small bowel (SB) (see Figure 1)
3. Intervening regions between and below the villi represent the crypts of Lieberkuhn
4. Ratio of villous length to crypt length in SB varies between 3:1 to 5:1

B. Epithelium
1. Divided into villous and crypt compartments
2. Villous epithelium consists of tall, columnar cells and absorptive cells
   a. Apical surface contains brush border composed of microvilli and glycocalyx
   b. Microvilli-glycocalyx involved in complex function interluminal digestive processes
   c. Goblet cells, endocrine cells, and intraepithelial lymphocytes are also scattered among villous epithelium
   d. Usually 1 lymphocyte for every 5 epithelial cells
3. Crypt epithelium function in epithelial cell renewal
   a. Endocrine cells and Paneth cells are most abundant throughout the crypt epithelium
   b. Inflammatory cells such as neutrophils, or plasma cells, are not normally present within any of the epithelial compartments

C. Lamina propria
1. Intermediate layer of the mucosa; surrounds the crypts, extends up the villi, and rests upon the muscularis mucosa
2. Composed of smooth muscle layers that separate lamina propria from submucosa
3. Plasma cells are the most abundant in the lamina propria
4. Mast cells are also abundant, but generally decrease with distal progression in the small bowel

D. Muscularis mucosa
1. Outermost layer of mucosa
2. Composed of smooth muscle arranged in an outer longitudinal and inner circular layer (these layers, however, are not usually delineated on routine light microscopy)
3. Structural foundation for the mucosa

E. Submucosa
1. Lies between muscularis mucosa and muscularis externa, composed of collagenous and elastic fibers, as well as scattered migratory cells and adipose tissue
2. Vascular and lymphatic structures cross submucosa
3. Neural structures also prominent in submucosa, ie, submucosal plexus of Meissner

F. Muscularis externa
1. Thick, outer smooth muscle layer that surrounds submucosa
2. Composed of two distinct muscular layers oriented perpendicular to each other (inner layer is circular band, while outer layer is longitudinal running fiber)
3. Blood vessels, lymphatics, and nerve complexes (Auerbach’s plexus) course through
4. Fibrous tissue is minimal

II. Regional Characteristics of SB

A. Duodenum
1. Region of gastroduodenal junction, antral type mucosa may extend 1–2 mm into anatomic duodenum, which may lead to a short 2–3 mm segment of transitional type epithelium (features of both antral and small intestinal type epithelium)
2. First portion of duodenum (bulb) may contain shorter and broader villi with branching extensions; also may find increased mononuclear cells within lamina propria
3. Brunner’s glands
   a. Specifically localized in the duodenum, most concentrated just distal to gastroduodenal junction, and gradually decrease along the duodenum
   b. Collection of tubuloalveolar glands, predominantly within the submucosa, but often extends through the muscularis mucosa
   c. Function is not fully understood, but felt to play a role in protecting the duodenal mucosa from acidic gastric contents; contributes to increased luminal pH
   d. Hyperplasia of Brunner’s glands may impart a course nodularity to most of the duodenum, as well as discrete or solitary nodules in the proximal duodenum

B. Jejunum
1. Least distinctive segment of small bowel
2. Jejunal villi are tall, and typically more slender and fingerlike compared to villi in duodenum and ileum
3. Characteristic feature is the prominent plicae circulars (permanent circular folds), also termed valves of Kerckring; these folds are tallest and most numerous in jejunum

C. Ileum
1. Fewer and shorter plicae circulars
2. Increased proportion of goblet cells within epithelium
3. Villi are shorter, with predominant fingerlike shape
4. Terminal ileum
   a. Distal portion protrudes 2–3 cm into large intestine
   b. Mucosal transition demonstrates gradual loss of villi
   c. Ileocecal region can contain abundant fat within submucosa; amount is proportional to adipose content in rest of abdominal cavity
5. Lymphoid nodules gradually increase in quantity with distal progression
6. Peyer’s patches are specialized clusters of lymphoid aggregates, and are most prominent in the ileum
   a. Occupy mucosa and portion of submucosa
   b. Increase in size and number until puberty
   c. Hyperplastic Peyer’s patches (focal lymphoid hyperplasia) may be found in terminal ileum during childhood, and have been linked to idiopathic intussusception

III. Microscopic Examination
A. Aspects identified by light microscopy include the following:
   1. Organisms (luminal, surface attached, and intramucosal) such as *Giardia lamblia* or *E. coli*
   2. Epithelial cells (cell height and degree of vacuolization, which is increased in abetalipoproteinemia from fat deposition)
   3. Mitotic figures (evaluation of metaplasia, dysplasia, or malignant transformation)
   4. Numbers of goblet cells, Paneth, and enteroendocrine cells (enteroendocrine cells are increased in celiac disease)
   5. Intraepithelial lymphocytes (IELs are nonspecific and are commonly seen in celiac disease, cow’s milk protein allergy, autoimmune enteropathy, giardiasis, bacterial overgrowth or cryptosporidiosis).
      a. Available studies suggest a wide normal range of IELs (between 10–40 IELs/100 epithelial cells). Additional findings need to be taken into consideration for diagnoses of small bowel diseases
   6. Increased mast cells in the epithelium can be seen in systemic mastocytosis
   7. Eosinophils are increased in eosinophilic gastroenteritis
   8. Lamina propria cellularity (lacteals, lymphocyte subclass, cytokine secretion, mast cells)
   9. PAS staining (allows the preservation of the brush border and demonstrates mucus-containing goblet cells)
      a. Presence of PAS-positive material in the apical cytoplasm of the upper crypt and low villous epithelium indicates MID, which can be confirmed with electron microscopy
      b. PAS-positive macrophage inclusions in lamina propria are seen in Whipple’s disease, which is caused by bacterium *Tropheryma whippelii*
      c. Paneth cells are found in the intestinal tract. They contain zinc and lysozyme (an enzyme that lyses certain kinds of bacteria) as well as large eosinophilic refractile granules within their apical cytoplasm (see Figure 3)
Figure 1 and Figure 2 show normal villous structure compared with villous flattening

IV. Electron Microscopy
   A. Glutaraldehyde fixation is used, ultra-structural studies should be routinely performed in protracted diarrhea cases
      1. MID can be detected and confirmed
      2. Cryptosporidiosis or effacing of E. coli in EPEC, microspordiosis in AIDS

V. Immunohistochemistry (IHC)
   A. Requires snap-frozen tissue, because formalin fixation crosslinks tissue proteins and may alter tertiary structure enough to prevent antibody recognition
   B. IHC has a role in the diagnosis of celiac disease or autoimmune enteropathy

VI. Disorders in Which Biopsy Is Valuable
   A. Celiac disease (villous atrophy, crypt hyperplasia, and increased IELs)
   B. Immunodeficiency (lack of plasma cells in lamina propria, but mucosa pathology can be varied, such as in common variable immunodeficiency [CVID] and severe combined immune deficiency [SCID])
   C. Autoimmune enteropathy (usually severely abnormal mucosa)
   D. Crohn’s disease (especially for granulomas)
   E. MID (diagnosed with microvillous inclusions and increased secretory granules on electron microscopy, abnormal PAS-positive epithelial cells, villi flattening without crypt hyperplasia)
VII. Disorders in Which Biopsy May be Valuable
   A. Giardiasis, strongyloidiasis, cryptosporidiosis
   B. Lymphangiectasia, lymphoma, hypogammaglobulinemia
   C. Eosinophilic gastroenteritis

VIII. Villous Atrophy
   A. There are degrees of villous flattening “atrophy”
      1. Mild: villous height and crypt depth are approximately equal
      2. Moderate: crypt depth greater than villous height
      3. Severe: flat mucosa represents severe villous flattening
      4. Villous flattening without crypt hyperplasia can be seen in conditions, including microvillous inclusion disease (MID)

IX. Diagnostic approach to children thought to have small intestinal diseases:
   A. History, anthropometrics, and physical examination
   B. CBC, ESR (older kids for IBD), serum and red cell folate, anti-TTG and EMA IgA
   C. Stool for bacteria culture, Ova and parasites, EM for viruses, *Giardia lamblia* and cryptosporidiosis, reducing substance
   D. Small bowel follow-through contrast study
   E. Invasive procedure such as small bowel biopsy, duodenal aspirate for *Giardia lamblia*
   F. Response to elimination diet is a good way to diagnose food intolerance

Recommended Reading

3C. Normal and Abnormal Motility

Definition: Antroduodenal manometry measures the intraluminal pressure of the antrum and duodenum. Clinically, manometry provides useful information regarding contraction patterns in the antroduodenal region.

I. Normal Antroduodenal Motility

A. Normal motility meets the following criteria:
1. At least 1 MMC/24 hours
2. Conversion to the fed pattern following meal without return of MMC for at least 2 hours
3. Distal postprandial contractility (motility index per 2 hours > 13.67)
4. Small intestinal contractions exceeding 20 mm Hg

B. During fasting, the stomach and small bowel show a cyclic pattern, known as the MMC, which serves as a marker of overall enteral neural function.
1. Each MMC (lasting 90–120 minutes) is usually divided into three phases
2. Phase III is the most characteristic, and consists of regular rhythmic peristaltic contractions that start proximally and migrate down to ileum (Figure 1)

C. After ingestion of nutrients, the fasting pattern is interrupted by the fed pattern, which is characterized by the irregular occurrence of contractions with various amplitudes.

D. After solid meals, strong, repetitive contractions are often induced in the antrum, and the duodenal response looks similar to that of Phase II, although the amplitude and frequency of contractions are greater in the fed state (Figure 2)

E. An antral motility index has been used to calculate both the amplitude and frequency of these contractions. The following formula is commonly used:
1. Motility Index = ln (Amplitude x No. of Contractions ± 1)
2. Normal value being 13.67–15.65 (5–95th percentile)

F. The presence of Phase III activity is a marker of neuromuscular integrity (Figure 1)
1. If no spontaneous Phase III activity is observed, intravenous erythromycin should be administered
2. Erythromycin at doses that are 10%–20% of those used for antibiotic properties acts as a motilin receptor agonist
3. The American Motility Society (AMS) Task Force recommends the use of erythromycin 1 mg/kg over 30 minutes if no MMC is recorded during fasting

II. Clinical Significance

A. Neuropathic disorders are associated with:
1. Antral hypomotility
2. Absence of Phase III activity
3. Abnormal propagation of MMC, bursts and sustained uncoordinated pressure activity (hypermotility)
4. Lack of fed response (Figure 3)

B. Myopathic disorders are characterized by low amplitude contractions of <10 mmHg (Figure 4)

C. Antral hypomotility: a reduced motility index of postprandial distal antral contractions correlates with impaired gastric emptying of solids from the stomach (Figure 5)

D. Mechanical obstruction: two patterns suggestive of obstruction have been described:
1. Postprandial clustered contractions (>30 min duration) separated by quiescence
2. Simultaneous prolonged (>8 seconds) or summated contractions

III. Pitfalls

A. Artifacts are characterized by simultaneous activity, e.g., cough, movement or straining artifact
B. Several dysmotility syndromes may share common manometric features, eg, diabetes mellitus, gastric surgery, chronic intestinal pseudo-obstruction, idiopathic dysmotility, IBS, etc.
C. Primary phenomenon vs epiphenomenon may be an issue
   1. The abnormal motor patterns do not necessarily imply a causative role in the patient’s symptoms. Thus, stress may delay gastric emptying, impair antral contractility, suppress MMC cycling, and induce intestinal irregularity
   2. Dysmotility may, similarly, be a consequence of the disorder, such as fasting, vomiting, weight loss, diarrhea and constipation

IV. Future
   A. Wireless technology to evaluate gastric emptying and small intestine motility has now become available in the form of an ingestible capsule
      1. The capsule is able to record pressure, temperature, and pH measurement data in both elapsed and real time
      2. Studies to validate its use in adults are now underway

Figure 1. Normal fasting antroduodenal manometry. A normal Phase III front originating in the antrum and migrating aborally along the duodenum into the jejunum can be observed. During Phase III, the antrum contracts at a frequency of 3/min, whereas the small bowel contracts at a frequency of 11–12/min. Phase III is followed by a period of quiescence (Phase I) and is preceded by intermittent irregular contractions (Phase II).

Figure 2. Normal postprandial pattern in a small bowel manometry. There are irregular persistent phasic contractions in the antrum and small bowel.

Figure 3. Antroduodenal manometry in a patient with neuropathy. The tracing shows abnormalities in Phase III of the MMC. Some uncoordinated clusters, as well as isolated irregular phasic contractions, can be observed. Throughout the study, there was no organized activity, and irregular phasic contractions were seen. No Phase III could be observed, even after provocative medications.

Figure 4. Antroduodenal manometry in a patient with visceral myopathy. The tracing shows a normal Phase III of the interdigestive motor complex, although the amplitude is much lower than normal (<10 mmHg).
Figure 5. Antroduodenal manometry in a patient with antral hypomotility. The tracing shows normal postprandial activity in the small bowel, and absent response in the antrum. This pattern is frequently seen in patients with gastroparesis.

Recommended Reading


3D-1. Meckel Diverticulum

Dina Al-Zubeidi, MD
Aliye Uc, MD

I. Embryology
A. True intestinal diverticulum. Contains all three layers of the intestine: mucosa, muscularis, and serosa
B. Most common remnant of the omphalomesenteric duct
C. Results from failure of obliteration of the omphalomesenteric duct during the 5th week of fetal development
D. The spectrum of duct anomalies include umbilicoileal fistula, umbilical sinus, umbilical cyst, and a fibrous cord connecting ileum to umbilicus.
E. Meckel diverticulum is lined by ileal mucosa. Up to 50% of diverticuli contain ectopic gastric mucosa, which can be a source of complications; mainly bleeding, ulceration, and perforation
   1. Gastrointestinal bleeding may develop due to ulceration within the gastric mucosa, or ulceration in the adjacent ileal mucosa
   2. Rarely, pancreatic, colonic, or hepatobiliary epithelium may be found

II. Clinical Features
A. It presents only when complications arise
B. The “rule of 2’s” is commonly used to recall the features of Meckel diverticulum, and they include:
   1. It occurs in 2% of the population
   2. It is located within 2 feet of the ileocecal valve, on the antimesenteric border
   3. It usually is 2 inches long
   4. It presents before age 2 in over 50% of cases
      a. 60% of patients present before 10 years of age
C. Painless major lower gastrointestinal bleeding is the most common presentation (up to 50% of all cases)
D. Intestinal obstruction due to volvulus, intussusception, hernia, or fecolith may occur
E. Meckelian diverticulitis occurs in 10%–20% of cases, more commonly in older patients
   1. The presentation is similar to that of appendicitis, but the location of the pain may be variable
F. Periumbilical and postprandial abdominal pain due to chronic peptic ulceration of the Meckel diverticulum may also rarely occur

III. Diagnosis
A. Only 25% of patients with Meckel diverticulum become symptomatic
B. Ectopic gastric tissue causing mucosal ulceration and bleeding may be identified by scintigraphy using 99m technetium scanning
   1. This test has 85%–90% sensitivity and 95% specificity in children
   2. False-negative studies are usually due to insufficient heterotopic gastric tissue in the diverticulum or brisk hemorrhage, leading to diluted intraluminal Tc99 activity
   3. The uptake of Tc99 may be obscured by activity of the bladder in AP images. Lateral or oblique images may help distinguish urinary activity from the Meckel's

IV. Management
A. All symptomatic Meckel diverticulae must be resected with the adjacent segment of ileum
B. Routine resection of an asymptomatic diverticulum encountered incidentally during an operation is controversial, but evidence exists that supports removal in children
   1. The risk of complications from a routine operation is 1%; potential lifetime risk of complications from a Meckel diverticulum is 4%–6%
Recommended Reading


3D-2. Malrotation

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Rotational anomalies represent a spectrum of defects, from complete nonrotation, in which the entirety of the small intestine is on the right side of the abdomen and the colon is positioned on the left, to relatively minor abnormalities associated with incomplete fixation of the cecum and ascending colon.

I. Background
   A. Nonrotation is thought to occur during the second stage of midgut development (10–12 weeks’ gestation)
   B. Nonrotation characterized by two components:
      1. The third part of the duodenum lies to the right of the vertebral column instead of curving across to the left
      2. The cecum lies in the upper abdomen to the left of the duodenum
   C. The midgut is liable to twist around the narrow pedicle of mesentery at the base of superior mesenteric artery
   D. True incidence is not known, because it may remain asymptomatic throughout life

II. Presentation
   A. Symptoms of obstruction either due to Ladd’s bands impinging on duodenum or when volvulus occurs
   B. Rotational anomalies may become symptomatic at any age
      1. However, 80% of patients who do become symptomatic do so in the first month of life
      2. Risk of acute volvulus is highest during the neonatal period
   C. In the infant, acute midgut volvulus presents with bilious vomiting, abdominal pain, progressive abdominal distention, and tenderness
   D. Rapid deterioration, with hypovolemia and persistent metabolic acidosis
   E. Chronic intermittent abdominal pain in older child, with or without vomiting
   F. Incidental finding

III. Diagnosis
   A. Should be in differential diagnosis for any child with vomiting and abdominal pain
   B. Higher index of suspicion for neonates with bilious emesis
   C. Upper GI series is modality of choice to demonstrate duodenal-jejunal flexure (ligament of Treitz)
   D. Role for small bowel follow through in questionable cases look for location of cecum
   E. Barium enema can be used in some cases

IV. Management
   A. Correct electrolytes and volume; resuscitate if acute presentation
   B. Surgical treatment with Ladd’s procedure
   C. Although there is some controversy, surgery is often indicated for asymptomatic or incidental malrotation, because advocates of this approach feel that benefits of preventing a catastrophic episode of bowel ischemia/loss outweighs the risk of surgery

Recommended Reading


Duplication cysts are uncommon congenital anomalies of the gastrointestinal tract. Understanding patterns of presentation and management is important, as they may be revealed unexpectedly during work-up for common symptoms/signs.

I. Incidence and Definition
   A. Congenital in origin
   B. Duplication cysts of the intestine are rare, 1 in 4,500–10,000 births
   C. Tubular or spherical cysts arise anywhere from mouth to anus
   D. Most common location is the ileocecal region
   E. Most common structural findings are:
      1. Well-developed smooth muscle layer
      2. Epithelial lining usually resembles adjacent intestine, but may also be gastric or pancreatic
      3. Attachment to a part of the gastrointestinal tract
      4. Usually not in continuity with the intestinal lumen
      5. Share a common blood supply with the native tract
      6. In general, small bowel cysts are on the mesenteric border; large bowel cysts are on the antimesenteric border.

II. Presentation: variable
   A. Asymptomatic or incidental
   B. Abdominal mass
   C. Obstruction of the adjacent intestinal lumen
   D. Volvulus
   E. Ectopic gastric tissue that may lead to bleeding, ulceration, or perforation

III. Diagnosis
   A. May be detected on prenatal US
   B. Most cysts are diagnosed before age 2
   C. Contrast radiography, CT scan, or MRI may be helpful

IV. Management
   A. Complete surgical excision of the cyst, with preservation of adjacent and arising organ, is the treatment of choice
   B. Cysts found incidentally have to be excised as well, as they are likely to enlarge and cause symptoms in time

V. Mesenteric Cysts
   A. Incidence and Definition
      1. Rare, benign abdominal masses in children
      2. The incidence is 1 in 20,000
      3. In contrast to duplication cysts, mesenteric cysts have an endothelial cell layer, they are minimally vascular, and they lack a muscular lining
      4. Most are located in the small bowel mesentery
   B. Presentation
      1. Mesenteric cysts tend to present acutely, requiring urgent admission and surgical intervention
      2. Abdominal pain is the most common presenting symptom, followed by abdominal distention or mass, anemia, anorexia, weight loss, and fever
C. Classification
   1. Developmental
   2. Traumatic
   3. Infective
   4. Neoplastic
D. Diagnosis
   1. US or CT scan
E. Management
   1. Complete surgical excision

Recommended Reading


Gastroschisis and omphalocele are both congenital abdominal wall defects. Omphalocele often has associated congenital anomalies; gastroschisis is not typically associated with other anomalies.

**Gastroschisis**

I. **Overview**
   A. Abdominal wall defect, typically to the right of the umbilicus
   B. Full thickness defect, with no sac or membrane covering the herniated, variable amount of intestines, and occasionally organs
   C. Occurs in 1/20,000 to 1/30,000 pregnancies
      1. Males and females are affected equally
   D. Etiology is currently unknown, but preconceptual (~30–90 days) maternal asthma and use of bronchodilators is associated with an increased risk of gastroschisis. Ten percent of bronchodilator is passed on to the fetus, producing vasoactive alterations. This risk is greatest for mothers <20 years of age, and folic acid supplements appear to be very protective

II. **Clinical Presentation**
   A. Associated intestinal anomalies (especially atresias) are seen in 10%–20% of affected children
   B. Malrotation in almost all affected children
   C. Other anomalies and chromosomal defects are rare
   D. Intestinal dysmotility is almost universal
   E. Gastroesophageal reflux is common

III. **Diagnosis**
   A. Prenatal ultrasound will visualize the abdominal contents external to the abdomen
   B. The intestines are thickened from chronic exposure to amniotic fluid
   C. Maternal serum alpha fetoprotein will be elevated

IV. **Treatment**
   A. Surgical repair after birth to minimize fluid balance issues and infection risks. Silo may be used to expand abdominal capacity. Silos are silastic funnels that protect the bowel from additional injury, minimize evaporative losses, and allow for bowel perfusion assessment while awaiting abdominal well, defect closure
   B. Parenteral nutrition may be required to provide adequate nutrition due to dysmotility and difficulty with enteral feeds

V. **Outcome**
   A. Survival is 90%–95%
   B. Prolonged parenteral nutrition due to intolerance of enteral feeds
   C. Gastroesophageal reflux may be severe
   D. 5%–10% risk of adhesions

**Omphalocele**

I. **Overview**
   A. Midline defect of the abdominal wall, with eviscerated abdominal contents contained in a membranous sac that develops at 5–10 weeks’ of gestation
   B. Prevalence is 1/3,000 to 1/20,000 live births
   C. Affects males more than females. Racial and ethnic associations have been documented
II. Clinical Presentation
A. Defect may be central, epigastric, or hypogastric region
B. Strong association with other anomalies
   1. Associated with midline defects (heart, sternum, diaphragm, bladder)
   2. Cardiac defects are the most commonly associated anomaly, with 50% of fetuses demonstrating a variety of conditions from septal defects to coarctation of the aorta
   3. Associated with other congenital anomalies, including Beckwith-Wiedemann syndrome and trisomies 13, 18 (10%–40%) and 21.
   4. Intestines with associated malrotation that may lead to volvulus
   5. If associated with defects of diaphragm, sternum, pericardium, and heart is known as the “Pentology of Cantrell”
C. Presence of anomalies is lower in the liveborn, due to increased risk of being stillborn (5%–60%) in infants with multiple anomalies. Recent association of the size of the defect and associated anomalies
   1. Large defects, including intestine and other organs, are more likely to have nongastrointestinal defects; smaller, intestine-only defects are more likely to have only other gastrointestinal anomalies

III. Diagnosis
A. Diagnosis by prenatal US, with the abdominal contents visualized in the umbilical stalk with a covering sac
B. Elevated maternal serum alpha fetoprotein
C. MRI has been used to document associated anomalies and contents of the omphalocele
D. Serial ultrasound is recommended to document continued growth, since there are concerns for fetal growth restriction (5%–35%)
E. Karyotype is also currently recommended due to strong association with chromosomal abnormalities

IV. Treatment
A. Delivery by cesarean section has only shown a benefit in children with large omphalocele that contains multiple organs, due to risk of rupture or dystocia
B. In some cases, silo or tenting of pouch may be necessary to allow gradual return of contents into the abdominal cavity, followed by surgical repair when the infant is stable
C. Intestinal necrosis may occur with increasing abdominal pressure, resulting in ischemia
   1. Ischemic bowel is resected and may lead to short bowel syndrome

V. Outcome
A. Outcome is dependent on the associated anomalies

Recommended Reading


Scherger JE, Blank C. Gastroschisis and Omphalocele. Available at http://das/pdxmd/body/0/0?type=med&eid=9-u1.0-_1_mt_5083101.
Necrotizing enterocolitis (NEC) is the most common cause of nonobstructive acute abdomen occurring in neonates, characterized by necrosis of the intestinal mucosa.

**I. Overview/Epidemiology**
Usually occurs between 7–14 days of life, but can occur during subsequent postnatal weeks
A. One of the most common surgical emergencies occurring in the NICU
   1. Occurs ~1–3/1,000 live births
B. Mainly affects low-birth weight, premature infants (>90% occur in infants weighing <2,000 g and delivered earlier than 36 weeks gestation)
   1. Occurs in 3%–7% of these infants
C. Occasionally occurs in full-term infants at a rate of 0.05 per 1,000 live births; usually within the first week of life
D. Mortality ranges from 10%–50%, with highest mortality in VLBW infants (<1,500 g), males, and African American infants

**II. Pathogenesis (multifactorial)**
A. Structural and functional intestinal immaturity contributes to the excessive inflammatory response associated with abnormal intestinal bacterial colonization
B. Early enteral feedings with large volume of hyperosmolar formula
C. Impaired premature immune response, with low IgA secretion
D. Decreased absorption of feeds and incomplete hydrolysis of toxins due to:
   1. Deficient gastric acid and pepsin production, with low lipolytic, proteolytic, and amylolytic secretion rates
   2. Increased permeability of intestinal wall
   3. Decreased intestinal motility
E. Immature intestinal mucosa has increased susceptibility to reduce mesenteric blood flow causing ischemic changes
F. Elective PRBC transfusion for anemia

**III. Clinical Manifestations**
A. Initial: temperature instability, apnea, bradycardia, and lethargy
B. Feeding intolerance, increased gastric residual volumes, abdominal distension (± bilious emesis), tenderness, gross or occult blood in stools, and peritonitis
C. Laboratory values may show leukocytosis (± bandemia), neutropenia, thrombocytopenia, or acidosis

**IV. Diagnosis**
A. Clinical Picture (see Table 1)
B. Evaluation
   1. Obtain complete blood count, comprehensive metabolic panel, and cultures from blood, sputum (if intubated), and urine
C. Imaging
   1. Plain abdominal radiographs (Two views: AP and left lateral decubitus)
      a. Initially may show mild distension +/- ileus, progressing to pneumatosis intestinalis, portal venous gas, or a sentinel loop (abnormal fixed bowel loop on two successive abdominal films, indicative of a lack of peristalsis).
V. Treatment/Management

A. Medical Management
   1. Bowel rest for 10–14 days (NPO)
   2. Gastrointestinal decompression with nasogastric tube
   3. TPN therapy
   4. Transfusion of blood products as necessary
   5. Broad spectrum antibiotics for 7–14 days for Gram-negative coverage

B. Surgical Management
   1. ~1 in 3 infants with NEC will require surgical intervention
   2. Relative indications for surgery include clinical deterioration or worsening radiographic features with any of the following:
      a. Oliguria, hypotension, metabolic acidosis, thrombocytopenia, ventilatory failure, portal venous gas, fixed abdominal masses, persistently dilated bowel loops, and abdominal wall erythema
   3. Absolute indications for surgery: intestinal perforation or stool/bile on paracentesis
   4. Surgical procedures may include peritoneal drain placement, exploratory laparotomy with resection of diseased bowel, and enterostomy with stoma creation

C. Prevention
   1. Nonaggressive enteral feeds, slow advancement with breast milk

VI. Differential Diagnosis

A. Neonatal sepsis, spontaneous intestinal perforation (usually occurs within first week of life, and not associated with enteral feeds), congenital cause of intestinal obstruction (atresia, malrotation, or volvulus), Hirschsprung disease, neonatal appendicitis, and neonatal pseudomembranous colitis

VII. Outcomes/Complications

A. Short-term: stricture and abscess formation (10%–35%), death (15%–30%, highest in infants requiring surgery)
B. Long-term: most frequent cause of short bowel syndrome (up to 42% of surgical NEC cases), disease recurrence (5%), adverse neurodevelopmental sequelae (25%)

---

Table 1. Modified Bell Staging Criteria for Necrotizing Enterocolitis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Classification of NEC</th>
<th>Systemic signs</th>
<th>Abdominal signs</th>
<th>Radiographic signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Suspected</td>
<td>Temperature instability, apnea, bradycardia, lethargy</td>
<td>Gastric retention, abdominal distention, emesis, hemepositive stool</td>
<td>Normal or intestinal dilation, mild ileus</td>
</tr>
<tr>
<td>IB</td>
<td>Suspected</td>
<td>Same as above</td>
<td>Grossly bloody stool</td>
<td>Same as above</td>
</tr>
<tr>
<td>IIA</td>
<td>Definite, mildly ill</td>
<td>Same as above</td>
<td>Same as above, plus absent bowel sounds with or without abdominal tenderness</td>
<td>Intestinal dilation, ileus, pneumatosis intestinalis</td>
</tr>
<tr>
<td>IIB</td>
<td>Definite, moderately ill</td>
<td>Same as above, plus mild metabolic acidosis and thrombocytopenia</td>
<td>Same as above, plus absent bowel sounds, definite tenderness, with or without abdominal cellulitis or right lower quadrant mass</td>
<td>Same as IIA, plus ascites</td>
</tr>
<tr>
<td>IIIA</td>
<td>Advanced, severely ill, intact bowel</td>
<td>Same as IIB, plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, DIC* and neutropenia</td>
<td>Same as above, plus signs of peritonitis, marked tenderness, and abdominal distention</td>
<td>Same as IIA, plus ascites</td>
</tr>
<tr>
<td>IIIB</td>
<td>Advanced, severely ill, perforated bowel</td>
<td>Same as IIIA</td>
<td>Same as IIIA</td>
<td>Same as above, plus pneumoperitoneum</td>
</tr>
</tbody>
</table>

*DIC: disseminated intravascular coagulation.
**Recommended Reading**


I. Overview/Epidemiology
   A. Described by anatomic location as ileo-colic, ileo-ileo-colic, colo-colic, and small bowel intussusception (jejuno-jejunal and ileo-ileo)
   B. Peak incidence is between 4 and 14 months, when most cases are idiopathic. Ninety percent are ileocolic, and 5% have a lead point. Enlarged Peyer patches may play a role as a lead point at this age
   C. Under the age of 6 months and over 3 years of age: can be located in any segments of the bowel; a pathologic lead point is possible and must be investigated
   D. Any structural abnormality of the bowel can be a cause, such as a Meckel diverticulum, intestinal polyps, or duplication cyst or small bowel lymphoma. Submucosal hemorrhage in HSP or other conditions may act as lead points
      1. Also described in conditions characterized by disturbances in intestinal muscular contraction, such as cystic fibrosis or postoperatively

II. Clinical Presentation
   A. Symptoms of intestinal obstruction: colicky abdominal pain, often with bilious vomiting
   B. Between bouts of colic, infants are quiet but irritable
   C. The characteristic sausage-shaped abdominal mass may be palpated
   D. Diarrhea occurs in 10% of patients prior to mucosal slough
   E. Hypovolemia is variable, and some children can present atypically with lethargy only
   F. Passage of blood and mucus per rectum is a later sign of intussusception
   G. The classic triad of paroxysmal pain, vomiting, and passage of currant jelly stools occurs in less than 1/3 of patients

III. Investigation
   A. A plain abdominal radiograph should be done if concern for other diagnosis, to include perforation
      1. In intussusception: normal, or will show nonspecific features of intestinal obstruction
      2. The typical finding of a soft tissue mass indenting the colon is seen in only about 25% of patients
   B. US: the doughnut sign in cross-sectional, or pseudokidney sign in longitudinal axis
      1. Usually done before proceeding to contrast enema
   C. CT can be highly accurate in the diagnosis, but is not commonly used

IV. Treatment
   A. Hydrostatic reduction (saline enema is liquid contrast medium of choice) has a success rate between 75%–90%
   B. Air enema is considered better at reduction, is safer and faster, and uses less radiation, when compared to liquid enema. Success rate up to 75%–95%
      C. During endoscopy, pneumatic reduction of intussusception has been described, with simultaneous identification of the intussuscipiens
      D. Possible complications of reduction: intestinal perforation and tension pneumoperitoneum
   E. Enema reduction is contraindicated in children in refractive shock or with signs of peritonitis
   F. Open surgical reduction is required when reduction is unsuccessful. In advanced cases, the necrotic intussusception will need to be resected
      1. An intussusception present for >48 hours, or one in an infant <6 months with bowel obstruction on plain films, has a high likelihood of perforation
      2. Other negative prognostic factors of successful reduction: isolated small intestinal intussusception, multiple recurrences
**Recommended Reading**


I. Classic Disease Description
   A. “A permanent sensitivity to gluten in wheat and related proteins found in barley and rye, occurring in genetically susceptible individuals, and manifesting as an immune-mediated enteropathy defined by characteristic changes seen on intestinal histology.”

II. Incidence and Prevalence
   A. US/European prevalence is approximately 1:300 to 1:80 children. Refer to Table 1 for worldwide data
   B. Female predominance 2:1
   C. Approximately 3 million people in the US with CD. Approximately 3 million cases in Europe
   D. It is estimated that 90% of cases are undiagnosed

Table 1. Worldwide Disease Prevalence of Celiac Disease Based on Serologic Screening Tests

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence 1:XX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saharawi</td>
<td>1:18</td>
</tr>
<tr>
<td>Sweden</td>
<td>1:77</td>
</tr>
<tr>
<td>Finland</td>
<td>1:99–1:67</td>
</tr>
<tr>
<td>UK</td>
<td>1:100</td>
</tr>
<tr>
<td>Italy</td>
<td>1:106</td>
</tr>
<tr>
<td>USA</td>
<td>1:105</td>
</tr>
<tr>
<td>Ireland</td>
<td>1:122</td>
</tr>
<tr>
<td>Spain</td>
<td>1:118</td>
</tr>
<tr>
<td>Switzerland</td>
<td>1:132</td>
</tr>
<tr>
<td>Russia</td>
<td>1:133</td>
</tr>
<tr>
<td>Netherlands</td>
<td>1:198</td>
</tr>
<tr>
<td>Australia</td>
<td>1:251</td>
</tr>
<tr>
<td>Israel</td>
<td>1:157</td>
</tr>
<tr>
<td>Iran</td>
<td>1:166–1:104</td>
</tr>
<tr>
<td>India</td>
<td>1:310</td>
</tr>
<tr>
<td>Brazil</td>
<td>1:66–1:119</td>
</tr>
</tbody>
</table>

III. Genetics of Celiac Disease
   A. Ninety-five percent of patients have HLA-II DR3-DQ2 haplotype (coded by α and β subunit alleles DQA1*0501- DQB*0201)
   B. Five percent of patients have DR4-DQ8 haplotype (α and β subunit alleles DQA1*03-DQB1*0302)
   C. Homozygotes for HLA-DQ2 comprise 25% of CD patients
   D. HLA-II genes are located on chromosome 6p21, also called the celiac 1 locus
   E. Lack of DQ2/DQ8 completely excludes the possibility of developing celiac (high negative predictive value, low positive predictive value)
F. DQ2/DQ8 on antigen-presenting cells with specific binding for deamidated gluten peptides, present bound peptides to CD4+ lymphocytes to initiate an immunologic reaction.

G. DQ2 or DQ8 molecule only accounts for 36%–53% of disease risk (genetic modifiers likely exist).

H. DQ2 gene is carried by 30% of the US population, but only 3% of these develop CD.

I. Strong prevalence of CD in 1st relatives of patients with CD. 5.5%–18% of siblings, with the highest rates in daughters and sisters of CD patients (Table 2).

IV. Pathogenesis: Current Model

A. Inciting event (i.e., viral infection) in individuals carrying DQ2/DQ8 while ingesting gluten proteins (wheat, barley, rye) catalyzes breakdown in tolerance.

B. Postinfection, epithelium is inflamed, with increased permeability to gluten peptides.

C. Gluten itself increases intestinal permeability, stimulates inflammation, and resists digestion.

D. When gluten peptides are deamidated by local TTG molecules, there is ↑ binding to HLA-II on antigen-presenting cells.

E. Activated APCs secrete inflammatory cytokines IL-15 and IFN-y.

F. Fibroblasts are recruited, which express MMP (matrix metalloproteinases) and directly injure epithelial cells.

G. IFNs ↑ the expression of HLA-DQ2/DQ8 on local APCs. ↑ binding/presentation of gluten peptides to specific CD4+ T-cells in the lamina propria, with further ↑IFN-y and IL-15 secretion.

H. IL-15 causes clonal expansion, with increased number of local intraepithelial lymphocytes (IELs). These are mainly CD8+ T-cells unique to CD. There is subsequent phenotypic conversion of IELs to cytotoxic NK cells, which then destroy local intestinal epithelium.

I. The combined effect of ↑ inflammatory cytokines, infiltration of cytotoxic converted IELs, and direct gliadin cytotoxicity leads to loss of epithelial cells, proliferation of crypt cells and mucosal flattening/villous atrophy seen on biopsy.

V. Clinical Presentation

A. The current trend is delayed onset of symptoms and older age at diagnosis.

B. GI symptoms predominate in children < 3 yr.

C. 50% of older children/adults have no GI symptoms at the time of diagnosis.

D. 30% of adults with CD have a previous diagnosis of IBS.

E. 30% or more of children with CD have ↑ liver function tests that normalize on a gluten-free diet. The prevalence of CD in patients with unexplained ↑ in LFTs ranges from 1.5%–9%.

Table 3. Presenting Features of Celiac Disease

<table>
<thead>
<tr>
<th>Classic Celiac Disease</th>
<th>Non-GI Manifestations</th>
<th>Neuropsychiatric Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to thrive</td>
<td>Dermatitis herpetiformis</td>
<td>Ataxia</td>
</tr>
<tr>
<td>Chronic/recurrent diarrhea</td>
<td>Dental enamel defects</td>
<td>Epilepsy ± cerebral calcifications*</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>Anemia</td>
<td>Migraines*</td>
</tr>
<tr>
<td>Muscle wasting</td>
<td>Aphthous stomatitis</td>
<td>Depression</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Arthritis/arthritisalgias</td>
<td>Fatigue/malaise</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Hepatitis/transaminitis</td>
<td>Anxiety*</td>
</tr>
<tr>
<td></td>
<td>Pubertal delay</td>
<td>Peripheral neuropathy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonclassical GI complaints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent abdominal pain</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>GERD*</td>
</tr>
</tbody>
</table>

| Short stature            |
| Inheritance              |
| Recurrent fetal loss*    |
| Osteoporosis/osteopenia  |
| Cutaneous manifestations |
| Vitamin deficiencies     |
| Alopecia                 |
| Autoimmune disease       |

VI. Diagnosis

A. NASPGHAN/FISPGHAN currently recommends CD screening of the following patients:

1. Patients with classic symptoms of CD (see Table 3).
2. Patients with failure to thrive or growth failure.
3. Patients with conditions carrying high risk for CD, noted in Table 4.
B. Begin screening at-risk, asymptomatic individuals at age 3 if gluten has been part of the diet for at least 1 year. Symptomatic individuals can be tested during the first year of life, but sensitivity of testing improves with age.

Table 4. Conditions Requiring Screening for Celiac Disease

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 diabetes mellitus</td>
</tr>
<tr>
<td>IgA deficiency</td>
</tr>
<tr>
<td>First-degree relatives of patients with CD</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
</tr>
<tr>
<td>Autoimmune thyroid disease</td>
</tr>
<tr>
<td>Short stature</td>
</tr>
<tr>
<td>Dental enamel defects</td>
</tr>
<tr>
<td>Unexplained iron deficiency anemia</td>
</tr>
<tr>
<td>Delayed puberty</td>
</tr>
<tr>
<td>Unexplained osteoporosis/osteopenia</td>
</tr>
<tr>
<td>Down/Turner/William syndromes</td>
</tr>
<tr>
<td>↑ Transaminases* (adults)</td>
</tr>
</tbody>
</table>

* Consensus statement and technical review by the American Gastroenterological Association recommends screening for CD in asymptomatic adults with increased alanine aminotransferase (ALT).

VII. Serologic Testing Current Recommendations by NASPGHAN/FISPGHAN

A. IgA antibodies against tissue transglutaminase (TTG) or antibodies against endomysium (EMA) are the single best CD screening test.

B. More complex “panels” of IgA and IgG antibodies against gliadin and reticulin are not recommended because of low specificity and high false-positive rate in healthy individuals, especially IgG antibodies.

C. Sensitivity and specificity of IgA antibodies against TTG for identifying CD are 93%–96% and 96%–99%, respectively.

D. Sensitivity of IgA anti-TTG and anti-EMA is reduced in patients < 5 years of age, especially those <18 months of age.

E. IgA antibodies are not sensitive or specific in IgA-deficient individuals.

F. In symptomatic individuals, the positive predictive value of IgA anti-TTG antibodies is approximately 1.0. The positive predictive value of IgA anti-TTG is lower when used in general population screening.

G. IgA anti-endomysial antibodies are similar in sensitivity and specificity to IgA anti-TTG, but are often more costly, time-consuming, and operator dependant.

H. Antibodies against deamidated gliadin peptide, a synthetic peptide, occur in patients with CD. As a test, antideamidated gliadin peptide antibodies are less sensitive than IgA anti-TTG, but useful in cases where IgA anti-TTG is borderline positive.

I. Always screen for IgA deficiency by measuring quantitative IgA in symptomatic patients.

J. IgG to TTG may be used in IgA-deficient patients, but specificity and sensitivity are slightly decreased.

K. If a patient is IgA deficient and there is a strong clinical suspicion of CD, proceed directly to upper intestinal endoscopy and duodenal biopsy.

L. DQ2/DQ8 testing: not a useful screening tool because of very low positive predictive value. Elevated negative predictive value makes it potentially useful in ruling out CD in at-risk individuals who are asymptomatic or have questionable biopsy results.

VIII. Interpreting Genetic Tests

A. Testing should report full DQ2/DQ8 subtyping, not merely DQ2 ± or DQ8 ±, and should include α AND β subunit typing, since both infer risk (beta>alpha).

IX. NASPGHAN Recommendations Concerning Endoscopy and Duodenal Biopsy

A. Perform duodenal biopsy in all patients with IgA anti-TTG above the cutoff value.

B. Take 4–6 biopsies from the 2nd portion and distal duodenum. The addition of duodenal bulb biopsies may increase diagnostic yield.

C. Marsh histologic grade ≥ 3 is diagnostic of CD (see Table 5). Marsh grade 2 plus IgA antibodies to TTG is also diagnostic.
D. Repeat biopsy after challenge with a gluten-containing diet is not recommended to confirm the diagnosis if a patient has obviously improved on a gluten-free diet.

E. If the patient has been on a gluten-free diet prior to biopsy, or is receiving steroids or immunosuppressants, biopsy results may not reflect the true level of disease.

F. Four weeks on a gluten-containing diet is adequate to insure that pathologic changes will be present on duodenal biopsy in patients taking a gluten-free diet before diagnostic biopsies.

Table 5. Marsh Criteria for Grading Duodenal Biopsies for Potential Celiac Disease

<table>
<thead>
<tr>
<th>Marsh 0</th>
<th>Normal mucosa and villous architecture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marsh 1</td>
<td>Normal mucosa and villous architecture, but increased IELs (infiltrative)</td>
</tr>
<tr>
<td>Marsh 2</td>
<td>Enlarged crypts, increased crypt cell division, increased IELs (hyperplastic)</td>
</tr>
<tr>
<td>Marsh 3a</td>
<td>Partial villous atrophy, shortened blunt villi, mild lymphocytic infiltration, enlarged hyperplastic crypts</td>
</tr>
<tr>
<td>Marsh 3b</td>
<td>Subtotal villous atrophy, enlarged crypts with increased immature epithelial cells, presence of inflammatory cells</td>
</tr>
<tr>
<td>Marsh 3c</td>
<td>Total villous atrophy and loss of villi, severe crypt hyperplasia, infiltrative inflammatory lesions</td>
</tr>
<tr>
<td>Marsh 4</td>
<td>Total villous atrophy, hypoplastic crypts with normal depth, normal numbers of IELs</td>
</tr>
</tbody>
</table>

X. Treatment and Clinical Course

A. The only recognized therapy of CD is lifelong adherence to a gluten-free diet. Oat gluten is safe for most CD patients if it has not been contaminated with wheat protein during milling.

B. Resolution of symptoms occurs within several weeks on a gluten-free diet. Normalization of small bowel biopsy may take 6–12 months.

C. Recheck TTG 6 months after starting gluten-free diet to measure compliance and response. Thereafter, recheck TTG at intervals of 1 year or longer for asymptomatic patients on gluten-free diet.

D. Mortality risk of untreated CD is 2–3-fold higher than that of the general population and directly related to duration of time on gluten-containing diet. Early compliance with a gluten-free diet reduces risk of mortality to near baseline.

E. The increase in all-cause mortality in CD is mostly due to GI malignancies (enteropathy-associated T-cell lymphoma, non-Hodgkin’s lymphoma, and small bowel adenocarcinoma).

Recommended Reading


Tropical sprue (TS) is an acquired disease of unknown etiology, characterized by malabsorption, multiple nutritional deficiencies, and mucosal abnormalities in the small bowel. The exact etiology remains controversial, but infection is believed to play an important role. The diagnosis is typically made after excluding other known causes of malabsorption.

I. Overview/Epidemiology
   A. TS is endemic to tropical areas of the world. It can affect travelers in addition to native residents of the tropics.
   B. In the era of globalization and worldwide travel, it is important for clinicians practicing in North America and Europe to be aware of the possibility of TS in patients who present with nonspecific GI complaints.
   C. Clinical impressions from around the world suggest that the incidence of TS is declining, possibly related to the wide use of antibiotics for traveler’s diarrhea, and improved hygiene and sanitation.
   D. Geographic distribution of TS is interesting, as it does not occur in all tropical areas in a similar fashion.
   E. TS accounts for ~40% of malabsorption in both adults and children in South Asia, and can occur in epidemic forms.

II. Pathology/Pathophysiology
   A. Exact etiology of TS remains unclear, but is likely related to nutritional insufficiency and intestinal infection, possibly with the liberation of cytopathic or secretory toxins.
   B. TS primarily affects the small bowel (initially proximally, then distally), but also causes structural changes in the colon and stomach.
   C. Enteropathic changes include reduction in villus height, increase in crypt depth, and an associated inflammatory infiltrate in the epithelium and lamina propria.
   D. These changes are similar to celiac disease, including the presence of intraepithelial lymphocytes, but tend to be more severe in TS.
   E. The ability of the colon to absorb sodium and water is impaired, which significantly contributes to the diarrhea.
   F. Small bowel bacterial overgrowth is frequently a part of this disorder, likely in relation to delayed small bowel transit.
   G. Chronic atrophic gastritis is common, resulting in vitamin B12 deficiency that is corrected by administration of intrinsic factor (note that H. Pylori infection is very common in the tropics, and the interaction between H. Pylori and TS has not been well studied).
   H. Nutrient malabsorption in TS arises from involvement of the proximal and distal portions of the small intestine. Acute TS affects the jejunum, but chronic TS changes will eventually spread to the ileum.
   I. Folate and iron malabsorption represent proximal small bowel involvement, whereas vitamin B12 and bile acid malabsorption represent terminal ileal involvement.
   J. Pathologic changes include impaired small intestinal transport, disturbed intestinal motility, pancreatic insufficiency, and gastrointestinal peptide hormone abnormalities.

III. Clinical Features
   A. The typical patient of TS presents with chronic diarrhea, glossitis, bloating, prominent bowel sounds, and weight loss. Attack rates are more common in adults than in children.
   B. The illness often begins with an acute attack of watery diarrhea, with fever and malaise. Following resolution of the acute symptoms, patients develop milder chronic diarrhea with progressive weight loss. Fever is uncommon in the chronic form.
C. Some patients present with signs of nutritional deficiency, but without the diarrhea
D. The signs of nutritional deficiency include pallor due to anemia, angular stomatitis, chelitis and glossitis due to vitamin B deficiency, and peripheral edema and skin and hair changes secondary to hypoproteinemia. Megaloblastic anemia (due to vitamin B₁₂ deficiency) is common
E. Other signs include subacute combined degeneration of the spinal cord and night blindness (these are rare, and caused by deficiency of vitamin B₁₂ and vitamin A, respectively)
F. Other physical findings include loss of weight loss and hyperactive bowel sounds

Table 1. Summary of clinical manifestations of tropical sprue and their causative factors

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Malabsorbed nutrients with osmotic diarrhea; colonic water secretion due to unabsorbed fatty acids</td>
</tr>
<tr>
<td>Pale, bulky, foul-smelling stool</td>
<td>Fat malabsorption</td>
</tr>
<tr>
<td>Borborygmi, abdominal fullness</td>
<td>Carbohydrate malabsorption</td>
</tr>
<tr>
<td>Pedal edema, skin changes</td>
<td>Hypoproteinoemia secondary to loss of mucosal surface, protein loss, and pancreatic insufficiency</td>
</tr>
<tr>
<td>Pallor</td>
<td>Vitamin B₁₂ and folate deficiency</td>
</tr>
<tr>
<td>Angular stomatitis, glossitis</td>
<td>Vitamin B deficiency</td>
</tr>
<tr>
<td>Night blindness, corneal xerosis, Bitot's spots</td>
<td>Vitamin A deficiency</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>Hypophosphataemia, hypokalemia, hypomagnesemia</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Anorexia, malabsorption</td>
</tr>
</tbody>
</table>

IV. Diagnosis
A. For diagnosis of TS to be established, infectious, immunological and inflammatory causes of malabsorption must be ruled out
B. The three tests that are commonly used in investigating absorption are stool fat estimation and absorption of both D-xylose and vitamin B₁₂; two of the three tests have to be positive to establish the diagnosis of malabsorption
C. Endoscopically, TS resembles celiac disease with scalling of the mucosa. It is important to take biopsies beyond the second portion of the duodenum, as villi in the 2nd part of the duodenum may be shorter than they are more distally in the duodenum and the jejunum
D. Microscopy of small bowel biopsy typically shows reduction in villus height, increase in crypt depth, and an associated mononuclear (lymphocytic) inflammatory infiltrate in the epithelium and lamina propria
E. Performed small bowel series usually shows an increase in the caliber of the small intestine, and thickened folds; examination is usually notable for the slow transit of the barium column through the gut

V. Differential Diagnosis
A. Helminthic or protozoal infections (e.g., Strongyloides, giardia, isospora, and cryptosporidium)
B. Intestinal tuberculosis
C. Chronic pancreatitis (including tropical pancreatitis)
D. Small bowel bacterial overgrowth
E. Celiac disease
F. Crohn's disease
G. Primary immunodeficiency
H. Malignancy (immunoproliferative small intestinal disease and small intestinal lymphoma)

VI. Tropical Enteropathy
A. Structural differences of the small bowel mucosa seen in residents of the tropical areas
B. Differences include shorter villi, more elongated crypts, and increased lymphocytes, in the lamina propria
C. Cause subclinical malabsorption (mostly of fat and vitamin B₁₂, and, to a lesser extent, xylose)
D. Affected people are asymptomatic; a major distinction from tropical sprue which leads to overt diarrhea and malnutrition
E. Tropical enteropathy is believed to be the gut’s adaptation to recurrent infection, but could also be related to genetic factors.
F. Tropical enteropathy and TS may represent opposite ends of a spectrum.

VII. Treatment
A. Restoration of water and electrolyte balance, and replacement of nutritional deficiencies
B. Vitamin \(B_{12}\) should be given parenterally, but folic acid and iron can be given orally. These dietary interventions should result in prompt improvement of the hematological abnormalities (megaloblastic anemia) and restoration of appetite even before improvements in intestinal absorption.
C. Folate supplementation can also improve villous atrophy.
D. Although their role remains controversial, antimicrobial agents are widely used in the treatment of TS.
   1. Tetracycline 250 mg QID (or doxycycline 100 mg QD) for 3–6 months is the antibiotic of choice.
E. Restriction of long-chain fatty acids can help reduce the diarrhea.
F. The prognosis for complete and permanent recovery with treatment is excellent, especially for those who leave the area.

VIII. Prevention
A. Other than the usual advice that is given to travelers, there are no specific preventive measures. Early treatment of traveler’s diarrhea and the improving sanitary conditions worldwide are likely responsible for the declining incidence of TS.

Recommended Reading


Section 3 - Small Bowel

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3I. Protein-losing Enteropathy

Julie Bass, MD
William San Pablo, MD

Protein-losing enteropathy is the abnormal loss of proteins from the digestive tract resulting in decreased serum protein concentration.

I. Background
   A. Manifestation of variety of GI and extraintestinal diseases
      1. Leakage of protein across gut or decreased uptake by lymphatics secondary to altered mucosal permeability at any level of GI tract due to active inflammation
      2. In lymphangiectasia, the intestinal lymphatics are obstructed

II. Mechanism
   A. Normally sulfated glycosaminoglycan in basolateral portion of epithelium confines albumin to intravascular compartment
      1. Occurs due to strong electrostatic interaction between anionic sites in glycosaminoglycan carbohydrate chains and arginyl residues within protein molecules
   B. Pathologic state—loss of normal intestinal heparin sulfate proteoglycan expression allows diffusion of albumin and other proteins from bloodstream to lumen of gut via three mechanisms:
      1. Focal degradation by matrix-degrading metalloproteinases
      2. Failed synthesis in rare genetic defects
      3. Mislocalization in congenital disorders of glycosylation

III. Causes of PLE
   A. Metabolic
      1. Enterocyte heparin sulfate deficiency, congenital disorders of glycosylation
   B. Mucosal inflammation, erosion, or ulceration
   C. Infectious
   D. Non-Infectious
      1. Allergic gastroenteropathy, celiac, GI tumors, GVHD, HSP, IBD, polyposis
      2. Portal HTN, NEC, SLE
   E. Lymphatic obstruction (intestinal lymphangiectasia)
   F. Secondary causes
      1. Arsenic, CHF, pericarditis, thoracic duct damage, familial, tumors
      2. Following cardiac surgery, especially Fontan procedure

IV. Lymphangiectasia
   A. Dilation of lacteals, absence of inflammation, poor lymphatic drainage
   B. Primary: presents from premature infant to adolescent with diarrhea, vomiting, growth retardation, and lymphedema
   C. Secondary
      1. Cardiovascular: 4%–11% of Fontan patients develop PLE
      2. SLE
      3. Tumors


V. Clinical Manifestations
A. Variable, depending on degree of protein loss and nature of underlying disease
   1. Changes in clotting factors rarely show clinical findings
   2. Hypogammaglobulinemia not associated with infection
   3. Lymphopenia may result in altered cellular immunity
B. Peripheral edema due to decreased plasma oncotic pressure
C. Pleural effusions and pericardial effusions, especially if thoracic duct is obstructed
D. Fat and carbohydrate malabsorption may occur due to small bowel involvement in primary disease process

VI. Diagnosis
A. Labs: decreased albumin, transferrin, gamma-globulins (IgA, IgG, IgM), ceruloplasmin, and fibrinogen
B. Urinary protein loss and hypoalbuminemia secondary to liver disease and malnutrition should be excluded
C. Rule out eosinophilic gastroenteritis, IBD, and celiac disease
D. Diagnostic studies:
   1. Fecal alpha-1 antitrypsin (<54 mg/dL) or fecal calprotectin (<50 µg/g)
   2. Small bowel contrast studies: thickened folds
   3. Endoscopy: mucosa with snowflake pattern, lesions are patchy (need multiple biopsies)
      a. Histology findings: dilated lacteals

VII. Treatment
A. Treat underlying disease
B. Carbohydrate-deficient Glycoprotein Synthase Deficiency (CDG-1b): treatable-mannose supplementation circumvents enzymatic defect and corrects defective glycosylation
C. Intestinal lymphangiectasia
   1. High-protein, low-fat diet supplemented with MCT
   2. Octreotide helpful if MCT fails
   3. Heparin therapy
   4. Corticosteroids
   5. Antiplasmin therapy
   6. Surgery
D. PLE secondary to Fontan: medical treatment vs surgical treatment

Recommended Reading
Appendicitis is a clinical diagnosis that can only be confirmed by pathology and requires a low threshold for surgical consult to ensure timely intervention.

I. Pathophysiology
   A. Obstruction of the lumen (fecal matter)
   B. Swelling of the lymphoid tissue (post-infectious)

II. Peak age of onset
   A. Adolescence
   B. <2% of cases are children <2 years of age

III. Presentation
   A. Typical
      1. Pain, followed by vomiting, followed by right lower quadrant pain
      2. Caution: symptoms may temporarily improve after perforation
   B. Atypical Presentation
      1. Persistent periumbilical pain or hip pain (especially if appendix is retroperitoneal)
      2. Bloody diarrhea if appendix perforates against the sigmoid

IV. Physical Exam
   A. Progression from RLQ tenderness to voluntary guarding, to involuntary guarding, to rebound tenderness (signs of peritonitis)
   B. Other common (but not necessary) findings: ill-appearing, low-grade fever, unwillingness to move, anorexia

V. Labs
   A. Elevated WBC, sterile pyuria, elevated CRP
   B. None are specific to appendicitis
   C. All may be normal, especially in the first several hours

VI. Radiology
   A. Plain films
      1. Only helpful in infants with perforation (paucity of gas, soft tissue edema)
      2. Can possibly see a fecalith. Not needed in older children
   B. Ultrasound
      1. Highly operator-dependent
      2. Can detect swollen/noncompressible appendix, periappendiceal fluid, or an abscess
      3. Has most value in adolescent females, to distinguish from adnexal pathology
   C. CT scan
      1. Most extensively used
      2. Can detect appendiceal wall thickening, periappendiceal fat stranding, or abscess
      3. Ideally, should give IV and oral contrast
      4. Sensitivity and specificity are >90%, and even higher with newer 3-mm thin cuts
VII. Perforation
   A. Typically occurs 36 hours after the onset of pain
   B. More common in infants (up to 70%) and those with fecalith (50%)
   C. Change in symptoms/signs that may suggest perforation
      1. High fever, tachypnea, right leg in drawn up position, diffuse abdominal tenderness,
         low-volume diarrhea or bowel obstruction
      2. Retroperitoneal appendicitis is more varied: may have psoas/obturator signs
   D. Walled-off abscess
      1. Symptoms can persist for days
      2. Can develop extreme toxicity/sepsis

VIII. Pitfalls
   A. Children <2 years (unable to obtain history well)
   B. Obesity (may not be able to appreciate tenderness)
   C. Narcotics (may mask pain)

IX. Differential Diagnosis
   A. Infectious gastroenteritis (including yersinia)
   B. Constipation
   C. Urinary tract infection
   D. Crohn disease
   E. Pelvic inflammatory disease
   F. Ovarian cyst
   G. Right lower lobe pneumonia
   H. Mesenteric adenitis
   I. Typhlitis (immunocompromised patients)
   J. Other etiologies of a surgical abdomen (obstruction, omental torsion)

X. Treatment
   A. IV fluids
   B. Broad-spectrum IV antibiotics (such as piperacillin-tazobactam)
   C. Open or laparoscopic appendectomy is usually performed the same day
   D. In cases of perforation or abscess, antibiotics and/or percutaneous drain may be done first, with
      interval appendectomy following at a later time

Recommended Reading


3K. Food and Waterborne Diseases

Misam Abu-El-Haija, MD
Dawn Ebach, MD

Food and waterborne illnesses result from ingestion of food and water containing preformed microbial toxins, invasive microorganisms or microorganisms, that secrete toxin in situ. The most common causes are rotavirus, adenovirus, shigella, salmonella, and campylobacter.

Definitions
A. The Centers for Disease Control and Prevention (CDC) estimates 76 million cases, 323,000 hospitalizations, and 5,000 deaths annually in the United States
B. Globally, there are 1.5 billion episodes of acute gastroenteritis in 500 million children <5 years of age
C. Five million of these children die; 20% from rotavirus

Main Etiologic Agents
I. Bacterial
   A. Salmonella spp
      1. Major cause of foodborne illness and second leading cause of death from foodborne illness
      2. Outbreaks have resulted from bacterial contamination of commercial products—eggs, chicken, peanut butter, cheese
      3. See Enteric Infections
   B. E coli
      1. The main species causing foodborne illness are enterohemorrhagic E coli (EHEC) and enterotoxigenic E coli (ETEC)
      2. See Enteric Infections
   C. Shigella spp
      1. Food and water contamination
      2. Outbreaks of bloody diarrhea
      3. Most common US strain is S sonnei, which does not produce shiga toxin
      4. See Enteric Infections
   D. Staphylococcus aureus
      1. Food (egg, meat, and milk products, especially) at room temperature supports the growth of S aureus
      2. Some strains produce an enterotoxin while incubating in food which is ingested, causing nausea, vomiting, and diarrhea within hours
      3. Disease is self-limited but can cause death from hypovolemic shock
      4. Disease severity and incubation period depend on the amount of enterotoxin ingested
      5. There are almost twenty different enterotoxins and related toxins produced by S aureus, with some differences in structure and biological activity
      6. Staph toxins are superantigens. At picomolar concentrations, they massively activate mononuclear cells and T cells, regardless of the antigenic specificity of the T cells
   E. Campylobacter: jejuni 95%, fetus 5%
      1. Occurs in meats, poultry, dairy
      2. Resembles shigella in presentation
      3. See Enteric Infections
F. *Bacillus cereus*
   1. Endospore-forming bacterium transmitted to humans, often via fried rice and Chinese food
   2. 1-8 hour incubation period
   3. Nausea, vomiting, diarrhea, abdominal pain
   4. Symptoms of nausea and vomiting are due to intoxication by the *B cereus* emetic toxin, cereulide, produced in foods before ingestion
   5. Symptoms of diarrhea are due to ingestion of viable cells or spores, producing protein enterotoxins in the small intestine

G. *Clostridium perfringens*
   1. Organism found in soil, uncooked or reheated meat, unpasteurized milk or juice, and some canned foods (especially bean and pea products)
   2. Enterotoxin produced by the organism within the GI tract
   3. Diarrhea is the main symptom, and can be fatal
   4. Disease is caused by *C perfringens* enterotoxin, which interacts with intestinal tight junction proteins, creating pores. Other *C perfringens* enteric toxins include the epsilon-toxin and the beta-toxin, which also form pores in intestinal or extraintestinal target tissues

H. *Aeromonas*
   1. Various species common in waters, usually contracted during summer months
   2. Generally under 3 years of age with bloody diarrhea in 25%, fever and vomiting in 35%
   3. Duration is 5–7 days

I. *Yersinia enterocolitica*
   1. Invasive bacteria
   2. See Enteric Infections

II. Protozoal
   A. All of these protozoal organisms are food or water borne
      1. Amoebic:
         a. *Entamoeba histolytica*
         b. *Entamoeba coli*
         c. *Endolimax nana*
         d. *Iodamoeba butschlii*
      2. Flagellates:
         a. *Giardia lamblia*
         b. *Chilomastix mesnili*
         c. *Dientamoeba fragilis*
      3. Coccidia:
         a. *Isospora belli*
         b. *Sarcocystis hominis*
      4. Ciliata:
         a. *Balantidium coli*
         b. *Blastocystis hominis*
   B. *E histolytica*
      1. Incidence: 3%–10% worldwide, asymptomatic in 90% of cases
      2. Globally, the second leading cause of death from parasites
      3. Two distinct species co-exist: *E histolytica*, the pathogen; and *E dispar*, the commensal. Size: 8–30µ
      4. Transmission: fecal-oral cyst ingestion, excysts in the ileocecum and forms trophozoites
      5. *E histolytica* secretes three cytolytic peptides—amoebapores—in trophozoites, which immobilize mucosal cells quickly. Cells lose cytoplasmic granules and, eventually, the nucleus
      6. Release of cysteine proteinases produces the classic “collar-button” abscess
      7. Symptoms are bloody diarrhea, dysentery with tenesmus, weight loss
      8. Unusual manifestations include NEC, toxic megacolon, and perianal ulceration/fistula
      9. Diagnosis by O&P, serum mucosal IgA antibodies, and PCR
      10. Treatment: paromomycin, metronidazole
      11. Complications: trophozoites breach mucosal barrier, travel through portal system, and produce liver abscess, with 7%–20% contiguous pulmonary infection
      12. Liver abscess is 10x more common in men, and rare in children
      13. Jaundice is due to biliovesicular fistula resulting from hepatonecrosis
C. *Balantidium coli*
   1. Transmission is fecal-oral (swine-human). Size: 75–200 µ
   2. Symptoms: most infections are asymptomatic. *B coli* lives on intestinal bacteria, but can produce hyaluronidase, resulting in ulcers, bloody dysentery
   3. Diagnosis by fresh stool exam, biopsy
   4. Treatment: tetracycline, metronidazole

D. *Giardia lamblia*
   1. Incidence: 1%–20%, with geographical variations; and transmission is via fecal-oral or water contamination
   2. See Enteric Infections

E. *Blastocystis hominis*
   1. Incidence: found in 1%–20% of O&P, asymptomatic carrier common
   2. Size: 8–10 µ, granulated or vacuolated
   3. Symptoms: appear with infection >5 cysts/HPF, and include cramping, bloating, diarrhea, eosinophilia
   4. Diagnosis by stool hematoxylin or trichrome stain
   5. Treatment: metronidazole or nitrazoxanide

F. *Isospora belli*
   1. A coccidian protozoa only of humans
   2. Transmission is by fecal-oral cyst ingestion, more common in tropics
   3. Size: sporozoites 9–11 µ, oocysts 12–30 µ
   4. Symptoms: asymptomatic, or invade mucosa and produce diarrhea, pain, weight loss, anorexia, steatorrhea, and eosinophilia
   5. Diagnosis by O&P, duodenal aspiration
   6. Treatment: TMP/S for 4 weeks

G. *Cryptosporidium parvum*
   1. A coccidian intracellular protozoa 2–4 µ, with 30%–60% crèche transmission
   2. Food (predominantly berries) and water-borne outbreaks
   3. General incidence among hospitalized gastroenteritis is 2.5%–6%
   4. Incubation is 7–10 days, 90% of patients develop a watery diarrhea of 2 weeks’ duration
   5. Symptoms: diarrhea, pain, weight loss, fever, anorexia
   6. Patients with AIDS can develop a fulminant syndrome
   7. Biliary cryptosporidiosis is the most common extraintestinal manifestation, evident by US revealing thickening of biliary ducts
   8. Diagnosis: acid-fast counterstain. In HIV, check sputum, lung biopsy, and biliary tract
   9. Treatment: if necessary, nitazoxanide or paromomycin

### III. Diagnosis

A. Based on clinical presentation
B. Physical exam may show signs of dehydration
C. Polymerase chain reaction (PCR) is available for rapid detection of some infections: *Salmonella*, *Campylobacter*, and *E coli*
D. No reliable commercial PCR test for *Bacillus cereus*, *Clostridium perfringens*, or *Staphylococcus aureus*
E. Serologic and stool analysis

### IV. Management

A. Symptomatic treatment and hydration
B. Most cases of food poisoning resolve within 24 hours
C. Immunocompromised hosts may have chronic severe disease with high mortality
D. Specific antimicrobials and antiparasitic agents are available (see above)
Recommended Reading


I. Bacteria

Enteric bacterial infections, causing diarrhea, dysentery and enteric fevers, are important health problems throughout the world. These bacterial infections represent a notable burden, in particular, for children living in less-developed regions of the world, where the number of diarrheal episodes and childhood deaths reported worldwide remains of apocalyptic dimensions. They are also a risk for travelers from industrialized countries who visit less-developed areas.

A. *Salmonella*

1. Gram-negative, motile bacilli
   a. Genus of family of *Enterobacteriaceae*
   b. Human pathogens: *S. enterica* subspecies
   c. O-oligosaccharide cell wall antigens and flagellar H-protein antigens (2,300 species)

2. Epidemiology:
   a. *S. typhi* and *S. paratyphi*
      1) Colonize only humans
      2) Fecal-oral transmission
      3) 12.3 million cases/year (excluding China)
      4) Annual incidence 0.5% worldwide
          a) US decrease from 1/100,000 (1955) to 0.2 case per 100,000 (1966)
          b) Estimated 21.6 million illnesses and 216,500 deaths worldwide in 2000
   b. Nontyphoidal salmonella: wild animals, poultry, swine, cattle, rodents, reptiles
      1) Host factors influence: (congenital and acquired immunodeficiency), age <3 months, achlorhydria, antacid treatment, or antibiotics
      2) Leading reported foodborne disease outbreak in US (grade A eggs, raw fruits and vegetables)
      3) Person-to-person and vertical transmission
          a) Incidence greatest <5 years old, peak < 1 year old
      4) Increase between 1970 and 1987 from 12 to 20/100,000
          a) Estimated 94 million cases (mostly foodborne) and 155,000 deaths worldwide

3. Clinical Manifestations
   a. Gastroenteritis
      1) Incubation 6 hours–10 days
      2) Acute self-limited enterocolitis
      3) Bacterimia (infancy, peak at 3 months)
      4) Diarrhea: blood, mucus, fecal leukocytes
      5) Fever 70%
      6) Detected in stool for 5 weeks–1 year
   b. Extraintestinal manifestations
      1) Infants (meninges, bones, lungs)
      2) Osteomyelitis in sickle cell disease, HIV (prolonged diarrhea, bacterimia, weight loss)
      3) Meningitis: high mortality and neurologic sequelae
The NASPGHAN Fellows Concise Review of Pediatric Gastroenterology, Hepatology and Nutrition

Enteric fever

1. Incubation 5–21 days
2. Chills, headache, cough, weakness, muscle pain (prodrome)
3. 30% develop rose spots on the trunk; most resolve by 4th week
4. Others improve initially, but then develop abdominal pain, Peyer’s patches inflammation, secondary bacteremia

4. Diagnosis: stool culture, blood culture

5. Treatment
   a. Contraindicated in patients 2–50 years old who are immunocompetent and are only mild-to-moderately ill, especially if improving clinically, since treatment prolongs carrier state
   b. Antibiotics do not speed resolution, nor eliminate fecal excretion
   c. Antibiotics are administered to patients with suspected or proven salmonellosis who are at high risk of complications, such as: <3 months of age, toxic appearing, hemolytic anemia, malignancy, chronic colitis, immunodeficiency, elderly
   d. Antibiotics for immunocompetent individuals who are severely ill: Bactrim (160 mg/800 mg PO BID), amoxicillin (500 mg TID), cefotaxime (2 grams IV TID), ceftriaxone (1–2 grams IV QD)
      1) Length of treatment: bacteremia 2 weeks, osteomyelitis 4–6 weeks, meningitis 4 weeks
   e. Hygienic practices for prevention

B. Shigella dysenteriae

1. Gram-negative, non-lactose-fermenting, nonmotile bacilli
2. Genus of family of Enterobacteriaceae
   a. S dysenteriae – group A (less developed countries)
   b. S flexneri – group B (less developed countries)
   c. S boydii – group C
   d. S sonnei – group D (industrialized countries)

3. Clinical Manifestations
   a. Incubation 1–4 days
   b. Systemic symptoms (fever, headache, malaise, anorexia, vomiting)
   c. Watery diarrhea → dysentery (tenesmus; small, frequent blood and mucus containing stools)
   d. Shiga toxin – HUS (children) or TTP (adults); shiga neurotoxin may cause seizures
   e. Self-limited in healthy individuals, lasting 5–7 days
      1) Life-threatening in malnourished or immunocompromised

4. Diagnosis, Treatment, Prevention
   a. Stool culture, rapid incubation at 37°C
   b. Antibiotics: decreased duration of fever, diarrhea, intestinal protein loss and pathogen excretion
      1) May reduce the risk of developing complications
   c. Medication regimen is determined by severity of illness, local resistance patterns, and history of travel to an area of frequent resistance
      1) TMP-SMX: 10 mg/kg TMP and 50 mg/kg SMX per day in two divided doses for 5 days (max 160 mg TMP and 600 mg SMX)
      2) Ampicillin 100 mg/kg/day in four divided doses for 5 days
      3) In areas of high resistance to TMP-SMX and ampicillin, azithromycin is the suggested first-line oral treatment
         a) 12 mg/kg for first day (max 500 mg), then 6 mg/kg/dose (max 250 mg) for an additional 4 days
   4) Hand-washing for prevention
   5) Oral vaccine in clinical trials

C. Yersinia

1. Gram-negative, non-lactose-fermenting, aerobic and facultatively anaerobic bacilli (grow at 25°C)
   a. Family Enterobacteriaceae (enterocolitica and pseudotuberculosis) – human pathogens
2. Epidemiology
   a. Swine is major reservoir for human infection (food-borne)
   b. Most episodes occur in infant and young
   c. More common in N. latitudes – N. Europe, Scandinavia, Canada, US, Japan
      (1-8% of diarrhea)

3. Clinical Manifestations
   a. Incubation 3–7 days
   b. Younger than 5 years old, watery diarrhea (blood 25%–30%), fever, and
      abdominal pain
   c. Cervical adenitis (pharyngitis)
   d. Abdominal complications: appendicitis, diffuse ulceration of intestine and co-
      lon, intestinal perforation, peritonitis, ileocecal intussusception, toxic mega-
      colon, cholangitis, mesenteric venous thrombosis
   e. Pseudoappendicitis syndrome
   f. Associated with immunopathologic sequelae, including reactive arthritis, uve-
      itis, Reiter’s syndrome, and erythema nodosum

4. Diagnosis, Treatment, Prevention
   a. May be isolated from stool, but should use selective media; alternative is
      detection of the microorganism by PCR methodology
   b. Most cases resolve, uncomplicated
   c. 3rd generation cephalosporins (combination with aminoglycosides),
      aztreonam, imipenem
      1) Start IV and PO for total 2–6 weeks
   d. No vaccines

D. *Campylobacter*
   1. Small, nonsporing, motile, spiral-shaped, Gram-negative bacteria, microaerophilic,
      seagull appearance
      a. Family *Campylobacteriaceae*; thirteen species pathogenic to humans; *C jejuni*
         and *C coli* are the most common species isolated from patients with diarrhea
   2. Epidemiology
      a. Reservoir in the intestines of wild and domestic animals
         1) Half of cases from poultry
         2) Also unpasteurized milk or contaminated water
      b. Does not multiply in food to high concentrations, as does Salmonella, but
         inoculum required to cause infection is lower
      c. Annual incidence about 1% (summer months)
      d. Bimodal incidence: 0–5 and 15–29 year olds
   3. Clinical Manifestations:
      a. Incubation: 3–6 days
      b. Abdominal cramps (mimic appendicitis) and watery diarrhea, then bloody
         diarrhea (lasting 4–5 days)
      c. Fecal excretion for one month (immunocompromised longer)
   4. Diagnosis, Treatment, Prevention
      a. Stool culture
      b. Controversial use of antibiotics (may shorten course of diarrhea), as may
         develop drug resistance
         1) Used for immunocompromised
         2) Erythromycin
      c. Vaccine development: concerns about post-exposure arthritis or Guillain-
         Barré syndrome

E. *Escherichia coli*
   1. Gram-negative, lactose-fermenting, motile bacilli
      a. Most *E coli* are part of normal fecal flora
   2. Enteropathogenic *E. coli* (EPEC): first group shown to be pathogens
      a. Nosocomial, neonatal and infant diarrhea
      b. Ability to induce attaching and effacing lesion in intestinal enterocytes
      c. Epidemiology: infantile diarrhea, nursery outbreaks
d. Clinical Manifestations: 109 colony-forming unit, self-limited watery diarrhea (incubation: 6–48 hours) that may last up to 14 days
e. Treatment and prevention: course of triple oral antibiotics, shortens course (bactrim, gentamicin, colistin); encourage breastfeeding and improving social/economic conditions

3. Enterotoxigenic *E. coli* (ETEC); enterotoxins (heat stable or heat labile)
   a. Epidemiology
      1) Leading cause of dehydrating diarrheal disease among weanling infants in the developing world
      2) Traveler’s diarrhea
      3) Contaminated food and water (peak in warm, wet season)
   b. Clinical Manifestations: high inoculum (incubation: 14–30 hours); watery diarrhea, fever, abdominal cramps, vomiting, self-limited for up to 5 days
   c. Treatment and Prevention: self-limited; antibiotics shorten duration of illness by 1–2 days (doxycycline, bactrim [resistant], ciprofloxacin; quinolones, furazolidone)

4. Enteroinvasive *E. coli* (EIEC); almost identical genetically, biochemically, and chemically to *Shigella*
   a. Epidemiology: developing countries, 1%–5% diarrhea
   b. Clinical manifestations: watery diarrhea

5. Enterohemorrhagic *E. coli*: shiga-like toxins; cause diarrhea or HUS
   a. Epidemiology: food outbreak (*E. coli* O157:H7); vehicles include raw meat, fruits, vegetables, drinking or swimming water; person-person in daycare
   b. Clinical Manifestations: follows 3–9 days after ingesting 100 organisms
      1) Crampy abdominal pain, non-bloody diarrhea initially, then bloody
      2) 25% hospitalized, 5%–10% develop HUS, 1% die (risks: young or old age, bloody diarrhea; fever, high WBC, antimotility agents)
         a) 2/3 of HUS don’t excrete organism at presentation
      3) Complications include rectal prolapse, appendicitis, intussusception, pseudomembranous colitis
   c. Diagnosis, Treatment, Prevention: stool culture, antibiotic-treated patients have same or poorer outcome than untreated; cooked meat; vaccines in development

6. Diffusely Adhering *E. coli* (DAEC)
   a. Epidemiology: diarrhea <6 years old; frequent in warm season
   b. Clinical Manifestations: self-limiting watery diarrhea
   c. Diagnosis: DNA probe technique (epidemiologic surveys)

7. Enteroaggregative *E. coli* (EAggEC): not all species are human pathogens
   a. Epidemiology and Clinical Manifestations: sporadic outbreaks; watery, mucoid, secretory diarrhea; 1/3 bloody diarrhea, low-grade fever
   b. Diagnosis and Treatment: stool culture, PCR assays, self-limiting, some benefit for antibiotic use if known susceptibility

F. Intestinal Tuberculosis
   1. The pathogen is *Mycobacterium tuberculosis*
   2. Routes of Gi infection include:
      a. Ingestion of infected sputum in patients with active pulmonary TB
      b. Spread through a hematogenous route from tuberculous focus in the lung to submucosal lymph node
      c. Local spread from surrounding organs involved by primary tuberculous infection
   3. Clinical features of intestinal TB include abdominal pain, weight loss, anemia, night sweats; symptoms of obstruction such as palpable mass or pain in the right iliac fossa
   4. Jejunuleum and ileocecal involvement is seen in >75% of patients
   5. Diagnosis: colonoscopy, with multiple biopsies at the ulcer margins and tissue sent for routine histology, smear, and culture; exploratory laparotomy is necessary if the diagnosis is in doubt
   6. Treatment: full course of antituberculous chemotherapy
II. Viral Infections

A. Rotavirus
   1. Pathophysiology: virions are ingested, activated by trypsin in the small intestine, and invade the villus enterocytes, leading to their destruction and the release of thousands of progeny, which are then locally activated by trypsin to infect more enterocytes
      a. Small intestinal epithelium is rapidly repopulated with less differentiated enterocytes from the crypts, which lack digestive enzymes and mechanisms for active sodium and water absorption (Na/K, ATPase), therefore diarrhea (osmotic and secretory diarrhea)
   2. Each year rotavirus causes 111 million episodes of gastroenteritis worldwide, 25 million clinic visits, 2 million hospitalizations, and 352,000–592,000 deaths in children <5 years old
      a. Children in poorest countries account for 82% of deaths
   3. Clinical Features
      a. Incubation period of 2–7 days, abrupt onset of vomiting and fever, then profuse watery diarrhea, causing dehydration, acidosis, and electrolyte imbalance
      b. Irritability, lethargy
      c. Respiratory symptoms possible in 20%–40%
      d. Vomiting settles in 24–48 hours, and diarrhea in 2–7 days
      e. Acute complications: hypo/hypernatremia, febrile convulsions, AST elevation
   4. Treatment
      a. Correct dehydration, acidosis, and electrolyte imbalance
      b. Encourage breast feeding; very small percentage have lactose malabsorption, requiring lactose-free diet
      c. Drugs (antiperistaltic or antiemetics) should be avoided
      d. If mild disease, probiotics lactobacillus GG may decrease duration of diarrhea
   5. Prevention
      a. Hand-washing
      b. Breastfeeding reduces the overall incidence of diarrheal diseases in the first year of life
      c. Vaccine
         1) Rotashield (link to intussusception)
         2) Rotateq (live) – Three oral doses in first 6 months of life (90% protection against severe dehydrating disease)

B. Enterovirus
   1. Belong to Picornaviridae family (small RNA viruses)
      a. Includes coxsackie, echovirus, and poliovirus
   2. Most common route of transmission is fecal-oral route
   3. Resilient, remain viable at room temperature for several days, can survive acidic pH of GI tract
   4. Nonpolio enteroviral infections cause an estimated 10–15 million symptomatic infections per year in the US
   5. Risk factors include poor sanitation, crowded living conditions, and lower socioeconomic status
   6. Children younger than 5 years old are more susceptible because of poor hygiene habits and lack of prior immunity
   7. No specific antiviral medication or treatment is available for an enteroviral infection; use supportive measures, fluid hydration, and antipyretics

C. Enteric Adenovirus
   1. Ubiquitous human pathogens causing a variety of syndromes ranging from respiratory infections to hepatitis
   2. Account for 3%–5% of acute pediatric enteritis
   3. Diagnosis made by EIAs
   4. Replicate in host nuclei in patients with diarrhea
5. No specific treatment, although use of ribavirin in immunocompromised hosts has been reported.

D. Calicivirus (noroviruses and sapoviruses)
1. Pathophysiology: villus shortening and crypt hypertrophy in the proximal duodenum associated with villus tip vacuolization and infiltration of the lamina propria with inflammatory cells
   a. Gastric and colonic mucosa are completely normal

2. Rapid onset of symptoms, rapid spread of disease through groups
3. Mild and self-limited 12–24 hours, with 1–2 days' incubation
4. Asymptomatic shedding of virus
5. No specific treatment is available

E. Norwalk-like virus
1. May cause 10% of sporadic cases of diarrhea in developed countries
2. Affects especially the immunocompromised
3. Rapid onset of symptoms, predominant vomiting and rapid spread of disease through groups, with high attack rate across all age groups
4. Illness is generally mild and self-limited
5. Infantile enteritis is clinically similar to rotavirus gastroenteritis, although resulting in less severe dehydration

III. Parasitic Infections
A. Giardia lamblia
1. Motile trophozoite and also as a cyst, with the latter being the infective form
2. Infection transmitted by food, water, and person-to-person contact
3. Incubation period from the time of ingestion of cysts until the onset of symptoms is 3–20 days
4. Clinical Manifestations
   a. Acute infection begins with persistent, watery diarrhea, and is associated with anorexia, abdominal distention, flatulence, abdominal cramps, malodorous, greasy stools; weight loss, and urticaria
   b. Chronic giardiasis can be associated with immunoglobulin deficiency, which may be associated with diffuse nodular lymphoid hyperplasia involving the small and large intestine
   c. 50% of persistent diarrhea will have fat malabsorption
   d. Lactase deficiency is common
5. Diagnosis
   a. Gold standard—identification of Giardia forms by microscopy of feces, duodenal fluid, or mucosal biopsy specimens
   b. Multiple stool samples may miss 50%
   c. Motile trophozoites identified on a wet saline mount of fresh liquid stool obtained during the illness
   d. Antigen-based fecal detection assays are specific, but not sensitive (80%)
6. Treatment:
   a. Metronidazole (30 mg/kg/dose for 3 days)
   b. Albendazole (400 mg daily for 7 days)
B. Ascaris lumbricoides
1. Largest human intestinal nematode; adult worms can reach 10–30 cm in length
2. Lifecycle:
   a. Transmitted by fecal-oral route from ingestion of agricultural products or food contaminated with parasite eggs
   b. Swallowed eggs hatch in the intestine, producing larvae, which then migrate through the blood to the pulmonary circulation, penetrate the alveoli, and migrate upward through the blood to the pulmonary circulation, penetrate the alveoli and migrate up the tracheobronchial tree
   c. A host swallows the larvae which, develop into adult worms in the intestine
3. Clinical manifestations:
   a. Anorexia and abdominal cramps
   b. Partial or total intestinal obstruction
      1) May migrate into pancreatic and biliary systems, causing duct obstruction with jaundice
c. Rare complication: Loffler’s syndrome—fever, cough, sputum, asthma, eosinophilia, and radiological pulmonary infiltration

4. Diagnosis
   a. CBC with peripheral eosinophilia
   b. Ova and adult worms in feces, and larvae in sputum or gastric washings
   c. Ultrasound, ERCP, MRCP, and CT scanning are useful in the diagnosis of biliary ascariasis

5. Treatment
   a. Albendazole (single dose of 200 mg in children 2–5 years old, and 400 mg for older children and adults)
   b. Mebendazole (single dose of 500 mg)
   c. Levamisole (single dose of 2.5 mg/kg)
   d. Pyrantel pamoate (single dose of 10 mg/kg)

C. Tapeworm
   1. Adult worms reside in the intestinal tract. Larvae reside in muscle tissue
   2. Taenia saginata (Beef tapeworm)
      a. Human is the definitive host, and cattle are the significant intermediate hosts
      b. Human infection is acquired by eating undercooked beef
      c. Contaminated feed or grazing ground with human feces is the source of infection for cattle
      d. Most patients are symptom-free, some with vague abdominal discomfort, occasional diarrhea, or awareness of motile proglottids spontaneously emerging from the anus
      e. Diagnosis when Taenia eggs seen in feces by microscopy
      f. Praziquantel as single dose 10 mg/kg
   3. Taenia solium (Pork tapeworm)
      a. Similar to T saginata; however, serious complication when autoinfection with T solium larvae results in their dissemination to many sites (called cysticercosis), including skeletal muscle, brain, subcutaneous tissue, eye, myocardium
         1) The cysts remain alive for many years, but eventually produce a local inflammatory reaction and calcify
         2) Cerebral involvement presents as epilepsy, as space-occupying lesion, or as focal neurologic deficits
         3) Ocular involvement produces retinitis, uveitis, conjunctivitis, or choroidal atrophy
      b. Praziquantel 10 mg/kg single dose
   4. Diphyllobothrium latum (Fish worm)
      a. Found in Scandinavia, Baltic countries, Japan, and Swiss lakes
      b. Ingestion of raw or undercooked fish
      c. Infection is asymptomatic, although may cause abdominal discomfort, vomiting, weight loss
      d. Cleaves vitamin B12
      e. Diagnosis and treatment as for other tapeworms
   5. Hymenolepis nana
      a. Infects children more often than adults
      b. Has other natural hosts in rats and mice
      c. Generally produces no symptoms, although very heavy infection may result in diarrhea and abdominal pain
   6. Hookworm (Ankylostoma duodenale and Necator americanus)
      a. Adult worms attach firmly to the small intestinal mucosa by a buccal capsule consisting of tooth-like or plate-like cutting organs
      b. Infection acquired percutaneously from larvae in the soil contaminated by human feces, or orally after ingestion of contaminated food or consumption of uncooked meat containing the larvae
      c. Man is the only reservoir of infection; favorable larvae development in warm, moist soil
         1) Infection occurs by contaminated soil, or via the skin when larvae secrete a protease that facilitates boring into the skin and entry into subcutaneous tissue
2) Larvae migrate through the venous and lymphatic circulation into pulmonary capillaries, get into lung alveoli, and ascend the airways
3) Coughed up and swallowed, larvae then develop into adult worms in the proximal small intestine, then attach to the mucosa and begin to feed
   a) Every 4–8 hours, worms change the site of attachment, producing minute, bleeding mucosal ulcerations which lead to hypochromic anemia
d) Hookworm infection is the leading cause of iron deficiency anemia (proportional to worm load) in developing countries, and may affect cognitive development
e) May cause protein-losing enteropathy
f) Diagnosis and Treatment
   1) Detected in stool and duodenal fluid
   2) Mebendazole 200 mg/day for 3 days
   3) Albendazole 400 mg once
   4) Levamisole and pyrantel pamoate
   5) Anemia is treated with oral ferrous sulfate or gluconate, and continued for 3 months after a normal hemoglobin level has been achieved

7. Whipworm (*Trichuris trichiura*)
   a) Infection is transmitted by ingestion of ova that have matured outside the host for several weeks
   b) Colonization involves the distal ileum and cecum, although the entire colon may be involved
c) Clinical Manifestations
   1) Light infection is usually asymptomatic, but with >20,000 ova per gram of feces, diarrhea with blood and mucus is characteristic
   2) Abdominal pain, anorexia, weight loss, tenesmus, rectal prolapse
   3) May impair growth and development in young children
d) Diagnosis and Treatment
   1) Barrel-shaped eggs detected in feces
   2) Adult worms can endoscopically be seen attached to the colonic mucosa, often with the presence of ulceration and inflammatory changes
   3) Albendazole or mebendazole as a single dose; multiple courses may be necessary to clear infection

D. STD-related gastroenteritis
1. HIV-infected patients with chronic diarrhea should be treated symptomatically
2. If an enteric pathogen is cultured, specific therapy should be administered
3. A flexible sigmoidoscopy is recommended if a diagnosis is not obtained with stool analysis
4. Small intestinal infections include the following pathogens
   a. *Cryptosporidium*, *Microsporidium*, *Isospora*, *Cyclospora*, *Giardia*, and *Entamoeba*
   b. CMV

E. Fungal Infections
1. A well child with intact host defense mechanisms is generally not considered to be susceptible to fungal infections of the digestive tract
2. Chronically immunosuppressed patients secondary to myelotoxic agents, immunosuppressive therapies, and/or HIV/AIDS are susceptible to intestinal fungi infections
3. *Candidiasis*: *Candida* species, most common in intestinal illness *Candida albicans*; major risk factor is neutropenia
   a. Esophagitis seen in immunosuppressed children and hematologic malignancy; oral thrush seen in only 20% of cases; nystatin oral; ketoconazole or fluconazole
   b. Peritonitis seen after bowel surgery or in patients with chronic peritoneal dialysis
c. _C. albicans_ may invade the small bowel and large intestine in terminally ill patients

4. **Aspergillosis**: genus _Aspergillus_
   a. Most cases seen in severely immunocompromised
   b. Amphotericin B is treatment of choice

5. **Zygomycosis** (aka mucormycosis or phycomytosis)
   a. Ubiquitous agents found in organic debris, on fruit and in soil; grow rapidly on any carbohydrate substrate
   b. May invade subcutaneous or submucosal tissues in an immunocompetent host
   c. Intestinal zygomycosis in the immunosuppressed host or severely malnourished, may cause acute fulminant invasive infection
   d. Treatment includes amphotericin B (1–1.5 mg/kg) and surgical debridement

6. **Coccidioidomycosis**
   a. _Coccidioides_ is a dimorphic fungus endemic in the southwest United States
   b. Usually a pulmonary infection, but spores may escape and, with dissemination, the terminal ileum and colon are involved
   c. Treatment of primary pulmonary disease with fluconazole (6–12 mg/kg daily), and disseminated disease requires amphotericin B

**Recommended Reading**


Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI.

Autoimmune enteropathy (AIE) is an important cause of diarrhea in infancy and early childhood. The target of the autoimmune attack is the epithelium. AIE is a T-cell–mediated disorder resulting in profuse diarrhea and protein-losing enteropathy.

**Types of Autoimmune Enteropathy**
AIE is divided into 3 forms:
1. X-linked IPEX syndrome
2. IPEX-like form in boys and girls
3. Autoimmune manifestations limited to GI tract
4. Autoimmune Polyendocrinopathy–Candidiasis-Ectodermal Dysplasia

**I. AIE Type 1, Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) Syndrome**

A. Pathogenesis
   1. IPEX syndrome is a rare X-linked disorder
   2. Result of specific mutation in the FOXP3 gene, which results in compromised suppressor function of regulatory T-cells

B. Clinical Presentation — early onset of the following:
   1. Diabetes mellitus due to islet cell destruction, which is usually present before the intestinal manifestations and requires insulin supplementation
   2. Severe secretory diarrhea with stool volume of 75–150 mL/kg/day, potentially bloody/mucoid stools, possible hypoalbuminemia and electrolyte disturbances requiring bowel rest and TPN
   3. Eczema-like dermatitis

C. Other Clinical Features
   1. Thyroiditis (usually hypothyroidism)
   2. Hematologic abnormalities (Coombs positive anemia, neutropenia, and thrombocytopenia)
   3. Chronic hepatitis in some cases

D. Evaluation
   1. Endoscopic Findings
      a. EGD varies from normal-looking mucosa to some mild granularity and erythema
      b. Colonoscopy will show diffuse erythema and loss of vascularity throughout the colon

2. Histology
   a. Villous atrophy
   b. Massive mononuclear (T cell) infiltration of the lamina propria (as opposed to celiac disease, which has intraepithelial lymphocytic infiltrate)

3. Blood Work
   a. No pathognomonic laboratory abnormalities for AIE
   b. Normal lymphocyte count
   c. Normal immunoglobulin levels, except for IgE levels, which are usually markedly elevated
   d. Periodic peripheral eosinophilia can be noted
   e. Antitenterocytes/anticolonocyte antibodies are highly sensitive for AIE
   f. Anti-75-AIE (antibody against gut and kidney antigen 75 kDa) is a highly specific antibody that is usually detected in patients with IPEX and AIE
   g. Abnormal T-cell activation studies

4. Genotyping of suspected mutations based on clinical presentation
II. AIE Type 2, IPEX-like Without FOXP3 Mutation
   A. Pathogenesis
      1. Regulatory T-cell dysfunction
   B. Clinical Presentation
      Affects girls and boys
      1. Multiple autoimmune symptoms and IPEX-like disease (see above)
      2. No FOXP3 mutation

III. AIE Type 3
   A. Patients present with secretory diarrhea
   B. Antienterocytes/anticolonocytes and anti-75-AIE antibodies positive
   C. No extraintestinal manifestations

IV. AIE Type 4, Autoimmune Polyendocrinopathy–Candidiasis-Ectodermal Dysplasia (APECED) Syndrome (Newer terminology = Autoimmune Polyglandular Syndrome-1 [APS-1])
   1. Polyendocrinopathy
   2. Mucocutaneous candidiasis
   3. Ectodermal dysplasia
   4. Associated with AIRE gene (autoimmune regulator) on 21q22.3
   5. More frequent in Finns, Iranian Jews, and Sardinians
   6. Usually present with milder clinical course, because the immune target is the enteroendocrine cells rather than the absorptive cells
   A. Differential Diagnosis
      1. Immune deficiencies (low immune globulins or lymphocytes)
      2. Wiskott-Aldrich syndrome (low CD8)
      3. APECED syndrome (AIRE gene mutation)
      4. Omenn syndrome (low B-cell count, mutation in RAG1 or RAG2 genes)
      5. Celiac disease (intraepithelial lymphocyte infiltration)
   B. Treatment and Outcome
      1. AIE has high mortality rates
      2. Bowel rest and TPN are needed to compensate fluid and protein loss, and manage electrolytes disturbances
      3. Chronic immune suppression using combination of steroid, tacrolimus, and azathioprine
      4. Bone marrow transplant (BMT)

Recommended Reading


Small bowel obstruction can be due to either mechanical or functional etiologies. The functional causes are either myopathic, neuropathic, or secondary to other underlying disease. Identification and treatment prior to bowel injury is critical.

I. Mechanical: Intrinsic or Extrinsic (See Table 1)

Table 1. Causes of Mechanical Small Bowel Obstruction in Infants and Children

<table>
<thead>
<tr>
<th>Anatomic Location</th>
<th>Intrinsic</th>
<th>Extrinsic (intraluminal or extraintestinal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenum</td>
<td>Duodenal atresia/stenosis</td>
<td>Ladd’s bands/midgut malrotation</td>
</tr>
<tr>
<td></td>
<td>Duodenal web</td>
<td>Annular pancreas</td>
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<tr>
<td></td>
<td>Duodenal hematoma</td>
<td>Preduodenal portal vein</td>
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<tr>
<td></td>
<td>Intestinal duplication cyst</td>
<td>Adhesions</td>
</tr>
<tr>
<td></td>
<td>Pyloric stenosis</td>
<td>Neoplasm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SMA syndrome (Cast or Wilkie’s syndrome)</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>Intestinal atresia/stenosis</td>
<td>Malrotation/midgut volvulus</td>
</tr>
<tr>
<td></td>
<td>Crohn’s disease</td>
<td>Meconium ileus/meconium plug syndrome</td>
</tr>
<tr>
<td></td>
<td>NEC</td>
<td>Meckel diverticulum</td>
</tr>
<tr>
<td></td>
<td>Neoplasm</td>
<td>Neoplasms</td>
</tr>
<tr>
<td></td>
<td>Intestinal duplication cyst</td>
<td>Adhesions</td>
</tr>
<tr>
<td></td>
<td>Intussusception</td>
<td>Hernias (ex: inguinal)</td>
</tr>
<tr>
<td></td>
<td>Ascariasis</td>
<td>Distal intestinal obstruction syndrome</td>
</tr>
</tbody>
</table>

II. Functional

A. Visceral Myopathies

1. Primary (disorders of the intestinal smooth muscle)
   a. Familial (primary) visceral myopathies (4 types)
   b. Sporadic infantile or childhood visceral myopathy
   c. African degenerative leiomyopathy
   d. Megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS)
   e. Mitochondrial neurogastrointestinal encephalopathy disease (MNGIE)

2. Secondary (systemic diagnosis involving the intestinal smooth muscle)
   a. Connective tissue diseases: dermatomyositis/polymyositis, SLE, mixed connective tissue diseases, Ehlers-Danlos type IV, scleroderma
   b. Myopathies: myotonic muscular dystrophy, Duchenne’s dystrophy, desmin myopathy, mitochondrial myopathy
   c. Infiltrative and inflammatory disorders: amyloidosis, ceroidosis (Brown bowel syndrome), leiomyositis

B. Visceral Neuropathies

1. Primary (disorders of the enteric nervous system)
   a. Familial visceral neuropathies
   b. Sporadic visceral neuropathies (hyper or hypoganglionosis)
   c. Ganglioneuromatosis with MEN type IIB
d. Sporadic and familial aganglionosis  
e. Disorders of the intestinal cells of Cajal (reduced density, delayed maturation)  
f. Unclassified enteric neuropathies

2. Secondary (systemic diagnosis affecting the enteric nervous system)  
a. Central or peripheral neural disease: Riley-Day syndrome, diabetic polyneuropathy, mitochondrial neurogastrointestinal encephalopathy  
b. Infectious/postinfectious: Chagas, postviral (CMV, VZV, HSV-1, EBV, Rota, HIV), Lyme disease, Kawasaki disease, Guillain-Barré syndrome  
c. Toxic agents: fetal alcohol syndrome, jellyfish envenomation, drugs (prokinetics, opioids, macrolides, calcium channel blockers, vinblastine, anticonvulsives)  
d. Radiation  
e. Autoimmune: celiac, eosinophilic gastroenteritis  
f. Endocrine/metabolic: electrolyte imbalance, uremia, thyroid disease, porphyria, carnitine deficiency, vitamin E deficiency  
g. Tumor-associated: chemotherapy, neural crest tumors, paraneoplastic syndrome, thymoma  
h. Miscellaneous: Ogilvie’s syndrome (acute chronic pseudoobstruction), Crohn’s, angioedema, anorexia nervosa/bulimia

III. Pathophysiology:

A. Manifestations and Diagnosis  
1. The age of the patient, time of presentation, and signs/symptoms are the major keys for diagnosis.  
a. Examples:  
   1) The most common causes (33%) of obstruction in the newborn period are atresia and stenosis  
   2) Gastroschisis is associated with intestinal atresia  
   3) Pyloric stenosis presents in the first two months of life
2. Adhesive obstructions are most common one to two years following surgery, and the most commonly implicated procedures are for gastroschisis and malrotation in the newborn period and appendicitis and IBD in children. Up to 45% of polyhydramnios etiologies are due to fetal malformations and genetic disorders
   a. The most common structural defects associated with polyhydramnios are those that interfere with fetal swallowing and/or absorption of fluid, such as gastrointestinal obstruction due to esophageal or intestinal atresia
   b. Congenital small intestinal abnormalities associated with polyhydramnios are:
      1) Duodenal atresia
      2) Jejunal atresia
      3) Ileal atresia (the most commonly affected site)

3. Imaging modalities used to diagnose intestinal obstruction are:
   a. Abdominal radiography:
      1) Diagnostic in 45%–60% of the time
      2) Remains the cornerstone as the initial radiographic assessment
   b. Abdominal CT scan:
      1) Accuracy is excellent
      2) Helps identifying the underlying cause of the obstruction in most cases
      3) The use of IV and PO contrast is recommended
   c. Ultrasound: Preferred if you are suspecting intussusception or pyloric stenosis
   d. Upper GI and SB contrast series: preferred in suspected cases of malrotation or SMA

4. Manometric studies help in identifying and differentiating between myopathic and neuropathic forms of functional obstructions

Table 2. Summary of Manifestations and Modalities of Diagnosis of SB Obstruction

<table>
<thead>
<tr>
<th>Signs &amp; Symptoms</th>
<th>Partial or Complete Obstruction</th>
<th>Strangulation Obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal polyhydramnios</td>
<td></td>
<td>Constant abdominal pain</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td></td>
<td>Hematochezia (15% of patients with volvulus)</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>Peritoneal signs</td>
</tr>
<tr>
<td>Failure to pass meconium within the first 24–48 hours</td>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td>Currant jelly stools (intussusception)</td>
<td></td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Colicky abdominal pain</td>
<td></td>
<td>Leukocytosis</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td></td>
<td>Acidosis</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstipation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperactive bowel sounds</td>
<td></td>
<td>Absent bowel sounds</td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td></td>
<td>Painful mass</td>
</tr>
<tr>
<td>Abdominal mass (intussusception and volvulus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distended loops of bowel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Air fluid levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paucity of colonic air (presence of colonic gas suggests partial obstruction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finding fluid luminal contents and/or fluid-filled loops of bowel proximal to the obstruction</td>
<td></td>
<td>Bowel wall thickening</td>
</tr>
<tr>
<td>Presence of localized transition zone</td>
<td></td>
<td>Target sign</td>
</tr>
<tr>
<td>Presence of collapsed loops of small bowel or colon distal to the obstruction</td>
<td></td>
<td>Serrated beak sign</td>
</tr>
<tr>
<td>Pneumatosis intestinalis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portal venous gas</td>
<td></td>
<td></td>
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<tr>
<td>Mesenteric haziness</td>
<td></td>
<td></td>
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<tr>
<td>No enhancement with IV contrast</td>
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</tr>
</tbody>
</table>

*Bowel distension is more prominent with distal (ileal) obstruction.

**Emesis is usually bilious and more prominent with proximal (jejunal) obstruction.

*Patient with intestinal obstruction may pass stool early on due to the peristalsis below the level of obstruction, but continued passage of gas or stool >6–12 hours after the onset of symptoms suggests partial obstruction.
IV. Management

A. Bowel decompression (inserting large-bore NG tube)
B. Fluid resuscitation (NS or Ringer's lactate)
C. Use of antibiotics is not well supported by data
D. Close observation and monitoring of fluid status and electrolytes
E. Trial of conservative management in partial obstruction
F. Early surgical intervention in complete obstruction or malrotation (to prevent volvulus and ischemia)
G. Prokinetic agents (e.g., erythromycin and cisapride) may be useful for acute and chronic therapy of intestinal pseudoobstruction

Recommended Reading


Small bowel injury can result from both blunt and penetrating trauma to the abdomen. The GI tract is damaged in 5%–20% of blunt abdominal trauma injuries, and in 70% of penetrating abdominal injuries.

I. Blunt Trauma
   A. Occurs most frequently from motor vehicle collisions, assaults, recreational accidents, or falls
   B. This is the most common mechanism of injury to the small bowel
   C. 5%–20% of patients with blunt abdominal trauma will have intestinal and mesenteric injury
   D. Blunt injuries often occur near points of fixation, such as the ligament of Treitz or ileocecal valve
   E. Intestinal rupture often occurs along the antimesenteric border
   F. The postulated mechanisms involved in blunt intestinal injury include the following:
      1. Crush injury—acts by compressing fluid-filled bowel between vertebral bodies and the blunt object (e.g., duodenal compression between the spine and steering wheel). The spectrum of injuries ranges from stretching of the bowel wall to full-thickness perforation
      2. Deceleration injury—causes stretching, shearing, and tearing of bowel loops at points of fixation, such as the ligament of Treitz, the ileocecal valve, and the phrenocolic ligament. Spectrum of injury ranges from tearing the bowel wall, to shearing the mesentery, to loss of vascular supply
      3. Closed-loop rupture—caused by a sudden increase in intraabdominal pressure

II. Penetrating Trauma
   A. Occurs more frequently in urban areas and typically is secondary to knife or gunshot wounds
   B. These types of injuries include abrasion of the serosa, full-thickness penetration of the bowel wall, and mesenteric or other vascular injury

III. Clinical Presentation
   A. Abdominal pain
   B. Edema and ecchymosis of the abdominal wall
   C. Skin laceration and penetration
   D. Decrease or absence of bowel sounds
   E. Guarding
   F. Direct and rebound tenderness
   G. Gastrointestinal hemorrhage
   H. Shock (hypotension, narrow pulse pressure, and tachycardia)

IV. Small Intestinal Injury
   A. The small bowel is the most frequently injured organ after penetrating injuries
   B. Hollow viscous injuries are often characterized by a delay in diagnosis after blunt abdominal trauma
   C. Delay in the diagnosis and management of blunt hollow viscous injury is associated with increased morbidity and mortality, as shown by recent studies
   D. Occasionally, a large tear in the mesentery occurs without bowel involvement. In these instances, bowel necrosis and subsequent perforation occur hours or even days after the initial injury, and the patients may have frank peritoneal signs, acidosis, and sepsis
V. Postoperative Complications After Resection of the Small Bowel

A. Intraabdominal abscess
B. Sepsis
C. Anastomotic leakage
D. Wound infection
E. Enteric fistulas
F. Intestinal obstruction
G. Short bowel syndrome

VI. Duodenal Injury

A. Duodenal injuries have different characteristics than the rest of small bowel injuries
B. The majority of duodenal injuries are caused by penetrating trauma
C. A motor vehicle accident causing impact of the steering wheel on the epigastrium is the most common mechanism of blunt duodenal injuries
D. Isolated injury to the duodenum is rare and does not usually cause significant clinical signs of peritonitis or hemodynamic instability
E. Most duodenal injuries are accompanied by other intraabdominal injuries because of the close anatomic relationship of the duodenum with other solid organs and major vessels
F. Hyperamylasemia occurs in about 50% of patients with blunt injury to the duodenum
G. Definitive diagnosis requires an upper gastrointestinal series (gastrografin) or a CT scan of the abdomen with oral and IV contrast in hemodynamically stable patients
   1. The radiographic finding of a duodenal hematoma (coiled spring or stacked coin sign) is not an indication for surgical exploration
   2. The presence of retroperitoneal hematomas around the duodenum should raise suspicion of an associated pancreatic injury
   3. Duodenal hematomas are expected to resolve in 10–15 days, and management consists of nasogastric suction until peristalsis resumes and after the slow introduction of solid food
H. Exploration is indicated in the event of persistent duodenal obstruction
I. Complications
   1. Duodenal Fistula: (5%–15% of patients)
      a. Duodenal fistulas are generally managed nonoperatively with nasogastric suction, IV nutritional support, and aggressive stoma care. Usually, closure will occur within 6–8 weeks
   2. Abscesses: (10%–20% of patients)
      a. Abscesses are initially managed by percutaneous drainage
      b. Surgical drainage is indicated if multiple abscesses are present or when located between small bowel loops

VII. Diagnostic Tests

A. All currently available diagnostic modalities have advantages, disadvantages, and limitations
B. In modern trauma centers in the 21st century, better noninvasive technology favors the use of ultrasound and CT in the evaluation of trauma victims
C. The test of choice depends on the hemodynamic stability of the patient and the severity of associated injuries
D. A chest radiograph is a useful test to reveal:
   1. Pneumoperitoneum
   2. Abdominal contents in the chest (ruptured hemidiaphragm)
   3. Lower rib fractures
E. An abdominal radiograph is a useful test (in blunt trauma) to identify:
   1. Presence of free air (intraperitoneal air or trapped retroperitoneal air)
   2. Fractures of thoracolumbar vertebral bodies, lower ribs, and pelvis
      a. Transverse fracture of a vertebral body (i.e., Chance fracture) suggests a higher likelihood of significant blunt injury to the bowel
   3. Radiopaque foreign bodies (e.g., bullets, shrapnel)
Section 3 - Small Bowel

F. Abdominal Ultrasonography (see Table 1)
1. The objective of ultrasound evaluation is to search for free intraperitoneal fluid and hemoperitoneum
2. Also helpful in identifying dilated bowel loops secondary to ileus or obstruction
3. Sensitivity in adults for identifying bowel injury ranges from 85%–99%, with specificity 97%–100%
   a. No further workup needed after negative ultrasound in stable patient
   b. Variably low sensitivity in children suggests that it should not be used to exclude intraabdominal injury

G. Computed Tomography of Abdomen (see Tables 2, 3 and 4)
1. CT is the preferred and most frequently used method for evaluation of blunt abdominal trauma in the hemodynamically stable patient, as well as in selected instances of penetrating trauma to the posterior abdomen
2. Use of oral contrast in children with potential bowel perforation is controversial, because false-negative scans are common
3. Retroperitoneum is best evaluated by CT
4. Accuracy of CT in evaluation of bowel injury is 82%, with sensitivity of 64% and specificity of 97%
5. Usually, the presence of free abdominal fluid on CT without solid organ injury should raise suspicion for mesenteric, intestinal, or bladder injury, and exploratory laparotomy is often warranted
   a. Extravasation of contrast material is an absolute indication for laparotomy or, more recently, angiography and embolization

H. Diagnostic Peritoneal Lavage (DPL) (see Table 5)
1. DPL is a rapid and accurate test used to identify intraabdominal injuries after blunt trauma in a hypotensive or unresponsive patient without obvious indication for abdominal exploration
2. DPL is highly sensitive to the presence of intraperitoneal blood; however, its specificity is low
3. Overall, DPL is not a reliable test to identify small bowel injuries, particularly small injuries with minimal leakage
4. Disadvantages of DPL:
   a. Invasiveness
   b. Significant injuries, including diaphragmatic tears and retroperitoneal hematomas, duodenal, minor intestinal, renal, and pancreatic injuries may be under diagnosed by DPL alone
   c. Low accuracy in the diagnosis of hollow viscous injuries
   d. DPL results can be misleading in the presence of a pelvic fracture
   e. Low to moderate specificity, and because positive DPL findings prompt surgical exploration (therapeutic laparotomy), a significant number of explorations will be nontherapeutic

I. Focused Assessment Sonography for Trauma (FAST)
1. Noninvasive, and takes less time than DPL
2. High sensitivity (up to 100%) for detecting intraperitoneal fluid, which accumulates in dependent areas around the liver, spleen, and pouch of Douglas

J. Angiography
1. The only role of angiography in acute bowel trauma is to identify the site of visceral bleeding
2. It is also used to evaluate renal artery thrombosis, manage pelvic hemorrhage in patients with pelvic fractures, and bleeding from minor hepatic and splenic injuries

K. Laparoscopy (see Table 6)
1. The use of diagnostic laparoscopy in blunt trauma patients is very limited. It is an invasive and expensive method, and does not seem to be superior to other methods, with reported missed small bowel, splenic, and retroperitoneal injuries
   a. Laparoscopy is the best method for evaluating diaphragmatic injuries after thoracoabdominal penetrating injuries
Table 1. Advantages and Disadvantages of Ultrasound

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninvasive</td>
<td>Examiner dependent</td>
</tr>
<tr>
<td>Low cost</td>
<td>Obesity</td>
</tr>
<tr>
<td>Can be repeated</td>
<td>Gas interposition</td>
</tr>
<tr>
<td>Does not require radiation</td>
<td>Lower sensitivity for free fluid &lt;500 mL</td>
</tr>
<tr>
<td>Useful in the emergency department</td>
<td>False negatives: Retroperitoneal and hollow viscous injuries</td>
</tr>
<tr>
<td>Patients unstable hemodynamically to undergo CT scan</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Indications and Contraindications for Abdominal Computed Tomography

<table>
<thead>
<tr>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blunt trauma</td>
<td>Clear indication for exploratory laparotomy</td>
</tr>
<tr>
<td>Hemodynamic stability</td>
<td>Hemodynamic instability</td>
</tr>
<tr>
<td>Normal or unreliable physical examination</td>
<td>Agitation</td>
</tr>
<tr>
<td>Mechanisms causative of duodenal and pancreatic trauma</td>
<td>Allergy to contrast media</td>
</tr>
</tbody>
</table>

Table 3. Advantages and Disadvantages of Abdominal Computed Tomography

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninvasive</td>
<td>Expensive</td>
</tr>
<tr>
<td>Adequate assessment of the retroperitoneum</td>
<td>Time (need to transport the patient to the radiology department)</td>
</tr>
<tr>
<td>The most sensitive and specific study to identify and assess solid organ injuries (liver and spleen)</td>
<td>Specialized personnel and equipment required</td>
</tr>
<tr>
<td>Assessment of renal perfusion</td>
<td>Hardware</td>
</tr>
<tr>
<td>High specificity</td>
<td>Limited in evaluation of hollow viscous injuries</td>
</tr>
</tbody>
</table>

Table 4. Abdominal CT Findings in Abdominal Trauma

<table>
<thead>
<tr>
<th>Type of Injury</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowel injury</td>
<td>Oral contrast extravasation indicating bowel wall disruption (the most specific finding). Free intraperitoneal/retroperitoneal air</td>
</tr>
<tr>
<td></td>
<td>Free intraperitoneal/retroperitoneal fluid</td>
</tr>
<tr>
<td></td>
<td>Intramural air</td>
</tr>
<tr>
<td></td>
<td>Focal areas of bowel wall thickening</td>
</tr>
<tr>
<td></td>
<td>Abnormal bowel wall enhancement</td>
</tr>
<tr>
<td></td>
<td>Bowel wall hematoma (i.e., duodenal hematoma)</td>
</tr>
<tr>
<td>Mesenteric vascular injury</td>
<td>Diffuse bowel wall thickening</td>
</tr>
<tr>
<td></td>
<td>Diffuse bowel wall enhancement</td>
</tr>
<tr>
<td></td>
<td>Mesenteric infiltration</td>
</tr>
<tr>
<td></td>
<td>Mesenteric hematoma</td>
</tr>
</tbody>
</table>
Table 5. Indications and Contraindications for DPL

<table>
<thead>
<tr>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Equivocal physical examination</td>
<td>Clear indication for exploratory laparotomy</td>
</tr>
</tbody>
</table>
| • Unexplained shock or hypotension | Previous exploratory laparotomy
| • Altered sensorium and obtunded or intoxicated patients (closed head injury, drugs, etc.) | Pregnancy
| • Patients with potential intraabdominal injury who will undergo general anesthesia for extraabdominal procedures | Obesity
| • Spinal cord injury | |

*Relative contraindications

Table 6. Indications for Laparotomy: Abdominal Injury

<table>
<thead>
<tr>
<th>Blunt Injuries</th>
<th>Penetrating Injuries</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Continued hemodynamic instability despite resuscitation</td>
<td>• Most gunshot wounds</td>
</tr>
<tr>
<td>• Signs of continuing hemorrhage</td>
<td>• Selective operation for stab wounds with:</td>
</tr>
<tr>
<td>• Need for blood replacement</td>
<td>o Hypotension</td>
</tr>
<tr>
<td>• Pneumoperitoneum or hemoperitoneum</td>
<td>o Unexplained blood loss</td>
</tr>
<tr>
<td>• Physical signs of peritoneal irritation</td>
<td>o Evisceration</td>
</tr>
<tr>
<td>• Signs of significant injury to the intestine, pancreas, bladder, ureter, renal vasculature, or rectum</td>
<td>o Physical signs of peritoneal irritation</td>
</tr>
<tr>
<td></td>
<td>o Signs of significant amounts of blood or intestinal contents on peritoneal lavage or CT</td>
</tr>
</tbody>
</table>

Recommended Reading


Radwan MM, Abu-Zidan FM. Focused Assessment Sonograph Trauma (FAST) and CT scan in blunt abdominal trauma: surgeon’s perspective. Afr Health Sci. 2006;6(3):187-190.


3P. Short Bowel Syndrome: Intestinal Failure

Molly Dienhart, MD

I. Definition: Anatomical as well as functional
   A. Short bowel syndrome is the most common cause of intestinal failure
      1. Loss of intestinal length or competence below the minimal amount necessary to maintain normal digestion and absorption of nutrients and fluids required for maintenance in adults or for growth in children
   B. More simply, it has also been defined as the need for parenteral nutrition

II. Etiologies
   A. Congenital malformations—gastroschisis, malrotation with volvulus, atresias, omphalocele, or aganglionosis
   B. Necrotizing enterocolitis
   C. In older children: malrotation, trauma, and intraabdominal neoplasia

III. Goal of Therapy
   The goal of therapy is to achieve intestinal adaptation, weight gain, and linear growth, with maximal enteral nutrition and minimal parenteral support

IV. Bowel Adaptation
   A. Process by which the function of the remaining bowel gradually improves
   B. Begins within 1–2 days after surgery
      1. Continues for up to 2–5 years
   C. Involves the development of increased surface area through a combination of hyperplasia, dilatation, and elongation
      1. Hyperplasia involves increased crypt cell production, crypt depth, and lengthening of villi, as well as increased number of transporters per cell, with a subsequent increase in enzyme activity
      2. This leads to increased absorption of nutrients and electrolytes per unit of bowel length

V. Enteral Feeds
   A. The most potent stimulus for intestinal adaptation, as they provide fuel for enterocytes
      1. In the absence of enteral feeds, mucosal hypoplasia will occur
   B. More complex nutrients (i.e., intact proteins and long-chain triglycerides vs free amino acids and MCTs) are more effective at stimulating cellular hyperplasia
   C. Enteral tolerance continues to improve for up to 2–5 years following resection
   D. Stimulate the normal physiologic flow of intestinal secretions as well as peristalsis, which may help decrease the risk of small bowel bacterial overgrowth

VI. Anatomic Considerations
   A. The impact of short bowel syndrome is related not only to the length, but also the location of the lost bowel
      1. Secretion and absorption of fluids are in complicated balance in the normal human GI tract, and the loss of a section of bowel will disrupt this balance and likewise the absorption of nutrients
   B. Proximal Loss
      1. Loss of the most proximal portion of the small intestine is actually generally well tolerated
      2. Depending on the exact location of loss, there is potential for increased acidity of secretions due to decreased bicarbonate secretion
      3. Biliary and pancreatic secretions may be impaired, and the absorption of iron may need to be considered
C. Distal Loss
   1. The distal small bowel has a larger effect on nutrient absorption, with the distal ileum having more of an impact than the proximal jejunum
      a. Distal ileum is more specialized and can have greater consequences
      b. Sole segment for active reabsorption of bile salts
         1) Compensatory increase in bile acid production is commonly inadequate
         2) Decrease in bile salt concentration leads to fat malabsorption and fat-soluble vitamin deficiency
      c. Subsequent increase in colonic fluid loss:
         1) LCFA and BA in the colon act as a stimulus for colonic water secretion
         2) Digestion of LCFA by colonic bacteria stimulates further colonic electrolyte loss
      d. Loss of the ileal brake—decreases exposure time of the luminal contents to the mucosal surface and further impairs absorption
      e. Absorption of vitamin $B_{12}$ will also be impaired
   2. Colon
      a. The colon serves to reabsorb water (10%–15% of total water absorption) and electrolytes, as well as short-chain fatty acids, which are salvaged from starches and soluble fibers that pass into the colon
      b. In the absence of the colon, one has increased loss of intestinal fluid, which can in some cases result in ongoing need for additional fluid supplementation
      c. The salvage function of the colon is amplified in importance in the setting of a significant loss of small bowel

VII. Function
   A. A major factor which contributes to one’s ability to adapt and tolerate enteral nutrition
   B. Initial insult can affect function
      1. e.g., gastroschisis
      2. Early prenatal insults resulting in obstruction, leading to longstanding dilatation of the more proximal bowel
      3. Prolonged decreased perfusion

VIII. Time of Injury
   A. The intestine doubles in length during the 3rd trimester of gestation, and continues to grow in early childhood
      1. Subsequently, an infant, and potentially a premature infant, has a greater capacity for growth following injury than would an older child or adult
   B. The greatest capacity for normal intestinal growth is in the first 3–4 years of life, making this the most opportunistic window for adaptation to occur
   C. Furthermore, the ability of portions of the GI tract to adapt and take on additional functions of the lost portions of bowel is increased in younger patients

IX. Length of Residual Bowel
   A. Residual bowel length has been shown to be a predictor of mortality and also of independence from parenteral nutrition
   B. Greater than 10% of predicted small bowel length
      1. Decreased mortality
      2. Increased probability of weaning from parenteral nutrition support
   C. The expected small bowel length is again determined by age:
      1. 19–27 weeks of gestation ~115 cm
      2. 27–35 weeks ~172 cm
      3. >35 weeks ~240 cm
      4. Final length averaging between 400 and 700 cm
   D. This is also strongly influenced by the presence or absence of the colon, as well as by the presence of the ileocecal valve
      1. It has been shown in studies with adults and older children that the tolerable length of small bowel decreases as the colon length increases
X. Management

A. Early in the postoperative period, focus is on fluid and electrolyte management to account for intestinal losses
   1. High enterostomy: losses may be significant even in the absence of enteral feedings, given the high secretory function of the proximal GI tract. Can be exacerbated by gastric hypersecretion (up to 30–50 mL/kg/day)

B. Loss of the normal hormonal feedback loop occurs with loss of bowel
   1. This results in hypergastrinemia, which in turn leads to gastric acid hypersecretion
      a. The low duodenal pH results in decreased pancreatic enzyme activity and precipitation of bile acids, which impairs micelle formation and fat absorption and can damage the proximal small bowel
         1) Excess fluid secretion contributes to a secretory diarrhea
         2) Generally resolves after 6–12 months, but can last longer
         3) The use of acid-blocking medications can help to moderate this effect
      b. Proximal intestinal losses have a high concentration of sodium and chloride, which need to be adequately replaced to prevent electrolyte imbalances
      c. The longer the small bowel, the more potential for continued reabsorption of fluid and electrolytes
         1) Patients with shortened small bowel that is in continuity with part or all of the colon are at much lower risk of such high fluid losses, as there is potential for reabsorption of fluid and electrolytes in the colon
         2) Relatively more potassium and bicarbonate and less sodium and chloride are needed in patients with some colon

XI. Enteral Feeding

A. Initiation of enteral feedings can begin once bowel function has started, following the initial surgical intervention

B. Consideration must be given to carbohydrate, protein, and fat choice

C. More complex substances have the potential to be a better stimulus for the developing enterocytes; however, in patients who have sustained mucosal damage, these complex substances may be harder to digest and absorb
   1. Elemental formulas are less likely to cause increased hypersensitivity
   2. Long-chain triglycerides are a potent stimulus if cholestasis exists; may be harder to absorb

D. Generally, enteral feeds are initially delivered to the stomach via continuous drip
   1. Decrease the risk of increased gastric emptying and subsequent rapid transit of nutrients through the already shortened GI tract
      a. In patients with poor gastric emptying, or those at high risk of reflux/aspiration or proximal duodenal motility problems, jejunal feedings can be beneficial
   2. Allows for the constant saturation of nutrient receptors to aid in adaptation

E. Enteral nutrition choice is also influenced by the amount and location of the GI tract that remains intact
   1. If there is a substantial portion of small intestine intact, either as an end ileostomy or with a short rectosigmoid segment, there are little lipid restrictions and LCT can be used
      a. Soluble fibers will help increase the viscosity and slow gastric emptying
      b. These patients can also be maintained on high-dose antimotility or antisecretory agents, but will typically need significant fluid and sodium provision/replacement
   2. Patients who have short segment small bowel and all or most of the colon intact will often benefit from a combination of MCT and LCT
      a. Soluble fibers not only increase viscosity and slow gastric emptying, but also are a source of short-chain fatty acid calorie salvage in the colon
      b. These patients are more likely to require increased potassium and bicarbonate provision
   3. MCT are less likely to stimulate colonic salt and water secretion than malabsorbed LCTs
   4. Because production of SCFAs occurs in the colon, patients with a colon are more likely to benefit from the addition of complex carbohydrates and soluble fibers (cereals, unsweetened fruits, and lean meats)
F. Advancement of feeds should result in weight gain and growth of the patient. As growth is achieved, parenteral support is weaned
   1. Degree of parenteral weaning will be a lesser caloric quantity than the concomitant enteral increase to account for malabsorption
      a. Absorption can range from 30%–70% of what is ingested, and this needs to be accounted for in calculation of needs
      b. Will depend on how much and what bowel exists
   2. Reducing parenteral nutrition is based on estimates of enteral absorption as evidenced by weight gain, hydration status, stool output, physical exam (skin), and laboratory studies, including albumin
   3. In addition to caloric supplementation, one must consider electrolytes, vitamins, and trace elements
      a. With colon: potassium and bicarbonate supplementation
      b. Without colon: zinc, magnesium, and sodium
      c. Lack of terminal ileum: fat-soluble vitamins and B₁₂

XII. Pharmacologic Therapy
A. Acid blockade: decrease the water and sodium losses related to secretory diarrhea associated with gastric hypersecretion
   1. Acid duodenal pH can also interfere with pancreatic enzyme activity and micelle formation
B. Imodium: peripheral opioid analogue that inhibits small bowel and colonic motility, and thereby improves fluid absorption and decreases fluid loss through stool
C. Bile acid–binding resins: can be used in patients who have had a limited ileal resection
   1. Modulates increased BA colonic load in those who have a colon, to reduce secretory diarrhea
D. Motility agents: to enhance gastric or small bowel motility
   1. Erythromycin (primarily acts in antrum of the stomach)
   2. Amoxicillin-clavulanate (action in small bowel)
   3. Antibiotics for bacterial overgrowth:
      a. Metronidazole, trimethoprim-sulfamethoxazole, amoxicillin-clavulanate, ciprofloxacin
E. GLP-2: A new potential therapy for patients with short bowel syndrome, as it has been shown to improve energy absorption and lean body mass
   1. Studies with this therapy are ongoing
F. Zinc: Losses can be significant, 12 mg/dL in ostomy, 17 mg/dL in diarrhea
   1. Vicious cycle in that zinc depletion leads to diarrhea and also to impaired wound healing

XIII. Surgical Therapy
A. Indications for pursuing surgical options include:
   1. Recurrent bacteremia, dilated bowel, or SBBO that is not responding to therapy
   2. Options: longitudinal tapering procedures, longitudinal lengthening procedures, and ostomy takedowns to re-establish intestinal continuity
   3. Bowel transplant is an option in some centers
B. The goals of surgery include continuity, improvement in motility, prolongation of transit time, and enhancement of the mucosal surface area
   1. Tapering procedures can help, but have the increased risk of losing more potential surface area, and often need to be repeated
   2. Lengthening procedures not only decrease the caliber of the bowel, hopefully allowing for better motility and decreased risk of bacterial overgrowth, but also have the benefit of increasing the surface area available for absorption of nutrients
C. Preexisting liver disease increases mortality, and is now a contraindication

XIV. Other Considerations
A. Tube feeds: oral feeding skills, timing of feeds (day feeds—development; night feeds—increased night stoolsing)
B. PN: cycling as tolerated
   1. Some protected effect toward the liver
   2. Allows for some time that child is not connected to an infusion
XV. **Complications of SBS and Parenteral Nutrition**

A. **Cholestatic liver disease**
   1. Multifactorial, and its development has been associated with: shorter remaining bowel, longer need for PN, lack of enteral feedings, recurrent catheter associated infections, or sepsis and prematurity

B. **Calcium bilirubinate stones, leading to chronic cholecystitis**
   1. Risk factors: duration of PN, lack of enteral feeds and the potential decrease in enterohepatic circulation of bile acids secondary to intestinal loss

C. **Catheter-related complications are an important concern, including:**
   1. Infection, thrombus formation, and occlusion
   2. Sepsis is the leading cause of death in patients with intestinal failure
   3. Loss of central venous access secondary to thrombotic occlusion of all vessels can only be treated with intestinal transplant to end the need for PN

D. **Small bowel bacterial overgrowth**

E. **Enterocolitis**

F. **Pancreatitis and renal disease**

G. **Bowel obstruction:** anatomical (secondary to stricture or adhesions) or functional (related to motility or dysmotility through dilated sections of bowel)
   1. Challenges to advancement of enteral feeds, and therefore prolongation of PN
   2. Medical therapy is used to treat bacterial overgrowth and improve motility
   3. If progression of feeding continues to be impeded, surgical options must be considered

XVI. **Outcomes**

A. Overall survival for patients with SBS is ~85%

B. 70%–80% survive without the need for long-term PN

C. For those on long-term PN, survival rate is ~50%

D. Extreme short bowel, progressive liver disease, and recurrent bacteremia increase the mortality of these patients, and also exacerbate each other:
   1. Those with recurrent infections are at increased risk of severe liver disease
   2. Those with severe liver disease are more likely to succumb to sepsis
   3. Intestinal transplantation is sometimes the only option for some of these patients
      a. With low likelihood of achieving end of PN support and high subsequent risk of developing liver disease, combined intestinal and liver transplantation is sometimes indicated
   4. Progression to Stage 3 or 4 fibrosis is not generally considered to be reversible
      a. Isolated liver transplantation for patients who have been able to tolerate at least half of their estimated needs enterally but have not seen an improvement in liver disease
   5. Presumption that transplantation results in improvement of liver disease and subsequent increased tolerance of enteral feeds

**Recommended Reading**


I. Overview/Epidemiology
A. Small Bowel Bacterial Overgrowth (SBBO)
B. Definition: abnormally high bacterial counts in proximal small bowel (>10^5 colony-forming units of bacteria per mL of luminal aspirate)
C. Increased number of bacteria in the small intestine leads to nutrient malabsorption
D. Most common disorders associated with SBBO: short bowel syndrome, intestinal dysmotility syndromes, and chronic pancreatitis
E. SBBO also associated with inflammatory bowel disease, intestinal fistula, bowel surgery of any kind, immunodeficiencies, liver disease, cystic fibrosis, and hypochloridia associated with proton pump inhibitor use
   1. Possible association with irritable bowel syndrome and children with chronic abdominal pain.

II. Pathogenesis
A. Distribution and concentration of bacterial flora in the GI tract of a healthy child:
   1. Stomach and proximal small bowel: few bacteria, <10^4 CFU/mL of jejunal contents, primarily lactobacilli and Gram-positive aerobes (staphylococci and streptococci)
   2. Terminal ileum: transitional zone between aerobic flora in stomach and small bowel, and anaerobes in colon, 10^8–10^10 CFU/mL, primarily Bacteroides, Bifidobacterium, Clostridium, and Cloforms
   3. Colon: Mainly anaerobes, 10^11–10^12 CFU/mL, primarily Bacteroides, Bifidobacterium, Clostridium and Enterococci
B. Physiologic mechanisms preventing SBBO: antegrade peristalsis, presence of gastric acid and bile, digestion by proteolytic enzymes in the small intestine, intestinal mucous layer, ileocecal valve, intact immunity
   1. SBBO develops when host defenses are compromised by related conditions
   2. In general, SBBO involves multiple organisms in varying numbers. Common species are streptococci, Bacteroides, E coli, and Lactobacillus
C. SBBO can lead to mucosal inflammation and villous atrophy
   1. Light microscopy of small intestinal biopsies can show villous atrophy, increased cellularity in lamina propria
D. Ulceration and erosions can occur
E. Gram-negative bacteria produce endotoxins, which activate inflammatory cytokines, which in turn can alter the function of hepatocyte transporters and cause jaundice and liver injury
F. Malabsorption
   1. Fat malabsorption as bacteria deconjugate bile acids
   2. Steatorrhea and deficiency of fat-soluble vitamins A, D, E, and K
   3. Carbohydrate malabsorption occurs as bacteria ferment carbohydrates
      a. Bacteria decrease enterocyte disaccharidase and brush border hydrolase activity
      b. Malabsorbed carbohydrate can be fermented by bacteria to excessive amounts of D-lactate
      c. D-lactate encephalopathy and D-lactic acidosis can occur
   4. Protein malabsorption can occur with decreased uptake of amino acids and bacterial degradation of protein precursors
      a. Bacteria degrade protein and urea into ammonia
      b. Elevated ammonia levels can lead to encephalopathy
   5. Anaerobic bacteria utilize vitamin B_{12}. SBBO can lead to B_{12} deficiency
III. Clinical Manifestations

A. Can be asymptomatic
B. Symptoms can include diarrhea, steatorrhea, hematochezia, abdominal pain, bloating, cramping, anemia, weight loss, feeding intolerance, dyspepsia, and flatulence
C. Severe cases can present with unexplained acidosis, tetany (secondary to vitamin D deficient hypocalcemia), night blindness (vitamin A deficiency), dermatitis, arthritis, and hepatic injury
D. Other clinical signs and symptoms can include neuropathy from cobalamin (B12) deficiency, macrocytic anemia (B12 deficiency), microcytic anemia (bleeding ulcers), metabolic bone disease, or episodic ataxia and delirium with carbohydrate ingestion secondary to D-lactic acidosis
E. Additional physical exam findings may include scarring from previous surgery, abdominal distention, and borborygm

IV. Diagnosis

A. Diagnosis often made based on presenting symptoms, as currently available diagnostic tests can be invasive and may be inaccurate
B. Laboratory evaluation:
   1. Macrocytic anemia (B12 deficiency)
   2. Fat soluble vitamin deficiency (A, D, and E). Vitamin K less often deficient, as bacteria produce Vitamin K
   3. Hypocalcemia (secondary to Vitamin D deficiency)
   4. Microcytic anemia (secondary to bleeding intestinal ulcers)
   5. D-lactic acidosis (secondary to D-lactate production by bacteria)
      a. D-lactate is normally undetectable, and acidosis should be considered at D-lactate concentrations in excess of 3 mmol/L
   6. Elevated liver enzymes or cholestasis
C. Diagnostic tests
   1. Aspiration and culture of duodeno-jejunal fluid:
      a. Current gold standard
      b. Bacterial counts >10^5 CFU/mL in the proximal small intestine are diagnostic
      c. Test is invasive, subject to contamination by oropharyngeal bacteria, and SBBO can be patchy and therefore missed by single aspiration. Also, it is difficult to grow anaerobic bacteria unless sample is collected under research conditions
   2. Breath hydrogen tests
      a. Breath hydrogen produced by bacterial fermentation and measured after ingestion of a carbohydrate substrate
      b. Sensitive and less invasive
      c. D-glucose is preferred substrate, as lactose and lactulose are poorly absorbed in children and less likely to give false positive from disaccharidase deficiency
      d. Test considered positive if: baseline exhaled fasting breath hydrogen is 20 parts per million or greater, or exhaled levels increase by more than 10 ppm over fasting level
      e. Early peak within one hour of test carbohydrate is diagnostic
      f. Decreased motility may lead to false negatives, and rapid gastric and intestinal emptying may lead to false positives
      g. Coadministration of intestinal transit markers in combination with scintigraphy increases specificity
V. Treatment/Management
   A. Empiric treatment with antibiotics often given to patients with clinical picture of small bowel bacterial overgrowth
      1. Lack of clinical trials in children, and no specific approved therapy
   B. Involves suppression of strict and facultative anaerobes, with goal to reduce, not eradicate, the flora
   C. Rifaximin, a nonabsorbable antibiotic is the current antibiotic of choice is generally given for a 7–10 day course
      1. Other antibiotic choices include metronidazole, neomycin, or amoxicillin/clavulanic acid
   D. Probiotics may be useful in prevention of SBBO, or immediately following antibiotics in recalcitrant SBBO
      1. Probiotics should be used with caution in patients with central lines, as there have been reports of bacteremia
      2. More research is needed to investigate the risks, benefits, and efficacy of probiotic therapy
   E. Treatment of underlying disorder, such as prokinetics in motility disorders and surgical bowel lengthening in short bowel syndrome

VI. Differential Diagnosis
   A. Celiac disease
   B. Lactose intolerance
   C. Functional abdominal pain
   D. Irritable bowel syndrome
   E. Constipation
   F. Malabsorption
   G. Intestinal pseudo-obstruction
   H. Giardiasis
   I. Intestinal motility disorders

Recommended Reading


I. **Intestinal Failure Definition**
   A. Inability to maintain protein, energy, fluid, electrolyte, and/or micronutrient balance due to GI disease when on a normal diet
   B. Intestinal failure produces malnutrition, and even death, if the patient does not receive parenteral nutrition or an intestinal transplant
   C. Leading cause of intestinal failure is short bowel syndrome caused by surgical resection

II. **Diseases in Which Small Bowel Transplantation is Performed**
   A. Short bowel syndrome
      1. Volvulus
      2. Gastrochisis/ruptured omphalocele
      3. Trauma
      4. Necrotizing enterocolitis
      5. Ischemia (mesenteric thrombosis)
      6. Crohn disease
      7. Intestinal atresia
   B. Malabsorption (mucosal defect)
      1. Microvillus inclusion disease
      2. Secretory diarrhea
      3. Autoimmune enteritis
   C. Motility disorder
      1. Pseudo-obstruction
      2. Total intestinal aganglionosis
      3. Hirschsprung’s disease (long-segment)
   D. Desmoid tumors of the intestine
   E. Multiple polyposis syndromes with malignant potential
   F. Extensive radiation enteritis

III. **Indications for Small Bowel Transplantation**
   A. Anatomic or functional diseases that preclude enteral feeding plus failure of parenteral nutrition due to:
      1. Lack of vascular access
      2. Life-threatening complications of parenteral nutrition
         a. Liver injury
         b. Recurrent infections
         c. Frequent severe dehydration despite supplementing IVN with extra fluid
   B. High risk of death
   C. Severe short bowel syndrome: residual small bowel <10 cm in infants or <20 cm in adults
   D. Intestinal failure with frequent hospitalizations, narcotic dependency, or pseudo-obstruction
   E. Patient unwillingness to accept long-term parenteral nutrition

IV. **Contraindications to Intestinal Transplantation**
   A. Contraindications to intestinal transplantation are similar to those for other types of transplants
      1. Active infection such as pneumonia, sepsis, or fungal infection in recipient
      2. Significant coexistent conditions in the recipient with no potential for improvement after transplantation
      3. Uncontrolled infection or malignancy in the recipient that is not eliminated by transplant
      4. Psychosocial factors
         a. Lack of capacity to assume management after transplant
         b. Absence of family support
V. Types of Small Bowel Transplantation
   A. Three basic transplant procedures
      1. Isolated intestinal transplant: transplantation of jejunileum alone
      2. Composite liver: bowel transplant
         a. Pancreas and duodenum included to facilitate en bloc engraftment and obviate biliary reconstruction
         b. Some centers report that combined liver-intestine transplantation has lower incidence and severity of acute rejection than isolated intestinal transplantation
      3. Multivisceral transplant: Composite visceral or multi-organ transplant
         When the small intestine (jejunileum) is transplanted alone, it is referred to as an isolated intestinal transplant (Panel A), with systemic drainage to the vena cava. A composite liver and intestinal transplant usually includes the duodenum and an intact biliary system and portal circulation, with the native foregut preserved (Panel B). In a multivisceral transplant, which involves the liver, stomach, duodenum, pancreas, and small intestine, the foregut is removed and a new stomach is transplanted (Panel C). This type of transplant sometimes includes the colon, kidney, or both. The transplanted organs are shown in light gray, and the native organs or structures are shown in darker gray.

![A B C](image)

Figure 1. Three types of transplants in intestinal failure

VI. Post-transplant Management
   A. Induction therapy with monoclonal (alemtuzumab, basiliximab, daclizumab) or polyclonal (anti-thymocyte globulin) antibody preparations often administered pre- or intraoperatively
   B. Tacrolimus via enteric route and intravenous steroids begun immediately after surgery and maintained at discharge
      1. High levels of immunosuppression early in the postoperative period (tacrolimus levels, 20–25 ng/mL)
      2. Mycophenolate mofetil avoided because of GI side effects
      3. Sirolimus used in combination with tacrolimus by some programs
   C. Broad-spectrum intravenous antibiotics administered for about 1 week after the transplant
   D. Regular monitoring for evidence of bleeding
   E. Monitor serum pH and lactate levels to detect intestinal ischemia
   F. With return of GI function indicated by decreasing G-tube returns and increasing gas and enteric contents in the ileostomy, feedings are advanced as tolerated
   G. No-fat or low-fat diet used to avoid chylous ascites, a consequence of loss of graft lymphatic drainage during procurement
   H. Antiviral prophylaxis with ganciclovir and/or cytomegalovirus (CMV) immunoglobulin (CytoGam)
   I. Monitor regularly for:
      1. CMV antigenemia
      2. Epstein-Barr virus by polymerase chain reaction
      3. Routine bacterial culture
4. Ileostomal endoscopy and biopsy of graft for diagnosis of infection or rejection

J. Monitor fluid status, stool losses, and serum electrolytes

VII. Complications

A. Surgical complications
   1. Graft thrombosis
   2. Graft ischemia
   3. Technical failure

B. Graft rejection can occur any time, but is most common in the first 6–12 months
   1. No reliable serum marker for intestinal rejection
   2. Diagnosis based on multiple parameters, the three most important of which are:
      a. Clinical course
         i. Increased stomal output (>40–60 cc/kg/day)
         ii. Bloody stoma output
         iii. Cyanotic or congested ileal stoma
         b. Endoscopic appearance of the allograft
         i. Diagnosis can be difficult because of patchy findings and presence of bleeding
         ii. Endoscopy should be as extensive as possible, with numerous biopsies
         iii. Inflammation and ulceration are typical, but graft may appear normal in early rejection
      c. Histology of biopsy specimens
         i. Mucosal necrosis and loss of villous architecture, with transmural cellular infiltrate
         ii. Crypt cell apoptosis, cryptitis or crypt loss, necrosis, and endotheliitis

3. Treatment
   a. Intravenous bolus of methylprednisolone (10 mg/kg), followed by steroid cycle and optimization of tacrolimus serum level
   b. Antithymocyte globulin or muromonab for steroid-resistant rejection

4. If the graft includes other organs, monitor serum markers for rejection of those organs
   a. Liver: transaminases, GGT
   b. Kidney: serum creatinine
   c. Pancreas: amylase and lipase

5. 50% of intestinal rejection episodes occur without rejection of other transplanted organs

C. Infection
   1. Bacteria from the intestinal graft infect via two routes
      a. The lymphatics divided in procurement may leak infected lymph into peritoneal cavity, causing peritonitis
      b. Direct bacterial translocation into portal circulation, with dissemination to other sites
      c. Most common organisms include Escherichia coli, Klebsiella, Enterobacter, staphylococci and Enterococcus
      d. Pneumocystis carinii prophylaxis required
   2. Viral
      a. CMV infection reported in 15%–30% of patients with intestinal grafts
         i. CMV can cause loss of transplanted organ and death
         ii. Incidence of CMV disease highest in CMV-negative recipient with CMV-positive graft
         iii. CMV enteritis usually presents with fever, increased stoma output, GI symptoms, decreased WBC count, and flu-like symptoms
         iv. CMV DNA by quantitative PCR
         v. Endoscopic findings: superficial ulcers and CMV inclusion bodies
6) Treat CMV infection
   i. Ganciclovir and CMV immunoglobulin (CytoGam)
   ii. Immunosuppression should be reduced until the CMV infection is controlled, but should not be discontinued, to avoid breakthrough rejection
b. Epstein-Barr virus (EBV)
   1) Highest risk in EBV-negative recipient with EBV-positive graft
   2) Acute EBV virus infection typically associated with severe malaise and fever, flu-like symptoms, increase of liver function tests, splenomegaly, and lymphadenopathy
c. Adenovirus
d. Rotavirus, norovirus, and enterovirus may produce severe malabsorption and inflammation in the transplanted intestine

3. Fungal

D. Post-transplantation Lymphoproliferative Disorder (PTLD)
   1. More common in intestinal transplant than other solid organ transplant
      a. Incidence higher after multivisceral transplantation than isolated intestinal transplantation
      b. Pediatric patients and EBV antibody-negative adult patients are at the highest risk
   2. Usually presents 2–6 months after transplant, but can appear at any time
   3. Begin surveillance for PTLD immediately after transplant using EBV polymerase chain reaction (PCR)
   4. Two approaches to prevent PTLD
      a. Prophylaxis with ganciclovir or intravenous immunoglobulin for 3–12 months
      b. Prophylaxis for 2–6 weeks, followed by surveillance and preemptive therapy, should surveillance identify increased EBV replication
   5. Initial treatment
      a. Reducing immunosuppression by about 50% relieves PTLD in about 1/3 of cases
      b. If improvement not evident after two weeks, discontinue all immunosuppression and consider possible additional therapeutics
         1) Chemotherapy
         2) Monoclonal antibody administration
         3) Adoptive immunotherapy
         4) Intestine-only graft can be removed

E. Graft vs host disease
   1. The small intestine is an immunocompetent organ; its population of lymphoid cells can mount an immunologic response to the host (see graft vs host disease)
F. Graft dysfunction/malabsorption
   1. Common symptom is diarrhea
      a. Carbohydrate and amino acid absorptive capacity of the transplanted intestine normalize within the first several months
      b. Fat absorption is impaired for several months following intestinal transplantation
   2. Eosinophilic gastroenteritis likely secondary to food allergies
   3. Vitamin B₁₂ deficiency occurs when reduced intestinal allografts are taken from adult donors for children, or when the abdomen will not close without distal intestinal resection

VIII. Outcomes
   A. The 1-year graft survival for recipients of intestinal and multi-organ transplants in North America increased from 52% in 1997 to 75% in 2005
   B. The 1-year rate of patient survival improved from 57% in 1997 to 80% in 2005
   C. Rates of patient survival at 3 and 5 years for transplantations performed between 1997 and 2000 have remained modest at 61% and 47%, respectively

Recommended Reading


I. Small Intestinal Polyps and Polyposis (See Polyp Chapter)

A. Polyp types: Common conditions in which polyps occur within the small intestine are summarized in Table 1.

1. Epithelial polyps: These are divided histologically into:
   a. Neoplastic polyps: malignant carcinoma and benign adenoma (abnormal epithelial growth with potential malignancy)
   b. Non-neoplastic polyps: hamartomatous polyposis syndromes, hyperplastic polyps, and inflammatory polyps

2. Non-epithelial polyps:
   a. Submucosal leiomyoma
   b. Lymphoid
   c. Paraganglioma
   d. Carcinoid tumor
   e. Submucosal lipoma
   f. Submucosal neurofibroma
   g. Submucosal schwannoma
   h. Ganglioneuroma

II. Small Intestinal Neoplasms

A. Small Intestinal Adenocarcinoma:
   1. Very rare in children
   2. Risk factors: familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome, and small bowel Crohn disease
   3. Symptoms: GI bleeding and small bowel obstruction
   4. Diagnosis:
      a. Contrast studies remain the primary investigative tool
      b. Capsule endoscopy may aid in the diagnosis
      c. Biopsy (via upper endoscopy with small-bowel enteroscopy, retrograde ileoscopy, or surgical enterotomy) and histopathological examination is the gold standard

B. Small Intestinal Lymphomas:
   1. The predominant malignant tumor of the small intestine in childhood
   2. The most common sites for primary extranodal non-Hodgkin’s lymphoma (NHL) in children are: distal ileum, cecum, and appendix
   3. Involvement of the GI tract with Hodgkin’s lymphoma is extremely rare
   4. Male-to-female ratio 2:1 in children
   5. Clinical features: abdominal pain, change in bowel habits, nausea and vomiting
   6. Diagnosis: biopsy for histopathology, immunophenotype, and cytogenetics
   7. Treatment: resection with associated mesentery and lymph nodes, and chemotherapy

C. Burkitt Lymphoma (BL)
   1. Represents the majority of pediatric intestinal lymphomas (up to 75% of all intestinal NHL)
   2. Very aggressive B-cell lymphoma with high proliferation rate
      a. Fatal within months if not treated
   3. Terminal ileum and ileocecal regions are the most common sites of origin
   4. Symptoms: abdominal pain due to intussusception and obstruction
   5. Diagnosis: imaging and endoscopic studies (submucosal or mural lesion)
   6. Endoscopic biopsies may only show nonspecific mucosal abnormalities
7. In endemic BL (equatorial Africa and Papua New Guinea), EBV genome is present in the majority of neoplastic cells.
8. Mandibular and CNS involvement are common in endemic BL.
9. Prognosis: timely diagnosis followed by aggressive chemotherapy (methotrexate and cytarabine) regimens cure ~90% of patients.

D. Immunoproliferative Small Intestinal Disease (IPSID)
1. Endemic in the underdeveloped regions of the Mediterranean basin, Middle East, and Far East.
2. IPSID is considered a variant of MALT lymphoma, characterized by infiltration of the small intestinal mucosa with a neoplastic population of marginal zone B cells.
   a. Characteristic plasma cells produce IgA heavy chain (alpha chain disease), which can be detected in the serum.
   b. Campylobacter jejuni is a possible environmental cofactor (while H pylori is associated with gastric MALT lymphoma).
   c. Genetic predisposition has also been suggested.
3. Symptoms: malabsorption, obstruction, protein-losing enteropathy, weight loss, intermittent diarrhea, colicky abdominal pain, anemia, and clubbing of the fingers.
4. Radiological findings: luminal and mural small intestinal disease (masses, irregular filling defects, and wall thickening).
5. Endoscopy with biopsy is the diagnostic procedure of choice.
   a. Upper endoscopy shows thickening, erythema, and nodularity of the small intestinal mucosa.
6. Treatment: early antibiotics (tetracycline or metronidazole + tetracycline/ampicillin) may induce remission. Advanced stages are treated with surgery and chemotherapy (anthracycline-based combinations).

E. Intestinal T-Cell Lymphoma
1. Associated with Celiac disease (enteropathy-associated T-cell lymphoma [EATL]).
2. Represent <5% of all GI lymphomas, but has very poor prognosis.
3. Peak in late adult life.

F. Large Cell Lymphoma
1. Diffuse large B-cell lymphoma (DLBCL) is the most common (30%) subtype of all NHL (intestinal and nonintestinal).
2. Characterized by diffuse proliferation of large neoplastic B cells, that often destroys the underlying architecture of the site of involvement.
3. DLBCL is an aggressive (fast-growing) lymphoma.

III. Mesenchymal Tumors
A. Smooth Muscle Tumors
1. Intestinal Leiomyomatosis
   a. Much more common in the proximal gut (especially esophagus) than the small and large intestine.
2. Intestinal Leiomyosarcomas
   a. Rare (0.3% of all neoplasms in children <15 years of age and 20% of all small intestinal malignancies in some pediatric centers).
   b. Often arises from the smooth muscle of the muscularis propria.
   c. Slight female predominance and slight preference for the distal small intestine.
   d. Nearly 50% of intestinal leiomyosarcoma occur during infancy.
   e. In general, metastatic disease is unusual in the pediatric population.
   f. Symptoms: bleeding, obstruction, intussusception, and perforation.
   g. Prognosis: relatively favorable with complete resection (5-year survival 40–50%).

B. Neural Tumors
   a. These include benign ganglioneuromas, schwannomas/neuromas, neurofibromas and granular cell tumors, as well as malignant peripheral nerve sheath neoplasms.
1. Intestinal ganglioneuromas are the only type that may be encountered as polypoid lesions.
   a. This benign tumor consists of a mixed proliferation of ganglion cells and various glial elements.
   b. Sessile or pedunculated polyps may occur anywhere in the intestinal tract as:
1) Solitary ganglioneuromas are most likely incidental findings
2) Multiple or diffuse ganglioneuromas alert to the presence of underlying syndrome (MEN2B, NF I, JPS and Cowden’s syndrome) or familial disease

2. **Intestinal neurofibromas** are less common
   a. These neurofibromas consist of a proliferation of bland spindle cells with a prominent collagenous stroma
   b. Presence of plexiform neurofibroma or multiple neurofibromas raise the possibility of underlying neurofibromatosis

3. **Intestinal Schwannomas** are very rare in children
   a. Schwannomas constitute <3% of all small and large intestinal tumors

C. **Vascular Tumors**

1. **Benign Hemangiomas**
   a. Intestinal hemangiomas are rare
   b. Consist of proliferation of capillaries and/or other small intestinal vessels
   c. Constitute the most common tumor of infancy in the Western population
   d. Symptoms: GI bleeding and intussusceptions

2. **Benign Lymphangiomas**
   a. Found in the mesenteric soft tissue of the small and large intestine
   b. Symptoms: intestinal obstruction or intussusception

3. **Malignant vascular tumors** (angiosarcoma and Kaposi sarcoma) of GI tract
   a. Very rare during childhood
   b. Pediatric intestinal Kaposi Sarcoma (KS) is often associated with immunosuppression and EBV infection

4. **Lipomas**
   a. Benign intestinal lipomas are found primarily in the colon, but can also appear in the small intestine
<table>
<thead>
<tr>
<th>Gene</th>
<th>Clinical Features</th>
<th>Diagnosis</th>
<th>Pathology</th>
<th>Cancer Risk</th>
<th>Management &amp; Surveillance</th>
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<tbody>
<tr>
<td><strong>Adenomatous Syndromes</strong></td>
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<tr>
<td><strong>Familial Adenomatous Polyposis (FAP)</strong></td>
<td>APC</td>
<td>~100s-1,000s colonic polyps</td>
<td>- Colonoscopy: ≥100 adenomatous polyps</td>
<td>Adenomatous polyps (tubular, tubulovillous and villous adenomas)</td>
<td>• Colon cancer 100%</td>
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<td>Mutational analysis</td>
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<td>• Lifetime risk of duodenal &amp; periampullary malignancy 1%–5%</td>
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<td>• Hepatoblastoma (0.7% of children &lt;5 years old)</td>
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<td>• Thyroid, brain, pancreatic cancers</td>
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<td>• Desmoid tumors (lifetime risk 15%–21%)</td>
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<td>- Colonoscopy annually at age 10 years</td>
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<td>- EGD q 3–4 years and annually if polyps detected</td>
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<td>- Chemoprevention (Celecoxib) has been proposed as a treatment for duodenal polyposis</td>
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<td>- Annual a-fetoprotein and hepatic U/S from infancy to 7 years</td>
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<td><strong>Surgical Treatment:</strong></td>
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<td>- Subtotal colectomy with IRA</td>
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<td>- Total colectomy with IPAA</td>
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<td><strong>Attenuated FAP (AFAP)</strong></td>
<td>APC</td>
<td>Oligopolyposis in the colon</td>
<td>- Colonoscopy: &lt;100 colorectal adenomas</td>
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<td>• Late onset of colorectal cancer</td>
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<td>Fundic gland polyps and duodenal polyps more prominent than colonic polyps</td>
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<td>Endoscopic examinations at later age (18–20 years) in patients with family history of atypical form of polyposis</td>
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<td><strong>Hamartomatous Polyposis Syndromes</strong></td>
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<td><strong>Juvenile Polyposis Syndrome (JPS)</strong></td>
<td>SMAD4</td>
<td>Age of presentation is 2–12</td>
<td>Giardello Criteria: ≥3 (some state &gt;5) polyps in the colorectum or polyposis throughout the GI tract or any number of polyps with a family history of JPS</td>
<td>Same as solitary juvenile polyp (cystic dilation of crypts and excess of lamina propria) No muscle fibers in the stroma</td>
<td>• Colorectal cancer (rare)</td>
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<td>BMPR1A</td>
<td>Rectal bleeding</td>
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<td>• Upper GI malignancies (stomach and duodenum)</td>
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<td>Rectal prolapse</td>
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<td>Abdominal pain</td>
<td></td>
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<td><strong>Surgical Treatment:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intussusception</td>
<td></td>
<td></td>
<td>Colectomy with ileorectal anastomosis</td>
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<tr>
<td></td>
<td></td>
<td>Juvenile polyps in the colon, stomach, jejunum, ileum and duodenum</td>
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</tbody>
</table>
Table 1. Polyposis Syndromes Affecting Small Intestine in Children

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Clinical Features</th>
<th>Diagnosis</th>
<th>Pathology</th>
<th>Cancer Risk</th>
<th>Management &amp; Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peutz-Jeghers Syndrome (PJS)</td>
<td>LKB1/STK11</td>
<td>▫50%–60% present before age 20&lt;br▫Mucocutaneous pigmentation (perinasal and perioral areas and buccal mucosa)&lt;br▫GI polyps preferentially in the small intestine (jejunum &gt; ileum &gt; duodenum) or equally distributed in the stomach, colorectum and small bowel&lt;br▫Abdominal pain due to obstruction/polyp intussusception&lt;br▫Anemia due to GI bleeding</td>
<td>Giardiello Criteria: Hamartomatous polyps + at least 2 of the following: 1-Family history 2-Mucocutaneous pigmentation 3- Small bowel polyposis</td>
<td>Hyperplasia of the smooth muscle layer extending in a tree-like manner toward the epithelial layer</td>
<td>▫GI tract and extraintestinal (pancreatic, breast and gonadal) malignancies&lt;br▫There have been reports of adolescents with PJS who developed gastric and jejunal adenocarcinomas</td>
<td>-EGD, colonoscopy &amp; SBFT/capsule endoscopy every 2 years&lt;br▫Regular screening with removal of polyps through upper and lower endoscopy and double balloon enteroscopy (or intraoperative enteroscopy) may reduce laparotomies for malignancy and infarction due to intussusception&lt;br▫Extensive small bowel resection is not recommended</td>
</tr>
<tr>
<td>Cowden Disease (CD)/Multiple Hamartoma Syndrome</td>
<td>PTEN</td>
<td>▫Hamartomatous neoplasms of the skin, mucosa, GI tract, bones, CNS, eyes and GU tract&lt;br▫Cutaneous manifestations (90%)&lt;br▫Thyroid involvement (66%)&lt;br▫Polyps in the esophagus, stomach, small bowel or colon (35%–40%)</td>
<td>International Cowden Consortium Operational Diagnostic Criteria (see Table 2)</td>
<td>Juvenile or hyperplastic</td>
<td>▫Breast&lt;br▫Thyroid&lt;br▫Skin&lt;br▫Malignant potential of polyps (colonic adenocarcinoma) is low</td>
<td>Routine occult blood tests. Barium swallow and enema to exclude hamartomas of the GI tract. Alternatively, upper and lower endoscopy may be used.</td>
</tr>
<tr>
<td>Bannyan-Riley-Ruvalcaba Syndrome (BRRS)</td>
<td>PTEN</td>
<td>▫GI hamartomas (45% of patients)&lt;br▫Macrocephaly&lt;br▫Speckled penis&lt;br▫Delayed development&lt;br▫Lipomatosis&lt;br▫Hemangiomatosis</td>
<td></td>
<td></td>
<td>▫Breast&lt;br▫Thyroid</td>
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</table>

*Mechanism of inheritance for all is AD with variable penetrance.
Table 2. International Cowden Consortium Operational Diagnostic Criteria

<table>
<thead>
<tr>
<th>Major Criteria</th>
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<tbody>
<tr>
<td>Breast cancer</td>
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<td>Thyroid carcinoma, especially follicular thyroid carcinoma</td>
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<tr>
<td>Macrocephaly (&gt;97 percentile)</td>
</tr>
<tr>
<td>Lhermitte-Duclos disease</td>
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<tr>
<td>Endometrial cancer</td>
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</table>

<table>
<thead>
<tr>
<th>Minor Criteria</th>
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<tbody>
<tr>
<td>Other thyroid lesions (e.g., adenoma, multinodular goiter)</td>
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<tr>
<td>Mental retardation (intelligence quotient &lt;75)</td>
</tr>
<tr>
<td>GI hamartomas</td>
</tr>
<tr>
<td>Fibrocystic disease of the breast</td>
</tr>
<tr>
<td>Lipomas</td>
</tr>
<tr>
<td>Fibromas</td>
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<tr>
<td>GU tumors (e.g., uterine fibroids, renal cell carcinoma) or malformations</td>
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<table>
<thead>
<tr>
<th>Pathognomonic Criteria</th>
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</thead>
<tbody>
<tr>
<td>Facial trichilemmomas</td>
</tr>
<tr>
<td>Acral keratoses</td>
</tr>
<tr>
<td>Papillomatous papules</td>
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<tr>
<td>Mucosal lesions</td>
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</tbody>
</table>

Recommended Reading


del Junco G. Pathology for Colon and Rectal Surgeons. 2002;21.