I. Acute vs Chronic Abdominal Pain
   A. Acute:
      1. Acute abdominal pain is one of the most common childhood complaints
         a. Often self-limited
         b. Need to rule out life-threatening causes (i.e., intestinal obstruction, perforation or hemorrhage)
         c. Consider nongastrointestinal causes (i.e., genitourinary tract, infection or extraintestinal conditions)
      2. Obtain thorough history of symptoms and perform physical exam:
         a. Is there emesis? If so, assess quality of emesis (bilious vs non-bilious; bloody vs non-bloody)
            1) Bilious emesis: consider obstruction (anatomic or functional)
            2) Coffee ground or blood tinged emesis: consider some form of esophagitis, gastritis, gastric or duodenal ulcer, Mallory-Weiss tear
         b. What are the quality and frequency of patient’s stools? (hard vs soft vs watery; bloody vs acholic vs melanotic)
            1) Watery: consider infectious diarrhea etiologies or bowel inflammation
            2) Harder stool (or decreased frequency): consider constipation
            3) Melena: assess for an upper gastrointestinal bleeding lesion (i.e., gastric or duodenal ulcer)
            4) Bloody stools: assess for an anal fissure, hemorrhoid, inflammatory or allergic colitis, polyp lesion, ischemic injury (NEC), intussusception (currant jelly stools)
            5) Acholic stools: assess for biliary or hepatic disease
      3. Acute gastroenteritis is most common gastrointestinal inflammatory process in children
         a. Often a viral process
      4. Appendicitis is the most common surgically treated source of abdominal pain in children

Table 1. Differential Diagnosis of Abdominal Pain by Location

<table>
<thead>
<tr>
<th>Epigastric:</th>
<th>Right Upper Quadrant:</th>
<th>Left Upper Quadrant:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroesophageal reflux</td>
<td>Hepatitis</td>
<td>Splenic injury</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>Cholecystitis</td>
<td>Left lower lobe pneumonia</td>
</tr>
<tr>
<td>Gastritis</td>
<td>Cholelithiasis/biliary colic</td>
<td>Kidney disease</td>
</tr>
<tr>
<td>Gastroduodenal ulcer</td>
<td>Cholangitis</td>
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<tr>
<td>Pancreatitis</td>
<td>Right lower lobe pneumonia</td>
<td></td>
</tr>
<tr>
<td>Gastric or small bowel volvulus</td>
<td>Kidney disease</td>
<td></td>
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<tr>
<td>Cholelithiasis/biliary colic</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypogastric:</th>
<th>Left Lower Quadrant:</th>
<th>Right Lower Quadrant:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Constipation</td>
<td>Constipation</td>
</tr>
<tr>
<td>Colon spasm or colitis</td>
<td>Colon spasm or colitis</td>
<td>Mesenteric adenitis</td>
</tr>
<tr>
<td>Bladder disease</td>
<td>Ovarian disease/torsion</td>
<td>Crohn disease</td>
</tr>
<tr>
<td>Uterine conditions</td>
<td>Ectopic pregnancy</td>
<td>Appendicitis</td>
</tr>
<tr>
<td>Pelvic inflammatory disease</td>
<td>Testicular torsion</td>
<td>Intussusception</td>
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<tr>
<td></td>
<td>Hernia</td>
<td>Ovarian disease/torsion</td>
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<tr>
<td></td>
<td>-Sigmoid volvulus</td>
<td>Ectopic pregnancy</td>
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<tr>
<td></td>
<td></td>
<td>Testicular torsion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hernia</td>
</tr>
</tbody>
</table>
### Periumbilical:
- Constipation
- Gastroenteritis
- Early appendicitis
- Pancreatitis
- Small bowel volvulus
- Incarcerated umbilical hernia

### Diffuse Pain:
- Gastroenteritis
- Celiac disease
- Perforation
- Constipation
- Functional abdominal pain
- Streptococcal pharyngitis
- Inflammatory bowel disease
- Henoch-Schönlein purpura
- Diabetic ketoacidosis
- Porphyria
- Sickle cell crisis
- Volvulus
- Abdominal migraine
- Cyclic vomiting syndrome
- Toxic ingestion
- Familial Mediterranean fever
- Angioneurotic edema
- Venomous bites

### Location Varies:
- Trauma
- Ischemic bowel disease
- Allergic disease

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5. **Evaluation:**
   a. Consider laboratory evaluation: CBC, electrolytes, urinalysis, inflammatory markers, liver enzymes, pancreatic enzymes, urine pregnancy, infectious studies if indicated (i.e., rapid strep Ag)
   b. Consider abdominal x-ray and/or ultrasonography

II. **Recurrent or Chronic Abdominal Pain:**
   A. Now referred to as Pain-related functional gastrointestinal disorders (FGID) involves a combination of chronic or recurrent abdominal symptoms not explained by known biochemical or structural abnormalities (see section on Functional Abdominal Pain)
      1. **Review Rome III criteria 2006**
      2. Prevalence in Western world 0.3%–19%
      3. Evaluate for chronic infectious, inflammatory, metabolic, autoimmune, or anatomic disorders leading to a patient’s chronic abdominal pain
         a. Consider non-gastrointestinal causes of chronic pain (i.e., genitourinary tract, infectious or extraintestinal conditions)
         b. Assess patient for alarm signals for pathologic chronic abdominal pain syndromes
            1) Involuntary weight loss
            2) Growth retardation
            3) Delayed puberty
            4) Significant vomiting
            5) Significant diarrhea
            6) Gastrointestinal blood loss
            7) Extraintestinal symptoms
            8) Unexplained fever
            9) Family history of IBD
            10) Consistent RUQ or RLQ abdominal pain
            11) Abnormal physical exam

III. **Innervation and Mechanisms of Pain**
   A. Broken down into visceral, parietal or referred pain
   B. **Visceral pain:** abdominal pain secondary to nonmyelinated pain receptors located in muscles, mucosa of organs, mesentery and serosal surfaces
      1. These pain receptors respond to stretching (i.e., bowel distension). Visceral pain is not well localized and often dull, diffuse, crampy or burning in nature
      2. Lower esophagus, stomach and duodenum → felt in epigastric area
3. Small intestine → felt around the umbilicus
   a. Example: nonspecific periumbilical pain often felt in early appendicitis
4. Colonic visceral pain → felt in lower abdomen
5. Not evoked from all viscera, especially liver and kidney
6. Often accompanied by motor and autonomic reflex responses (i.e., nausea, vomiting)

C. Parietal pain: abdominal pain secondary to myelinated pain receptors, in the parietal peritoneum, muscle and skin
   1. Pain receptors respond to stretching, tearing or inflammation
   2. Gives a localized pain and often sharp in nature
      a. Example: once there has been parietal peritoneal inflammation from acute appendicitis, a patient often localizes pain to his/her RLQ pain
   3. Movement often increases pain

D. Referred pain: abdominal pain often associated with visceral pain, which leads to activity of nerve fibers from cutaneous dermatomes entering spinal cord/CNS at the same level; get activation of nerve pathways distant to the affected site
   1. Acute cholecystitis → often leads to referred right scapular pain
   2. Acute pancreatitis → often leads to mid-back pain

Recommended Reading


I. Irritable bowel syndrome (IBS) is a diagnosis that should be considered in children with chronic abdominal pain. The diagnosis can be made in children who are able to provide a history of abdominal pain lasting for more than 3 months. The evaluation leading to the diagnosis does not identify any underlying organic disease.

II. IBS is a clinical diagnosis, a condition of unknown etiology characterized by episodes of abdominal pain or discomfort more than once per week accompanied by changes in bowel habit

A. Subtypes based on predominant symptoms
   1. Diarrhea predominant (IBS-D)
   2. Constipation predominant (IBS-C)
   3. Mixed (IBS-M)
   4. Pain predominant (IBS-P)

B. Prevalence of each subtype is equal

III. ROME III Criteria (www.romecriteria.org)
   A. Currently the best clinical definition of IBS must include:
      1. Recurrent abdominal pain or discomfort\(^a\) at least 3 days/month in the last 3 months\(^b\) associated with 2 or more of the following at least 25% of the time:
         a. Improvement of discomfort with defecation
         b. Onset associated with a change in frequency of stool
         c. Onset associated with a change in form (appearance) of stool
      2. No evidence of inflammatory, anatomic, metabolic or neoplastic process

\(^a\)Discomfort means an uncomfortable sensation not described as pain.
\(^b\)Criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

IV. Typical GI Symptoms
   A. Abnormal stool frequency (≥4/day or ≤2/week)
   B. Abnormal stool form: lumpy/hard or loose/watery
   C. Passage of mucous with or without stool
   D. Bloating/sensation of abdominal distension

V. Epidemiology
   A. Female to male ratio is 2–2.5:1
   B. Between 3%–20% of North American adults are affected
   C. Similar prevalence for pediatric patients with recurrent abdominal pain

VI. Pathophysiology: not well understood
   A. Genetic factors may play a role
      1. Family clusters of affected patients
      2. Mothers of children with recurrent abdominal pain are more likely to have a lifetime history of IBS than controls
      3. Concordance for IBS is greater in identical than fraternal twins
      4. No mutations proven, but polymorphisms in G-proteins have been found in dyspepsia and polymorphisms in IL10 and serotonin transporter gene in other forms of IBS
   B. Chronic stress has a likely role
   C. Infection may be the initiating event with chronic changes in motility and flora
      1. Giardiasis particularly associated with subsequent IBS
   D. Both high and low socioeconomic groups are affected
   E. Food allergy unproven as cause
VII. Comorbid Non-GI Conditions
   A. 48%–60% of patients have psychological comorbidities: depression, anxiety, abuse, somatic attribution and hypochondria
   B. Central pain processing disorders: fibromyalgia, chronic fatigue syndrome and chronic pelvic pain
   C. Other somatic complaints associated with IBS
      1. Headache
      2. Fatigue
      3. Myalgias
      4. Dyspareunia/menstrual pain
      5. Urinary frequency or dysuria
      6. Dizziness/syncope

VIII. Economic impact of irritable bowel syndrome is high
   A. Health care costs recently estimated to be
      1. Direct costs: US $348–$8,750 per patient per year
      2. Indirect costs: US $355–$3,344 per patient per year
   B. Impaired work productivity and quality of life

IX. Alarm signs and symptoms demanding further investigation
   A. New onset IBS after 50 years of age
   B. Unintentional weight loss, growth failure
   C. Nocturnal diarrhea
   D. Anemia
   E. Hematochezia
   F. Family history of colon cancer, celiac disease or inflammatory bowel disease
   G. Constitutional symptoms

X. Diagnostic Testing
   A. American College of Gastroenterology (ACG) IBS Task Force recommends that routine diagnostic testing should not be performed in patients with typical IBS symptoms who have no alarm features
   B. Colonoscopy is not recommended unless alarm signs and symptoms accompany pain
   C. IBS and celiac disease may co-exist
      1. Testing for celiac disease may be warranted for patients with IBS-D and IBS-M subtypes
      2. 4-fold increase in IBS symptoms in patients with biopsy proven celiac disease over healthy controls
   D. Lactose Intolerance
      1. Prevalence of lactose intolerance in IBS is about 35%
      2. ACG IBS Task Force recommends lactose breath testing if suspicion is high after lactose restricted diet trial
   E. Fructose intolerance may cause IBS-like symptoms
      1. Incompletely absorbed fructose is fermented in the colon producing H₂, CO₂ and short-chain fatty acids. The osmotic load and gas cause diarrhea, flatulence and pain similar to IBS-D
      2. Short-chain carbohydrates and sugar alcohols have a similar effect
      3. Exclusion diets lead to an improvement in 80% of patients with fructose intolerance
   F. Fermentable oligo-, di-, and monosaccharides and polyols also cause symptoms
      1. Fructan-containing vegetables – onions, asparagus, artichokes
      2. Sorbitol – plums, cherries and chewing gum
      3. Raffinose – cabbage and lentils
   G. Small bowel bacterial overgrowth rarely mimics IBS
      1. ACG IBS Task Force recommends lactulose or glucose breath test for bacterial overgrowth only in cases with severe diarrhea and nocturnal diarrhea
XI. Management

A. Team approach develops rapport with patient in nonjudgmental atmosphere
   1. Mild disease – education, reassurance and dietary and lifestyle modifications
   2. Moderate disease – add pharmacotherapy and psychological treatments
   3. Severe disease – to the management above, consider adding referral to pain treatment center

B. Diet
   1. 70% of IBS patients think that diet provokes their symptoms
   2. Some dietary changes that benefit some IBS patients
      a. Smaller meals
      b. Avoid fatty food
      c. Decrease dairy, lactose and total carbohydrates
      d. Decrease caffeine and alcohol
      e. Increase dietary fiber
   3. The ACG IBS Task Force does **not** recommend exclusion diets for IBS

C. Global treatment options
   1. Cognitive behavioral therapy to modify maladaptive behaviors and thinking
   2. Hypnotherapy
   3. Alternative medicine therapies have not been subjected to trial, including acupuncture, herbal therapy

D. Common pharmacologic treatments for IBS-C
   1. Psyllium, methylcellulose to improve straining and hard stools
   2. Osmotic laxatives – milk of magnesia, lactulose syrup, PEG
   3. Stimulant laxatives – senna, diphenylethyl derivatives (bisacodyl)
   4. Emollients – docusate, mineral oil
   5. Serotonin (5HT4) agonists – tegaserod only available by special release because of cardiac side effects
   6. Chloride channel activators – lubiprostone (prostaglandin derivative is FDA approved for IBS-C in women and adults with idiopathic constipation)

E. Common pharmacologic treatments of IBS-D
   1. Antidiarrheals – loperamide, diphenoxylate
   2. 5HT4 antagonists – alosetron available only for severe IBS-D in women. Severe side effects include constipation and ischemic colitis
   3. Tricyclic antidepressants – amitriptyline, doxepin, imipramine, clomipramine, desipramine, nortriptyline
      a. Treatment must be preceded by screening EKG because of potential long QTc syndrome and cardiac arrhythmia
      b. Doses are usually lower than those used for mood elevation

F. IBS-D and IBS-M
   1. Rifaximin has been associated with global improvement in IBS-D and IBS-M with decreased bloating

G. IBS-M and IBS-P
   1. Antispasmodics (hyoscine sulfate and dicyclomine) are often used and may improve postprandial symptoms.
   2. Tricyclic antidepressants (see above)
   3. Selective serotonin reuptake inhibitors – fluoxetine, citalopram, paroxetine, sertraline, escitalopram
      a. Limited controlled studies
      b. Some global improvement
   4. Probiotics
      a. **Bifidobacterium infantis** may improve gas-related symptoms
      b. VSL #3
Recommended Reading


I. **Differential Diagnosis**

The differential diagnosis for abdominal masses is large and includes both benign and malignant lesions.

A. **Epidemiology**
   1. Primary gastric neoplasms are rare
      a. GI malignancies account for ~1.2% of all childhood malignancies
      b. Gastric neoplasms are a very small subset of primary GI malignancies
   2. Non-Hodgkin lymphomas and sarcomas are most common gastric neoplasms

B. **Benign gastric tumors**
   1. Adenomatous polyps (see section on Colon Polyps)
      a. *Familial adenomatous polyposis* (FAP) may have multiple gastric polyps (fundic gland type > adenomatous)
      b. Fundic gland polyps in the setting of FAP may have neoplastic potential and require regular screening endoscopy every 1–3 years
   2. Fundic gland tumors and polyps are often seen in familial adenomatous polyposis syndrome and more frequently in patients on long-term PPI therapy
      a. PPI-related polyps are a result of hyperplasia of parietal cells and have been reported within 10–48 months of starting PPI therapy
         1) PPI-related gastric changes are currently not thought to have significant risk for cancer
         2) No definitive guideline for monitoring these polyps in children has been developed. One widely quoted authority suggests endoscopic monitoring for fundic gland polyps in children on long-term PPI
   3. Juvenile/hamartomatous polyp (see section on Colon Polyps)
      a. *Peutz-Jeghers syndrome*: 40% patients have gastric hamartomas, most commonly in the antrum
      b. *Juvenile polyposis*: hamartomas with inflammatory cells in the lamina propria. Juvenile polyps occur in the stomach in *generalized juvenile polyposis syndrome* or *juvenile polyposis of infancy* (usually fatal). Gastric juvenile polyps have lower risk of malignant transformation than colon polyps
   4. Gastric pseudopolyps: may be seen with Crohn disease, allergic gastritis, or other inflammatory polyps
   5. Teratomas:
      a. Rare tumor composed of mesodermal, endodermal and ectodermal elements (gastric teratomas comprise only 0.75% of all childhood teratomas)
      b. Almost all patients are male and <2 years old (majority <3 months). Excision is curative
      c. May produce irregular soft tissue mass with both solid and cystic components, as well as calcifications on abdominal imaging
      d. Mostly benign; because there are rare case reports of malignant gastric teratomas, all teratomas require complete resection
C. Malignant lesions

1. Adenocarcinomas:
   a. Very rare in children
   b. Can be associated with: IgA deficiency, common variable immunodeficiency, ataxia-telangiectasia, as well as FAP and Peutz-Jeghers syndrome (usually later in life)
   c. Also associated with familial diffuse gastric carcinoma syndrome (germline mutations in E-cadherin/CDH2 gene)
   d. *H. pylori* infection is mostly associated with non-cardia adenocarcinomas
      1) Currently, no definite recommendations for screening for *H. pylori* in asymptomatic children to prevent gastric cancer
      2) Testing for *H. pylori* should be considered if there is a family history of gastric cancer
   e. Symptoms: pain, anorexia, vomiting, GI bleeding, upper abdominal mass and weight loss

2. Gastric Lymphomas
   a. Small proportion of all intestinal non-Hodgkin lymphomas in children
   b. Most are Burkitt lymphomas
   c. MALT (mucosa-associated lymphoid tissue) lymphoma has been associated with *H. pylori* infection
      1) If diagnosed with MALT lymphoma, patient should be tested for *H. pylori*, as treatment of *H. pylori* may help regression/remission of gastric MALT lymphoma
   d. Primary immunodeficiencies are a risk factor for this tumor
   e. Treatment: surgical resection and adjuvant chemotherapy and radiotherapy if metastases are present

3. Gastrointestinal stromal tumor (GIST):
   a. Spindle or epithelioid mesenchymal neoplasm arising from interstitial cells of Cajal
   b. ↑ incidence in females
   c. Cells express C-Kit and CD34
   d. Extremely rare in children (only 1% present in children, most often occur in 2nd decade of life), but 60%–70% occur in stomach
   e. Common presentation is GI bleeding and intestinal obstruction

D. Miscellaneous tumors:

1. Gastric hemangioma: often associated with vascular skin lesions and vascular involvement of intestinal tract
   a. Hematemesis: frequent symptom
   b. Benign, but if symptomatic may require surgical therapy

2. Gastric lipoma: slow-growing tumors composed of adipose tissue

3. Inflammatory myofibroblastic tumor or inflammatory pseudotumors: made up of spindle cells, myofibroblasts, plasma cells and histiocytes
   a. Thought to be an aberrant response to tissue injury
   b. Treatment is by surgical resection; recurrence and metastases are common

4. Carcinoid tumor: has been reported in stomach (but most likely found in appendix)
   a. Treatment: full resection of tumor

5. Gastric Hamartoma
   a. Benign lesions with histologic variation (a mixture of components of the gastric wall)

6. Gastric leiomyosarcoma and leiomyomas: soft tissue tumors of smooth muscle origin that involve gastric wall
   a. Often present with GI hemorrhage, obstruction and perforation

7. Ectopic pancreas (or pancreatic rest): accessory pancreatic tissue, most often found in prepyloric gastric antrum
   a. Pancreatic tissue with no ductular connection to pancreatic gland
   b. Usually asymptomatic and discovered incidentally, although there have been reports of clinical symptoms if >1.5 cm (abdominal pain, dyspepsia, GI bleeding)
   c. On endoscopy, appear as round, smooth submucosal mass with central umbilication
   d. Treatment: observational; due to submucosal location of pancreatic rests, endoscopic removal has high risk of perforation
Recommended Reading


I. There are more than 80 primary and secondary immunodeficiency syndromes that affect children. IgA deficiency is the most common primary immune deficiency. Many of the immunodeficiency states have associated gastrointestinal manifestations.

II. IgA deficiency is the most common human immunodeficiency
A. Prevalence 1:300 to 1:700
B. Severe deficiency – IgA levels repeatedly <7 mg/dL with normal IgG and IgM
C. Mild deficiency/probable diagnosis – IgA >7 mg/dL but <2 SD below the mean for age
D. Diagnosis should not be made until child is 4 years or older because of normally low levels of IgA in younger children
E. Many IgA deficient children are asymptomatic
F. IgA deficiency may be associated with
   1. Autoimmunity (systemic lupus, juvenile rheumatoid arthritis) found in 20%–30% of deficient individuals
   2. Anaphylaxis to blood products (40% have IgG antibodies against IgA
   3. Infections
      a. Sinopulmonary infections more common than GI infections
      b. Chronic giardiasis
      c. Other GI infections not common
   4. Lymphoid nodular hyperplasia of the small and large intestine is common
   5. Celiac disease
      a. 2% of celiac disease patients are IgA deficient
      b. 10%–30% of IgA deficient patients have celiac disease
      c. Histology and response to diet are identical in IgA deficient and sufficient patients
G. Treatment of IgA deficiency is directed at managing clinical manifestations rather than correcting IgA deficiency

III. Chronic granulomatous disease (CGD)
A. Caused by defect in the NADPH oxidative burst pathway
   1. Prevents neutrophil oxidation and killing of catalase+ organisms
   2. Mutation may be in 1 of 4 genes (gp91, p47, p67, p22)
B. X-linked recessive disease (gp91): ~67% of cases
   1. Mean age at diagnosis: 4.9 year
C. Autosomal recessive: ~33% (p47 more common than p67 and p22)
   1. Mean age at diagnosis: 8.8 year
D. Found in 1/250,000 live births
E. GI related presentations are common especially in X-linked CGD
   1. Infection – 48%
   2. Oral aphthae – 11%
   3. Perirectal abscess (16%–21%)  
   4. Gastric or esophageal obstruction by granulomas
   5. Hepatic abscess (30%) due to Staphylococcus or Pseudomonas
   6. Colitis (11%–17%) occurs at similar rates in X-linked vs AR
F. Other infections in CGD - pneumonia>abscess>adenitis
   1. High risk for catalase + organisms
   2. Bacteria – *Staphylococcus aureus*, Gram-negative rods (*E coli, B cepacia, Serratia spp*) and *Nocardia*
   3. Fungi – Aspergillus, Candida

G. Autoimmune disease is less common in CGD than CVID

H. Diagnosis
   1. Preferred test is dihydrorhodamine reductase (DHR) assay to measure oxidative burst
   2. Nitroblue tetrazolium test is less reliable
   3. Genetic testing is available

I. Therapy
   1. Prophylaxis with antifungal (itraconazole) and antimicrobial (TMP-SMX) agents
   2. Interferon-γ to reduce frequency of serious infections
   3. Stem cell transplantation and gene therapies are available in some centers
   4. Colitis usually responds to steroids and/or Interferon-γ
   5. Colitis may be treated with anti-TNF and antimicrobials

IV. Common variable immunodeficiency (CVID)
   A. Hypogammaglobulinemia with poor response to immunization – B cells do not differentiate into plasma cells
   B. Multiple genes implicated (80% are sporadic mutations)
   C. Incidence 1:50–200,000
   D. Usually presents during adolescence or later
   E. Diagnostic criteria – two IgG subclasses > 2 SD below normal with poor titers after vaccination with tetanus (IgG1) or *Hemophilus/pneumococcus* (IgG2)
   F. Most common infectious manifestation is pneumonia
   G. GI related infections
      1. *Giardia* most common
      2. *Bacterial: Salmonella, Campylobacter, Yersinia*
      3. *Viral: CMV*
   H. Hepatosplenomegaly sometimes present
   I. GI histology
      1. Gastritis with apoptosis similar to that in acute GVHD
      2. Duodenitis: 30%–60% have increased intra epithelial lymphocytes, villous blunting and deficiency of plasma cells in lamina propria
      3. Mild colitis with increased apoptosis
   J. >25% of patients with CVID have autoimmune disease
   K. Therapy is IgG replacement

V. Severe combined immunodeficiency
   A. Lack of functional T cells (and sometimes lack of NK and B cells)
   B. Multiple genes implicated (ADA, PNP, JAK3)
   C. Occurs in 1:50–75,000 live births
   D. Manifestations
      1. Respiratory infection, diarrhea and failure to thrive in first months of life
      2. Hepatosplenomegaly, lymphoid hyperplasia
      3. Intractable diarrhea with shedding of viruses that cause self-limited infections in normal children
      4. Recurrent oral, cutaneous and GI candidiasis
      5. Death from viral sepsis, especially EBV, varicella, herpes, CMV
   E. Intestinal biopsy shows villous blunting, absent plasma cells
   F. Therapy: IVIG replacement, antimicrobial prophylaxis and prompt therapy for infections
   G. Bone marrow transplant is curative
VI. Bruton agammaglobulinemia – X-linked agammaglobulinemia
A. Mutation in Bruton tyrosine kinase gene results in defective B cell development
B. Incidence is 1:100,000–200,000 live male births.
C. Manifestations
   1. Recurrent sinopulmonary infections in first year after maternal antibody levels fall
   2. Recurrent GI infections with Campylobacter and Giardia – less commonly Salmonella and Shigella
   3. Chronic GI enteroviral infection may seed CNS
   4. Some develop Crohn-like disease
D. Diagnosis
   1. Markedly low Ig levels and paucity of B cells
   2. May be confused with SCID but T cell numbers are normal
   3. Genetic screening for Bruton tyrosine kinase gene
E. Therapy
   1. Prompt treatment of infection
   2. IVIG infusion

VII. Wiskott-Aldrich syndrome
A. X-linked disorder due to mutation in WAS protein (WASP)
B. 1 in 250,000 live male births
C. Triad of immunodeficiency, eczema, thrombocytopenia with small platelets
D. Wide spectrum of disease although thrombocytopenia present in nearly all
E. Mild mutations may cause only thrombocytopenia
F. Autoimmune phenomena: IBD in 3%, hemolytic anemia, vasculitis
G. Diagnosis:
   1. High IgA, low IgM, normal IgG
   2. Diagnosis confirmed with genetic testing
H. Treatment: Bone marrow transplant curative

VIII. IPEX Syndrome (see section on Autoimmune Enteropathy)
A. X-linked immune dysregulation, polyendocrinopathy, enteropathy
B. Mutation in FoxP3 gene causes minimal or absent FoxP3+ regulatory T cells
C. Typical presentation is failure to thrive and secretory diarrhea

IX. Graft vs host disease
A. Occurs when donor T cells (and potentially other immune cells) recognize host antigen and initiate reaction against host
B. Acute GVHD – occurs in the first 100 days after bone marrow transplant. Rarely can occur after liver transplants (<1%)
C. GI Symptoms: nausea, anorexia, abdominal pain, weight loss, diarrhea (watery becoming bloody)
D. Skin involvement is most common
E. Gastrointestinal involvement can be severe
   1. Hallmark finding is epithelial cell apoptosis leading to crypt degeneration/loss
   2. Upper GI involvement often occurs before colonic
   3. Duodenal biopsy often shows villous blunting
F. Initial therapy is steroids (50% effective)
G. No definitive second-line therapy, may use calcineurin inhibitor, mycophenolate, anti-thymocyte globulin
X. Hepatic GVHD is 2nd most common form of GVHD
   A. Occurs in 25% of pediatric bone marrow transplants compared to <1% in pediatric liver transplants
   B. Obstructive jaundice more common than transaminitis
   C. Diagnosis requires liver biopsy – showing portal fibrosis with cholestasis with no infectious diagnosis
   D. Therapy similar to non-hepatic GVHD with addition of Ursodiol

XI. Chronic GVHD – occurs >100 days after BMT
   A. Complicates 20%–50% of pediatric BMT (adults 50%–70%)
   B. Can involve any organ (as opposed to specific organs in acute GVHD)
      1. Often affects esophagus causing strictures
   C. Diagnostic criteria are less definitive
   D. May be confused with infection or autoimmune conditions (lupus, scleroderma)
   E. Initial therapy is steroids ± calcineurin inhibitor

XII. HIV – Acquired immunodeficiency syndrome
   A. RNA retrovirus infects CD4 cells and macrophages
   B. Inversion of CD4/CD8 ratio to <1
   C. Viral reverse transcriptase converts RNA to DNA, then cell machinery synthesizes viral RNA
   D. Most common manifestations
      1. Opportunistic infections
      2. Weight loss
   E. Primary acute retroviral infection
      1. Fever, lymphadenopathy, myalgia, oral ulcers
      2. No antibody response
      3. Viral RNA positive, very high viremia
      4. Virus found in lymph nodes
   F. AIDS-defining infections
      1. CMV, HSV, Cryptosporidia, Isospora, Giardia, Mycobacterium avium complex, Candida
   G. GI manifestations of HIV
      1. Infections with CMV are common – esophagitis, hepatitis, colitis
      2. Gastritis, duodenitis
      3. Chronic diarrhea
   H. Diagnosis
      1. Screen for HIV antibody with enzyme-linked immunoassay
      2. Confirm with Western blot
   I. Current therapy is highly active antiretroviral therapy (HAART)
      1. Consists of 2 nucleoside reverse transcriptase inhibitors (NRTI) and 1 non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor
      2. Children treated with HAART have better growth

XIII. Hereditary angioedema
   A. C1 inhibitor dysfunction in 20%. Deficiency of C1 inhibitor in 80%
   B. 0.4% of all urticaria cases in children are hereditary angioedema
   C. Often diagnosed in first decade but worsens at puberty
   D. Edema occurs because of vascular leak
   E. Clinical manifestations
      1. Recurrent angioedema and urticaria lasting 2–3 days
      2. Often initiated by trauma
      3. Swelling of proximal and distal extremities common
   F. Most common GI symptom is recurrent severe abdominal pain
   G. Treatment
      1. Mostly supportive
      2. C1 inhibitor replacement with danazol or fresh frozen plasma
      3. Aminocaproic acid may prevent spread of edema
XIV. Immunodeficiency due to medications used to treat GI disorders (see section on Anti-inflammatory/Transplant Medications)

A. Hypogammaglobulinemia may accompany the use of
   1. Sulfasalazine
   2. Anti-convulsants
   3. Anti-TNFα (see section on Major Biologic Medications)

B. Complications of 6-MP/azathioprine
   1. Dose-dependent bone marrow suppression causes leucopenia and sometimes thrombocytopenia
   2. Leucopenia risk can be decreased by evaluating thiopurine methyl transferase enzyme before therapy
   3. Repeat TPMT evaluation may be warranted while on therapy, as 6-MP/azathioprine induces enzyme activity
   4. 5-ASA and infections may affect TPMT activity
   5. Increased risk of CMV, varicella and severe EBV infections

C. Methotrexate in low dose rarely causes pancytopenia

D. Corticosteroids
   1. Increased risk of respiratory, urinary tract and liver infections
   2. Increased risk for infection with Herpes simplex and Pneumocystic jeroveci
   3. Children on >2 mg/kg or >20 mg/day of corticosteroids for >14 days should not receive live-attenuated vaccines until 1 month after cessation of therapy

Recommended Reading

Agarwal S. Gastrointestinal manifestations in primary immune disorders. *IBD.* 2010;16(44):703-711.


I. Cystic fibrosis (CF) is the most common lethal genetic defect in the Caucasian population. The gastrointestinal tract can be affected. Meconium ileus is the earliest gastrointestinal manifestation of cystic fibrosis. Distal intestinal obstruction syndrome is a gastrointestinal complication that can be seen at any time, but is more common in adolescence.

II. Meconium ileus
   A. Overview/Epidemiology
      1. Meconium ileus (MI) is an early clinical manifestation of CF, characterized by partial or complete intestinal obstruction in the neonate
      2. MI occurs in 10%–20% of patients with CF
      3. Prognosis for MI has improved over the years, but delayed diagnosis still causes significant mortality
   B. Pathogenesis/Pathophysiology
      1. MI occurs in utero almost exclusively in patients with complete exocrine pancreatic insufficiency. Other risk factors for MI have not been defined
      2. Meconium in patients with CF is thick and likely to become inspissated in the intestinal lumen. Thickness of meconium is caused by increased concentration of albumin and minerals, increased mucous and decreased water content
      3. Inspissation usually occurs in the terminal ileum, producing partial or complete small bowel obstruction
      4. Bowel distal to inspissated meconium is usually of small caliber (unused micro-colon)
      5. Bowel proximal to inspissated meconium is usually dilated
      6. Dilated proximal bowel is at risk for volvulus and perforation
      7. Antenatal intestinal perforation causes meconium peritonitis, with peritoneal calcifications
      8. Antenatal volvulus causes ileal atresia
   C. Diagnosis
      1. Evaluation
         a. The results of neonatal serum immunoreactive trypsinogen (IRT) will be falsely negative in patients with meconium ileus because of the profound pancreatic insufficiency
         b. In patients with MI, a mutation analysis for CF should be obtained, not IRT
      2. Imaging
         a. Diagnosis suggested by increased echogenicity of bowel on ultrasound in the first trimester (questionable reliability)
            1) Plain film
               a) Dilated bowel loops with ground glass appearance (no air within meconium) in the right lower quadrant
               b) Air-fluid levels are generally not seen because of inconsistency of bowel contents
               c) Calcification of intraluminal contents suggests prenatal perforation and peritonitis
            2) Contrast enema usually shows microcolon with filling defects caused by pellets of mucous and meconium
D. Clinical Manifestations
1. Signs and symptoms of intestinal obstruction in the newborn period: bilious emesis, distension, and failure to pass meconium within the first 2–48 hours of life
2. Filled loops of bowel may be palpable. The rectum is tight on digital examination
3. Nearly 50% of cases have complicated MI, where in addition to MI there is malrotation with volvulus, intestinal perforation, peritonitis, necrosis, meconium cysts or intestinal atresia requiring laparotomy
4. Most cases have microcolon in association
5. MI can be distinguished from other forms of neonatal gut obstruction by the lack of air fluid levels in erect or lateral radiographs in addition to the ground glass appearance
6. Diagnosis of MI should be suspected if there is a family history of CF. When an infant develops MI, the recurrence risk for siblings with CF significantly increases
7. Prognosis: children with CF born with MI go on to have more clinically significant lung disease and shorter life expectancy

E. Treatment/Management
1. Current surgical and nutritional modalities have significantly decreased the formerly high mortality rates in infants with MI
2. In uncomplicated MI, a gastrografin enema by a skilled pediatric radiologist not only helps establish the diagnosis, but, because it is hypertonic, it can also be therapeutic in washing out the insipissated meconium
3. Contrast radiography should be avoided in those with perforation or intraabdominal calcification
4. Great care is needed to avoid the perforation, shock and dehydration associated with the use of the hypertonic enemas
5. Secure IV access, adequate hydration and close monitoring are essential in a center where neonatal surgery is available
6. Failure to resolve the obstruction with gastrografin necessitates surgical intervention
7. The standard procedure is to milk out the insipissated material to wash out the residue with saline or solutions containing n-acetylcysteine. Intraoperative infusions of n-acetylcysteine or hyperosmolar contrast have been shown to decrease the need for surgical resection
8. There may be late complications from loss of resected intestine or development of stricture or band at the site of surgery. Persistent bowel symptoms despite adequate pancreatic enzyme therapy should be thoroughly investigated in any CF patient, especially in case of neonatal surgery

F. Differential Diagnosis
1. Hirschsprung disease
2. Intestinal volvulus
3. Intestinal atresia
4. Meconium plug syndrome (MPS): seen in infants with CF, Hirschsprung disease, hypotonia, and prematurity. Presentation similar to MI but the obstruction is distal (at the level of the colon rather than the ileum). Contrast enema shows a normal caliber colon with filling defects from insipissated meconium and is usually diagnostic and therapeutic. Surgery is rarely indicated

III. Distal intestinal obstruction syndrome (DIOS)
A. Overview/Epidemiology
1. DIOS replaces the vague term of meconium ileus equivalent
2. ESPGHAN CF Working Group defined DIOS and defined complete and incomplete DIOS (see Table 1)
3. Incidence is variable depending on definition used
4. 17%–24% of patients with CF experience DIOS. The diagnosis is being made more frequently now that the ESPGHAN guidelines are being used
5. Can occur at all ages but is more common in adolescents and adults. Patients with prior meconium ileus are at increased risk of developing DIOS
Table 1. ESPGHAN CF Working Group definition for DIOS in cystic fibrosis

<table>
<thead>
<tr>
<th>No.</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Complete intestinal obstruction as evidenced by vomiting of bilious material and/or fluid levels in small intestine on an abdominal radiography</td>
</tr>
<tr>
<td>2</td>
<td>Fæcal mass in ileo-cæcum</td>
</tr>
<tr>
<td>3</td>
<td>Abdominal pain and/or distension</td>
</tr>
</tbody>
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Complete DIOS: 1, 2, and 3
Incomplete/impending DIOS: 2 and 3 without 1

CF = cystic fibrosis; DIOS = distal intestinal obstruction syndrome; ESPGHAN = European Society for Paediatric Gastroenterology, Hepatology, and Nutrition.

B. Pathogenesis/Pathophysiology
   1. Believed to result from a combination of retained mucofeculent material, abnormal intestinal secretions and abnormal intestinal motility, leading to impaction of stool in the terminal ileum, cecum and proximal colon
   2. Symptoms are complete or partial intestinal obstruction
   3. Occurs almost exclusively in patients with pancreatic insufficiency
   4. Risk factors for developing DIOS
      a. Patients on insufficient pancreatic enzyme replacement therapy – iatrogenic or noncompliance
      b. Opiates, anticholinergic agents
      c. Dehydration
      d. Change in diet (high fat)
      e. CFTR dysfunction (certain genetic factors are believed to play a role, although not fully understood)
   5. Insipissated intestinal contents in the distal ileum and proximal colon can often be palpated as masses in the right iliac fossa

C. Diagnosis
   1. Diagnosis rests on history and physical examination. Imaging studies are helpful in confirming the diagnosis, ruling out other conditions, and following up on response to treatment
   2. Clinical Picture
      a. Symptoms: crampy lower abdominal pain, abdominal distension, vomiting, bilious vomiting and anorexia
      b. Signs: palpable mass in the lower right quadrant sometimes present
   3. Imaging
      a. Ultrasound and CT scan can help confirm the diagnosis and rule out concomitant pathology
      b. Abdominal radiography shows air fluid levels in small bowel and retained stool in the ileum and cecum appearing as bubbly granular opacities
      c. The diagnosis is initially achieved with obtaining supine and erect abdominal films. If there is obstruction, one should suspect concomitant pathology

D. Treatment/Management
   1. In DIOS without complete intestinal obstruction, GI lavage with balanced isotonic solution containing polyethylene glycol (Go-Lytley™), which can be administered orally or through an NG tube
   2. Endpoint of lavage is to relieve the partial obstruction manifested by passage of stool, resolution of pain and mass
   3. Enemas using water-soluble contrast or N-acetylcysteine are used less frequently due to success of antegrade lavage
   4. After resolution of acute episode, optimize enzyme dose or improve compliance with enzyme replacement, increase fluid intake, add dietary fiber and use regular osmotic laxatives to prevent recurrence
5. In DIOS with intestinal obstruction (distension and bilious emesis), it is mandatory to exclude other complications
   a. In presence of obstruction or if washout therapy fails, gastrografin enemas can help outline the colonic pathology and can be useful to relieve impaction
   b. In resistant cases of obstruction, US should be done to rule out intussusceptions
   c. Persistent obstruction despite therapy may necessitate laparotomy, although this is rare in the absence of appendicitis or intussusceptions

6. In patients with recurrent DIOS, appendectomy placement for routine administration of osmotic agents is an option

E. Differential Diagnosis
   1. In the presence of fever and peritoneal signs, high index of suspicion should be present for inflammatory conditions. DIOS can occur in association with the conditions listed below adding to the complexity of this condition.
      a. Appendicitis
      b. Purulent mucocele of the appendix
      c. Intussusception
      d. Volvulus
      e. Constipation
      f. Crohn’s disease
      g. Small bowel perforation or fistula
      h. Colonic stricture
      i. Pancreatitis
      j. Ovarian conditions

F. Some CF patients will have chronic fecal retention and an acquired mega colon syndrome. They will have reduced bowel frequency and sometimes even rectal overloading, resulting in incontinence. Fecal retention is differentiated from DIOS by the fact that the fecal loading is distal. Treatment is with laxatives and ensuring adequate pancreatic supplements.

Recommended Reading


I. Chronic diarrhea is defined as diarrhea lasting >14 days. The differential is extensive and varies with the age of onset. History and physical exam are vital to identifying the correct diagnosis.

II. Antibiotic-associated diarrhea (AAD)
   A. Definition
      1. Unexplained diarrhea (2 unformed stools per day for 2 or more days) occurring between 2 hours and 2 months after starting antibiotics
   B. Prevalence
      1. 11% of children have AAD starting on average 5 days after starting antibiotics and lasting 4 days
      2. Most common antibiotics involved are amoxicillin/clavulanic acid (23%) and erythromycin (16%)
      3. Most common in children less than 2 years old
   C. *C. difficile* colitis is associated with 15%–20% of all cases of AAD
   D. Treatment
      1. Discontinuation or changing of antibiotics
      2. Anti-motility agents should be avoided
      3. Metronidazole or oral vancomycin for *C. difficile* colitis diarrhea
   E. Prevention
      1. Probiotics (*Saccharomyces boulardii* or *Lactobacillus GG*) may have some benefit

III. Chronic nonspecific diarrhea of childhood
   A. Definition
      1. Stool volume of >10 grams/kg/day in infants and toddlers, or >200 grams/day in older children for more than 14 days
   B. Manifestations
      1. Chronic diarrhea, normal growth and exam, no weight loss or bleeding per rectum. Usually pass stools only during waking hours
   C. Potential causes
      1. Low-fat diet
      2. High osmolality carbohydrate intake especially sorbitol and fructose
      3. Possible fast motility due to prostaglandin effect
   D. Treatment
      1. Decrease carbohydrates, increase fat in diet
      2. May use loperamide if necessary

IV. Protracted diarrhea of infancy
   A. Sucrase and lactase deficiency
      1. Autosomal recessive
         a. Sucrase-isomaltase deficiency (SI deficiency)
            1) Prevalence is 1 in 5,000 people of European descent
            2) More prevalent in Native populations of Greenland, Alaska and Canada
         b. Congenital lactase deficiency
            1) Extremely rare
      2. Diagnosis
         a. Hydrogen breath test, + stool reducing substances, response to clinical challenge, and eventually biopsy and disaccharidase testing
      3. Treatment
         a. Avoid sucrose in patients with SI deficiency and lactose in lactase deficiency
         b. Treat with sucrase or lactase depending on the deficiency
B. Congenital glucose-galactose malabsorption
   1. Autosomal recessive
   2. Mutations in Sodium-Glucose Luminal Co-Transporter (SGLT-1)
   3. Marked osmotic diarrhea in neonatal period with lactose, glucose or glucose polymer containing feeds
   4. Mild renal glucosuria
   5. Infants should receive fructose based formula

C. Electrolyte malabsorption
   1. Congenital chloridorrhea
      a. Presentation
         1) Echogenic loops of bowel can be seen on antenatal ultrasound
         2) Diarrhea and dehydration at birth
         3) Abdominal distention and fluid-filled loops
         4) Metabolic alkalosis (↓Na+, ↓Cl–)
         5) Stool Cl– level >90 mmol/L
      b. Etiology
         1) Caused by a defect in the DRA gene
            a) Adjacent to CFTR
         2) Due to defective chloride-bicarbonate exchange in the enterocyte brush border
         3) DRA encodes a chloride transporter in the chloride-bicarbonate exchange
      c. Treatment
         1) Replacement of NaCl and KCl

D. Primary epithelial defects –
   1. General onset in 1–2 weeks from birth
   2. Microvillous inclusion disease
      a. Presentation
         1) Severe secretory diarrhea and additional osmotic diarrhea after oral intake
            a) Severe diarrhea begins in first week
               i) 50–300 ml/kg if NPO
               ii) 100–500 ml/kg if taking orally
               iii) High sodium content (100 mmol/L)
            b) Causes profound intestinal failure
      b. Prevalence and etiology
         1) Most are of Turkish descent
         2) Likely due to a major defect in membrane trafficking in intestinal epithelial cells
            a) Gene recently defined - MYO5B
      c. Pathology (see Figure 1)
         1) Intracellular inclusions and secretory granules
         2) Microvilli are depleted on the apical epithelial surface
         3) Microvilli are present in intracellular inclusion bodies
         4) Crypt epithelium show secretory granules
         5) Light microscopy shows villous atrophy
         6) No marked crypt hypertrophy
         7) PAS shows PAS+ material in upper crypt and villous epithelium with absent brush boarder staining
         8) Treatment
            a) TPN
            b) Intestinal transplantation has had variable success
            c) Past unsuccessful therapies include Corticosteroids, somatostatin, epidermal growth factor
   3. Tufting enteropathy (TE)
      a. Presents with moderate to severe diarrhea in the first day of life
      b. Differential includes microvillus inclusion disease
      c. Pathogenesis
         1) Recently discovered to be due to mutations in the EpCAM gene (an epithelial cell adhesion molecule)
d. Pathology (Figure 2)
   1) Presence of tufts of extruding epithelial cells
   2) These tufts are usually seen after 2 years
   3) Total or partial villus atrophy, crypt hyperplasia and normal or slightly increased density of inflammatory cells in the lamina propria
   4) Tufting may be due to abnormal adhesion of enterocytes to the basement membrane
   5) Rounded epithelial cells at the tips of the villi and are no longer attached to the basement membrane

e. Treatment
   1) TPN
   2) Possible small bowel transplant
   3) General facts
      a) Tufting can be seen in the colon but without inflammation
      b) Severe GERD and malabsorption are associated

f. Other primary epithelial defects
   1) Intestinal αβ4 integrin deficiency
   2) Enterocyte heparan sulfate deficiency
   3) Syndromic diarrhea (unknown cause with multiple abnormalities)
   4. Enterokinase deficiency (EK deficiency)
      a. Presentation
         1) Diarrhea at birth
         2) Failure to thrive
         3) Hypoproteinemia
         4) Vomiting in 50% of patients
      b. Pathogenesis
         1) Enterokinase is secreted by the enterocytes of the intestinal mucosa
         2) Without enterokinase, trypsinogen is not adequately activated and protein absorption is impaired
         3) Thought to be a genetic disease but no gene identified currently
      c. Treatment
         1) Pancreatic enzyme replacement

5. Autoimmune enteropathy (See autoimmune enteropathy)
6. IPEX (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked)
   (See section on Autoimmune Enteropathy)

E. Villous atrophy
   1. Differential diagnosis
      a. Total – Celiac disease if intraepithelial lymphocytes present
      b. Partial – dermatitis herpetiformis, Giardia infection, absence of HLA expression/immunodeficiency status, bacterial overgrowth, food protein sensitization, protracted diarrhea, post-infectious diarrhea
   2. Diagnosis – TTG/antiendomysial Ab/antigliadin Ab (Celiac disease), dermal IgA deposits (dermatitis herpetiformis), Giardia in stool or biopsy (Giardiasis), HLA typing (absence of HLA), duodenal bacterial counts/H₂ breath tests (bacterial overgrowth), food challenge (protein sensitization), clinical history (protracted diarrhea)
Recommended Reading


I. Food allergies are adverse immune responses to food proteins. Allergy can be IgE or non-IgE mediated. Diagnosis can be challenging, particularly in non-IgE-mediated allergy.

II. Overview/Epidemiology
   A. IgE-mediated food allergy
      1. Affects 6%–8% of children <4 years of age and 2% of the general population
      2. IgE-mediated allergic reactions are rapid in onset and are most common in young children, with about 50% of reactions occurring in the first year of life
      3. Milk, soy, egg, wheat, fish and peanut account for more than 90% of IgE-mediated food allergy in children
      4. Because there is little homology between milk and soy proteins, people with IgE-mediated milk allergy are able to tolerate soy and vice versa
      5. Early IgE-mediated food allergy is associated with later atopic respiratory illness
      6. Diagnosis of IgE-mediated food allergy is based on typical history with confirmatory skin prick or RAST testing
         a. Routine broad testing for food allergy is not recommended
         b. Titer of IgE food antibodies does not predict severity of reactions
      7. IgG antibodies against food proteins are not adequate for confirming food allergy
   B. Non-IgE or cell-mediated food allergy
      1. Insidious onset
      2. Includes dietary protein-induced or eosinophilic protocolitits, eosinophilic esophagitis and allergic eosinophilic gastroenteritis
      3. High degree of cross-reactivity between milk and soy protein in sensitized individuals with food protein–induced enteropathy syndrome (FPIES). Reported prevalence 15%–50%
      4. FPIES is a severe cell-mediated, GI food hypersensitivity typically seen with cow’s milk and soy protein
         a. Has been described with many food proteins
         b. Presentation: from mild vomiting and/or diarrhea, to hematochezia, dehydration, lethargy and shock (hypovolemic)
         c. Diagnosis is clinical. Skin prick and RAST testing not useful to identify offending protein. Skin patch testing may have a role in diagnosis
         d. Management: avoidance of inciting protein and use of protein hydrolysate or elemental formula

III. Manifestations
   A. IgE-mediated food allergies
      1. Signs and symptoms are caused by mediator release from tissue mast cells and circulating basophils
      2. Extra-GI manifestations common in IgE-mediated food allergic reactions: urticaria, angioedema, rhinoconjunctivitis, gastrointestinal anaphylaxis and generalized anaphylaxis
      3. Other presentations
         a. Oral allergy syndrome (oropharyngeal pruritus)
         b. Food-dependent, exercise-induced anaphylaxis
   B. Non-IgE–mediated and mixed food allergies:
      1. Diarrhea, hematochezia, increased mucus production
      2. Vomiting, abdominal pain, dysphagia
      3. Eczema
      4. Anemia
      5. Poor weight gain/malnutrition
C. Diagnosis
   1. Positive responses on in vitro and in vivo tests do not always predict clinically relevant reactions in blinded food challenges
   2. History is key to diagnosis for both IgE and non-IgE-mediated reactions
   3. Confirmatory testing for IgE-mediated reactions
      a. RAST tests for food specific IgE
      b. Skin prick test – more specific than RAST
      c. Oral food challenge performed in setting equipped to treat anaphylaxis
   4. Associated lab tests present in some non-IgE-mediated reactions
      a. Elevated eosinophil count
      b. Stool WBC, eosinophils, culture, ova and parasites and C difficile toxin to exclude infectious causes
      c. Celiac serology
      d. Flexible sigmoidoscopy may demonstrate colitis in FPIES with increased lamina propria eosinophils and normal crypt architecture
      e. Upper endoscopy useful for diagnosis of eosinophilic esophagitis, eosinophilic gastroenteritis and celiac disease

IV. Treatment/Management
   A. IgE-mediated food allergies
      1. Dietary restriction
      2. Subcutaneous epinephrine, corticosteroids, anti histamines and H2 blockers for anaphylaxis
      3. Epinephrine auto-injectors (EpiPen) for management of accidental exposure
   B. For non-IgE-mediated food allergies:
      1. Dietary restrictions
      2. Protein-hydrolysate or elemental formula
      3. Majority of children are able to tolerate the inciting food protein by age 1–3 years

V. Role of Breastfeeding
   A. Breastfeeding infants at high risk of allergic disease for ≥4 months may prevent or delay occurrence of cow’s milk allergy and eczema during the first 2 years
   B. Current evidence does not support any role for maternal dietary restriction during pregnancy or lactation to prevent allergy
   C. Insufficient data to recommend any dietary intervention beyond 4–6 months of age in effort to prevent atopic disease
   D. Current recommendations allow any food after 6 months of age, except those likely to cause aspiration or choking

VI. Influence of Age
   A. Majority of childhood food allergies diminish with time
   B. Timing of resolution varies among patients and foods
   C. IgE-mediated food allergies:
      1. Cow’s milk and egg allergies usually outgrown during childhood and adolescence
      2. Peanut, tree nut and shellfish allergies more likely to persist into adulthood (20% of patients with peanut allergy lose sensitivity with time)
      3. Food-specific IgE levels decrease with time in most patients with food allergies. This loss is the best-known predictor of the development of clinical tolerance
      4. Non-IgE-mediated food allergies usually resolve by 1 year of age
VII. Mast Cells
   A. Derived from hematopoietic progenitor cells in bone marrow
   B. Maturation and differentiation occurs in tissues under the influence of growth factors
   C. Found in all vascularized tissues and abundant in host-environment interfaces of skin and mucosal surfaces
   D. Mast cells classified by protease content
      1. Tryptase-containing mast cells found in mucosal tissues of intestine and respiratory tract
      2. Tryptase and chymase-containing mast cells found in connective tissues of skin, submucosa and muscularis propria of GI tract
   E. Mast cells are active in both IgE and non-IgE–mediated food allergy
   F. Antigen cross-linking of high affinity IgE receptors (FcεR1) on surface of mast cells causes degranulation and mediator release → allergic reactions
   G. Eosinophil-derived proteins also induce mast cell degranulation and probably mediate changes seen in eosinophilic esophagitis

Recommended Reading


I. Many endocrine disorders have gastrointestinal manifestation and complications. The underlying etiology for the gastrointestinal symptoms is not always known, but is likely due to hormone interactions with the organs of the digestive system. Thyroid dysfunction and diabetes are the most common endocrine disorders causing GI symptoms in children.

II. Hypothyroidism:
   A. Esophageal dysfunction
      1. Decreased LES pressure and low amplitude peristalsis cause dysphagia and reflux
      2. Local esophageal compression from goiter causes dysphagia
   B. Gastric dysfunction
      1. Pernicious anemia and hypochlorhydria secondary to parietal cell antibodies
      2. Delayed gastric emptying due to smooth muscle dysfunction, incoordination of antrum and duodenum, and/or pylorospasm
   C. Small bowel dysmotility
      1. Small intestine bacterial overgrowth. Improves with antibiotics but not with treatment of thyroid disease
   D. Colon dysfunction
      1. Delayed colon transit time. Oro-cecal transit time is usually normal
      2. Diminished motility of all hollow viscera occurs in myxedema. Usually reverses with treatment. Can result in paralytic ileus, megacolon, pseudo-obstruction, volvulus and ischemia
   E. Other
      1. Ascites may be associated with pleural and pericardial effusion. Due to increased capillary permeability

III. Hyperthyroidism
   A. Gastric Dysfunction
      1. Gastric emptying can be rapid, normal or delayed. All improve with treatment
      2. Reduced gastric acid secretion in 33%–37% of patients with thyrotoxicosis due to antiparietal cell antibodies
      3. Hypergastrinemia
         a. Possibly due to hypersensitivity of beta-receptors
         b. Response to low acid production
   B. Small Bowel Dysfunction
      1. Diarrhea due to low trypsinogen, bile acid output and rapid orocecal transit

IV. Cushing syndrome
   A. Main complications are central or generalized obesity, failure of longitudinal growth, hirsutism, weakness, nuchal fat pad, acne, striae and hypertension due to glucocorticoid excess. Patients may develop gastrointestinal complications of diabetes mellitus
V. Adrenal insufficiency (Addison disease)
   A. Gastric Dysfunction
      1. Symptoms: anorexia, weight loss, nausea, vomiting, diarrhea and abdominal pain
      2. May be associated with cyclic vomiting syndrome
      3. Associated with atrophic gastritis, achlorhydria and pernicious anemia
   B. Small Bowel Dysfunction
      1. Malabsorption, diarrhea, FTT due to functional defects in enterocyte
      2. Reversed with glucocorticoid therapy
   C. Liver dysfunction – Chronic elevation of aminotransferases

VI. Hypoparathyroidism
   A. Small bowel dysfunction
      1. Steatorrhea and malabsorption may be earliest sign of hypoparathyroidism.
         Hypocalcemia causes CCK release, gallbladder contraction and pancreatic enzyme release
      2. Diarrhea normalizes with correction of hypocalcemia and vitamin D therapy
      3. Must rule out magnesium deficiency which can also present with malabsorption and functional hypoparathyroidism

VII. Hyperparathyroidism – Sporadic adenoma, MEN type 1 or 2
   A. Gastric Dysfunction
      1. Colonic or gastric atony secondary to increased serum calcium and reduction in neuromuscular excitability cause nausea and vomiting
      2. Peptic ulcer disease due to gastric acid hypersecretion
   B. Colon Dysfunction
      1. Constipation due to colon or gastric atony secondary to increased serum calcium
   C. Acute pancreatitis occurs in 1.5% of patients with primary hyperparathyroidism

VIII. Diabetes Mellitus
   A. Pathogenetic factors in GI symptoms
      1. Autonomic neuropathy
      2. Hyperglycemia
      3. Neurovascular insufficiency
      4. Autoimmune damage
      5. Neurohormonal growth factor deficiency
   B. Gestational Diabetes
      1. Increases risk of abortion, macrosomia with increased heart and liver size, IUGR, hypoglycemia, jaundice secondary to polycythemia, and cardiomyopathy
      2. Neonatal small left colon syndrome produces postnatal obstructive symptoms
   C. Esophageal Dysfunction: Rare
      1. LES pressure, peristaltic amplitude and simultaneous a peristaltic contraction attributed to diabetic autonomic neuropathy (DAN) of vagus and motor nerves
      2. Increased risk of GERD
      3. ↑ risk of candida esophagitis
   D. Gastroparesis – rare in children, but occurs in 58% of adults
      1. Solid emptying most frequently impaired
      2. Due to antral dysrhythmia, abnormal gastroduodenal pressure, prolonged pyloric contractions limiting gastric outflow. Exacerbated by hyperglycemia
      3. Symptoms – postprandial epigastric discomfort, bloating, nausea, vomiting, indigestion, early satiety and weight loss
         a. Some medications worsen gastroparesis – anticholinergics, TCAs, benzodiaezepines and ganglionic-blocking agents
      4. Management
         a. Improve glycemic control
         b. Medical therapy
            1) Antiemetics
            2) Low-dose tricyclic antidepressants (reduce visceral hypersensitivity)
            3) Promotility agents – metoclopramide, domperidone, erythromycin
            4) Grehlin
         c. Gastric pacing for refractory gastroparesis
E. Acute erosive gastritis occurs in diabetic ketoacidosis
F. 15%-20% of patients with DM 1 have antiparietal cell antibodies, autoimmune chronic gastritis with pernicious anemia, iron deficiency anemia, hypochlorhydia and hypergastrinemia
G. Small bowel dysfunction – diarrhea is the main symptom
   1. Due to coexistent celiac disease, pancreatic insufficiency, bacterial overgrowth, drug therapy, islet cell tumor or fecal incontinence
   2. Drugs causing diarrhea - metformin, acarbose and miglitol (inhibit breakdown of oligosaccharides to monosaccharides in brush border)
   3. Diarrhea worse with poorly controlled type 1 DM with DAN
H. Colon Dysfunction
   1. Incontinence
      a. Usually in the setting of diabetic diarrhea
      b. Steatorrhea in 30% of patients
      c. Autonomic dysfunction – impaired internal anal sphincter resting tone and reflexive internal sphincter relaxation
   2. Constipation
      a. Related to DAN. Complicated by megacolon, pseudo-obstruction, stercoral ulcer, perforation, volvulus and overflow diarrhea
I. Biliary tree and liver
   1. Increased risk of cholelithiasis, cholecystitis, cholangitis
   2. Elevated transaminase levels
   3. Mauriac syndrome: hepatomegaly with increased glycogen, hypoglycemia, dwarfism and cushingoid appearance. Results from chronic elevation of serum glucose and excess hepatic glycogen
   4. Nonalcoholic fatty liver disease
J. Pancreas
   1. Increased prevalence of acute pancreatitis and exocrine pancreatic insufficiency
   2. New onset DM may be first sign of pancreatic cancer

Recommended Reading


12I. Secretory Tumors Affecting the GI Tract

Christopher J. Moran, MD
Brigitte Moreau, MD
Aubrey Katz, MD

I. Zollinger-Ellison syndrome (ZES)
   A. Syndrome of hypergastrinemia and gastric acid hypersecretion usually secondary to gastrin-secreting tumor
      1. Prevalence 1–3 per million
      2. Usually diagnosed in adults, but cases as young as 7 years old are reported
      3. 20% of mutations are inherited; 80% are de novo mutations
      4. Responsible for <1% of peptic ulcer disease
   B. Typical clinical findings
      1. Medically refractory peptic ulcer disease (usually duodenal) in 90%
      2. Most common finding is small solitary ulcer in proximal duodenum
      3. 80% have diarrhea due to acid interference with fat absorption and high-volume gastric secretions
      4. Suspect ZES in cases of recurrent ulcers or ulcers in abnormal locations
      5. 90% have prominent gastric folds
      6. Gastric histology shows gastritis and enterochromaffin cell hyperplasia
   C. Primary gastrinoma
      1. Located in duodenal wall (70%), pancreas (20%) or lymph nodes (10%)
      2. Pancreatic tumors are usually larger than tumors in other sites with highest malignant potential and highest gastrin levels
      3. Gastinomas also secrete smaller amounts of VIP and glucagon
      4. Metastasis occurs in >60%, most commonly to liver
   D. Diagnosis (See Figure 1)
      1. Diagnostic: fasting gastrin level >1,000 pg/mL (basal or after pentagastrin) or 10x upper limit of normal
      2. Suggestive: gastrin level between 15–1000
         a. Hypergastrinemia secondary to PPI use may produce elevations between 15–1000. Re-evaluate after discontinuing PPI
      3. Secretin stimulation helps clarify the source of intermediated gastrin elevation
         a. Secretin causes dramatic rise in serum gastrin in ZES
         b. Secretin inhibits gastrin secretion in normal individuals
      4. Elevated chromogranin A is suggestive of gastrinoma
         a. Chromogranin A is secreted from enterochromaffin cells and is a measure of enterochromaffin cell mass
         b. Hypergastrinemia induces enterochromaffin cell hyperplasia
         c. Chromogranin A may be elevated in other neuroendocrine tumors
      5. Radiographic localization recommended
         a. Somatostatin receptor scintigraphy is most sensitive
         b. CT or MR have poor sensitivity especially for small lesions
         c. Endoscopic ultrasound may reveal tumors in bowel wall or head of pancreas
   E. Treatment:
      1. Very high-dose PPI (60–80 mg/day) is usually effective for ulcer healing and prevention
      2. Because of the risk of malignancy, resection is recommended for localized tumors
At least 8 h fast

![Flowchart](image)

**Figure 1.** Evaluation for Gastrinoma

**Causes of hypergastrinemia**

I. Achlorhydria with compensatory hypergastrinemia  
   a. Pernicious anemia  
   b. Atrophic gastritis  
   c. Gastric ulcer  
   d. Vagotomy  
   e. H pylori infection  
   f. PPI therapy

II. Hypergastrinemia with gastric hypersecretion  
   a. Gastrinoma  
   b. Renal failure  
   c. Retained antrum  
   d. Antral G cell hyperplasia  
   e. Pheochromocytoma  
   f. Hypercalcemia  
   g. Duodenal ulcer  
   h. Pyloric obstruction with gastric retention
II. Multiple endocrine neoplasia Type 1
   A. Syndrome with parathyroid (95%), anterior pituitary and pancreatic tumors
   B. ZES occurs in 60% of MEN 1 cases
      1. It is presenting symptom in 40% of those cases
      2. Associated with duodenal gastrinomas
   C. Pancreatic tumors include gastrinoma, insulinoma, non-secreting tumors
   D. Autosomal-dominant inheritance
   E. Surgical resection of gastrinomas associated with MEN 1 is less effective than resection of gastrinomas not associated with MEN
      1. MEN gastrinomas are usually multifocal and difficult to eradicate
      2. Malignant potential of MEN gastrinomas is less than that of sporadic gastrinomas

III. VIPoma
   A. Neuroendocrine islet cell tumor produces vasoactive intestinal peptide
      1. VIP secretion is under neural control, which is lost in VIPoma
      2. Extrapancreatic VIP-secreting tumors include ganglioneuromas, ganglioneuroblastomas, neurofibromas and neuroblastoma
      3. VIP hypersecretion causes cAMP-mediated secretory diarrhea
      4. VIP also blocks gastric acid secretion causing hypokalemia and hypochlorhydria
   B. Incidence in adults is 1–10 per million. Incidence in childhood not established.
   C. In childhood cases, average age of onset <5 years old (adult onset near 40 years old)
      1. No sex predominance in children
      2. 75% of adult patients are female
   D. Rarely is found in patients with MEN
   E. 90% of VIPomas in adults are found in tail of pancreas
      1. Other sites: sympathetic ganglia, colon, bronchus, adrenals, liver
      2. Common locations for children: adrenals and sympathetic ganglia
         a. Children are more likely than adults to have extrapancreatic tumors
      3. 60% of adult VIPomas have metastasized at diagnosis
         a. Metastasis at diagnosis rare in children
   F. Symptoms: secretory diarrhea, hypokalemia, facial flushing (20%)
      1. 20–50 mL/kg/day of stool when kept NPO
      2. Hypercalcemia occurs due to a PTH-like effect by VIP
   G. Diagnosis:
      1. Serum VIP level >75 pmol/L (nl <20). Most VIPomas have serum levels ~200 pmol/L
      2. Testing must be done while patient is symptomatic, as serum levels vary widely
      3. Should screen for primary tumor and metastases with MR or CT
   H. Treatment:
      1. Increased fluids
      2. Octreotide highly effective due to inhibition of neuroendocrine protein secretion
      3. Glucocorticoids may slow diarrhea although mechanism unclear
      4. Consider surgical resection if no metastasis

IV. Carcinoid tumors
   A. Incidence: 1.5 per million
   B. 50% of all GI neuroendocrine tumors
   C. Commonly found in GI tract (67%)
      1. Ileum 28%
      2. Appendix and rectum are minor sites
   D. Can secrete many hormones (serotonin, histamine, gastrin, insulin, secretin, dopamine, VIP)
   E. Carcinoid syndrome
      1. Occurs in <10% of GI carcinoid tumors
      2. Rarely occurs when tumor limited to GI tract, because secreted hormones enter portal circulation and are inactivated in the liver
      3. Carcinoid syndrome occurs when there are hepatic metastases
4. Symptoms of carcinoid syndrome
   a. Flushing in 85% starting on face and neck lasting <30 seconds
   b. diarrhea
   c. bronchospasm
   d. GI mass effects – obstruction, perforation
   e. Carcinoid crisis – severe diarrhea, hypotension and flushing
   f. Peptic ulcer if tumor secretes histamine

F. Diagnosis:
   1. Elevated plasma chromogranin A or serotonin
   2. Elevated urinary 5-HIAA (24-hour collection)
   3. Bananas, pineapples, walnuts, tomatoes may elevate 5-HIAA
   4. Localization by CT or octreotide scintigraphy

G. Treatment:
   1. Surgical excision for isolated tumor
   2. If diffuse, octreotide is effective for flushing and diarrhea
   3. Carcinoid crisis: octreotide and volume resuscitation
   4. Avoid catecholamines as they provoke further mediator release from tumors

V. Systemic mastocytosis
   A. Elevated histamine levels secondary to increased mast cell numbers
   B. Activating mutation in c-kit tyrosine kinase receptor that regulates mast cell proliferation
   C. Non-GI symptoms: flushing, reactive airways wheezing, pruritus, neuropsychiatric
      1. Urticaria pigmentosa is the most common skin manifestation
      2. Worsens with hot showers, stress, certain foods, local trauma, medications
   D. Ulcers in 23% (GI complaints in 50%-80%, pain and diarrhea common)
      1. Duodenitis or duodenal ulcer is the most common finding
      2. Ulcers most likely due to histamine-induced acid hypersecretion
   E. Patients do not always have typical skin findings
   F. Can have urticarial nodules (mast cell infiltrates, edematous)
   G. Treat with acid blockade and antihistamine
      1. Trigger avoidance
      2. Steroids or mast cell stabilizers may be used in patients with malabsorption

Recommended Reading


Sokol H. Gastrointestinal involvement and manifestations in systemic mastocytosis. IBD. 2010;16(7):1247-1253.

I. Graft-vs-host disease (GVHD) is a common complication of hematopoietic stem cell transplantation. It is a clinical syndrome that requires synthesis of clinical, laboratory, and histopathologic findings for diagnosis.

II. Acute Graft vs Host Disease (aGVHD)
   A. Definition: Occurs before day post transplant 100
   B. Risk: Between 8%–85%
   C. Pathogenesis: Transplanted donor T lymphocytes recognize antigenic disparities between host and donor. Activation of T-cells is one step in complex process. Effect is mediated by dysregulated cytokine (IL-2, IFN-γ) release by other cells, which leads to tissue damage. Finally, activated T-cell mediate cytotoxic damage against host cells
   D. Findings/Progression: Skin to liver to GI tract (Table 1)
      1. Skin: Most common involved organ
         a. Manifestation: maculopapular rash, usually occurring at or near the time of the white blood cell engraftment (Figures 1 and 2). In severe GVHD, the maculopapular rash forms bullous lesions with toxic epidermal necrolysis
      2. Liver: second most commonly involved organ (see VOD vs GVHD)
         a. Manifestation: abnormal liver function tests, with the earliest and most common finding being a rise in the serum levels of conjugated bilirubin and alkaline phosphatase
         b. Pathology: damage to the bile canaliculi, leading to cholestasis
         c. Histology: Extensive bile duct damage (e.g., bile duct atypia and degeneration, epithelial cell dropout, lymphocytic infiltration of small bile ducts), leading to occasionally severe cholestasis (Figures 3 and 4)
      3. Luminal tract: third most common organ, described as a distinct entity initially in older patients
         a. Upper GI Tract: more responsive to immunosuppressive treatment than lower tract aGVHD
            1) Manifestations: anorexia, dyspepsia, food intolerance, nausea and vomiting
            2) Diagnosis: upper GI tract endoscopy and biopsies (Figures 5a and 5b)
         b. Lower GI Tract: the most severe and difficult to treat and may involve any location throughout the lower gastrointestinal tract
            1) Manifestations: Profuse secretory diarrhea and ileus
         c. Endoscopy/Colonoscopy: Findings do not correlate well with histopathologic findings and range from apparently normal mucosa to severe ulceration (Figure 6)
            1) Visible endoscopic lesions are found in a minority of cases (16%–32%) but when present, the most frequently described endoscopic findings are mucosal edema, erythema and friability; erosions and ulcers are less frequently encountered
         d. Histopathology:
            1) Apoptosis in the regenerative compartment of gland or crypts containing intracytoplasmic vacuoles filled with nuclear dust and other karyorrhectic debris and have been described as exploding crypt cells
            2) Scattered eosinophils and neutrophils in more severely affected tissue
            3) Cystic dilatation of glands or crypts, crypt abscesses, frank epithelial destruction has been noted (Figure 7)
E. Prevention/Treatment: immune suppression
   1. Steroids: 55% response rate
   2. Nonresponders receive second-line therapy, which includes high-dose steroids, cyclosporine, FK506 and mycophenolate mofitil

III. Chronic Graft vs Host Disease (cGVHD)
   A. Definition: after 100 days or as an extension of aGVHD, following resolution of aGVHD, or can occur de novo
   B. Risk: 10%–30% with related donor and 40%–50% with an unrelated donor. 25%–40% of long-term bone marrow transplant develops cGVHD 3–12 months after engraftment
   C. Pathophysiology: poorly understood and may be due to both allo- and autoreactive T cells
   D. Findings (Table 2)
     1. Skin: lichen planus (Figure 8) and sclerodermatous-like (Figure 9) manifestations
     2. Liver: biopsy usually shows extensive damage to small bile ducts (Figure 10) and, in severe cases, ductopenia; in patients receiving no, or tapering doses of, immunosuppression, liver GVHD may also present as an acute hepatitis
     3. Luminal: multisystemic and proceeded by acute GVHD (88%)
        a. Upper GI tract: sclerodermatous-like findings/symptoms
        b. Lower GI tract: chronic diarrhea, malabsorption, fibrosis of the submucosa and sclerosis of the intestine may be observed
           1) Often requires parenteral nutrition to maintain growth and nutritional status
   E. Treatment: combination therapy with prednisone and either cyclosporine or FK506 (see section on VOD vs GVHD)

<table>
<thead>
<tr>
<th>Skin Clinical</th>
<th>Liver Lab</th>
<th>Gastrointestinal Tract Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maculopapular rash (distal to proximal progression)</td>
<td>Hyperbilirubinemia</td>
<td>Secretory diarrhea</td>
</tr>
<tr>
<td>Erythroderma</td>
<td>Elevated alkaline phosphatase</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Bullae</td>
<td>Elevated liver transaminases</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Desquamation</td>
<td></td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GI bleeding</td>
</tr>
</tbody>
</table>

| | Histology | | Histology |
| | Lymphocytic infiltration | Intraepithelial lymphocytes in the absence of portal inflammation | Epithelial cell apoptosis |
| | Damage to interlobular bile ducts (dilatation of the ducts, flattening, vacuolization of the duct epithelium) | Occasional apoptotic cells and canalicular cholestasis within the lobules | |
| | Mucosal/submucosal edema | Rapid barium transit time | Non-bleeding ulcers |
| | Loss of haustral folds | Ileus | |
| | | Colonscopy | | |

Table 1. Typical Findings Associated With aGVHD
### Table 2. Typical Findings Associated With cGVHD

<table>
<thead>
<tr>
<th>Skin</th>
<th>Liver</th>
<th>Gastrointestinal Tract</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td><strong>Clinical</strong></td>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>• Lichenoid eruption (erythematous, papular)</td>
<td>• Hyperbilirubinemia</td>
<td>• Anorexia</td>
</tr>
<tr>
<td>• Sclerodermatous-dermis and/or fascia (thickened, tight, fragile)</td>
<td>• Elevated alkaline phosphatase</td>
<td>• Mouth/esophagus</td>
</tr>
<tr>
<td>• Joint contractures, severe disability</td>
<td>• Elevated liver transaminases</td>
<td>• Pseudomembrane</td>
</tr>
<tr>
<td>• Hypo or hyperpigmentation</td>
<td><strong>Other</strong></td>
<td>• Dysphagia</td>
</tr>
<tr>
<td>• Blister from poor lymphatic, ulcers from trauma</td>
<td>• Portal hypertension</td>
<td>• Odynophagia</td>
</tr>
<tr>
<td>• Hyperkeratosis pilaris</td>
<td>• Lobular hepatitis</td>
<td>• Sclerodermatous-like symptoms</td>
</tr>
<tr>
<td>• Hair loss, destruction of sweat glands</td>
<td>• Occasional apoptotic cells and canalicular cholestasis within the lobules</td>
<td>• Pancreatic insufficiency</td>
</tr>
<tr>
<td>• Premature graying of hair, eyebrows, lashes</td>
<td></td>
<td>• Lower GI tract</td>
</tr>
<tr>
<td>• Nails: vertical ridges, cracking</td>
<td></td>
<td>• Diarrhea</td>
</tr>
</tbody>
</table>

**Histology**
- Lobular hepatitis
- Occasional apoptotic cells and canalicular cholestasis within the lobules

**Gastrointestinal Tract**
- Portal hypertension
- Epithelial cell apoptosis

---

**Figure 1.** Painful red to violaceous maculopapular rash consistent with aGVHD in a 2-year-old girl involving the sole of the foot 11 days after HLA-nonidentical BMT.

**Figure 2.** Erythema and desquamation before treatment for aGVHD, day 27.
Figure 3. Hepatic GVHD, day 35. Portal spaces have extensively damaged bile ducts (arrows) with focally necrotic epithelium, nuclei of irregular size and shape, segmental loss of nuclei, shrinking of ductular lumens and an eosinophilic syncytium of cytoplasm.

Figure 4. Liver Histology: The graft versus host disease (GVHD) here is affecting the liver, and marked by yellow-brown collections of bile within the canaliculi, as well as chronic inflammatory cells within the liver parenchyma.

Figure 5a. Gastric biopsy with GVHD, day 35. Of all upper endoscopic biopsy sites, the most frequently showing histologic changes of GVHD is the stomach. In the area shown here, large numbers of lymphocytes infiltrate the lamina propria and the basilar portions of the gastric crypts. There is apoptosis of crypt epithelial cells and frank early crypt destruction. Inflammation and apoptosis of this intensity are not required for the diagnosis of GVHD.

Figure 5b. Gastric GVHD in which the severe mucosal erythema, edema, and erosion seen endoscopically on the left are more striking than the focal, mild, epithelial apoptosis (arrow) in the histological section on the right. Although a lymphocytic infiltrate is absent, apoptosis in multiple crypts is consistent with GVH activity. Inflammation may have been partially controlled by immunosuppressive therapy.
Figure 6. (Left) aGVHD lower GI tract: Endoscopic photograph of several linear, non-bleeding ulcers located in the distal colon. These ulcers represent findings in a patient, status post-bone marrow transplantation, who developed graft versus host disease.

Figure 7. (Below) aGVHD lower GI tract. A: Colonic biopsy with GVHD. Focal crypt abnormalities (crypt size variation and irregular crypt distribution) with decreased mucosal thickness [x]. Inset: Ectatic vessels [y] and slightly dilated crypt [z] with mild decrease in number of lymphocytes in LP. B: Colonic biopsy with GVHD, crypt abnormalities with focal ulceration [A], focal reactive surface epithelium [b], focal fibrosis [C], and many apoptotic cells in crypts [d].

Figure 8. Lichen planus-like chronic GVHD before treatment, day 220.
Recommended Reading


Colon GVHD: NASPGHAN.org; 2010.


Klatt EC. Immunopathology, Graft versus Host Disease Liver Cholestasis Microscopic: University of Utah; 2010.

**Figure 9.** Generalized scleroderma with atrophy, sclerodactyly, and joint contracture, day 540 after HLA-identical BMT.

**Figure 10.** Chronic GVHD at day 184 post-transplant: high-power view of a portal area, with damaged small bile ducts (arrows) infiltrated by lymphocytes.
12K. Drug-induced Bowel Injury

Razan Alkhouri, MBBS
Susan S. Baker, MD, PhD

I. Introduction
Drugs can cause bowel injury via different mechanisms, including mechanical injury, as seen in pill esophagitis, by cell death as seen in chemotherapy, by reduction in protective prostaglandins as is seen with NSAIDS, by changes in motility as is seen with erythromycin, chemotherapy and opioids, and by changes to bowel flora.

II. Pill Esophagitis
Refers to damage to the esophageal mucosa caused by impaction of a swallowed tablet or capsule with subsequent release of concentrated drug. The majority of injuries occur without underlying esophageal disease.

A. Incidence: 10,000 cases/year in the United States
B. Symptoms include dysphagia, odynophagia, and acute onset retrosternal chest pain. Rarely perforation and stricture
C. Drugs most commonly associated with esophageal injury:
1. Antimicrobials (Doxycycline, Tetracycline, Oxytetracycline, Minocycline, Penicillin, Ampicillin, Zidovudine)
2. NSAIDs and Salicylates
3. Others (Bisphosphonates, Potassium chloride, Ferrous sulfate, Corticosteroids, Theophylline, Quinidine)
D. Risk factors for esophageal ulcer or esophagitis include large capsules, assumption of supine position immediately after ingestion, inadequate liquid taken with medication causing slow passage of medication
E. Diagnosis confirmed by upper endoscopy
F. Differential includes herpetic or other acute esophageal infection, unrecognized foreign body
G. Treatment
1. Stop the offending medication
2. Carafate or gastric antisecretory medication may relieve pain until spontaneous healing occurs
H. Complications
1. Severe, but rare complications include esophageal stricture, esophageal perforation with massive hemorrhage or mediastinitis

III. Chemotherapy
A. Chemotherapeutic agents cause mucosal ulceration and inflammation throughout the gastrointestinal tract by causing death of rapidly dividing cells of the mucosal surface
B. Most common agents to cause mucosal damage are methotrexate, vinca alkaloids, dactinomycin, doxorubicin and bleomycin
C. Symptoms include abdominal pain, diarrhea, vomiting, melena and protein-losing enteropathy
D. Treatment is mostly supportive. Folinic acid rescue (leucovorin) can be used during or after treatment with methotrexate to prevent some toxicity

IV. Nonsteroidal Anti-Inflammatory Drug (NSAID) Ulceration
A. Ulcers induced by NSAIDs occur anywhere in the GI tract, but are most common in the stomach, duodenum and small bowel
B. Slow release NSAIDs shift the target site of damage from stomach to distal intestinal tract. Distal intestinal ulcers may cause intestinal perforation in adults
C. NSAIDS cause damage by inhibiting cytochrome oxidase (COX) in the mucosa of GI tract, thus reducing synthesis of protective prostaglandins
D. Risk factors: old age, previous history of ulcers, high-dose NSAID and concomitant use of steroids or anticoagulants. Among pediatric patient, preterm neonates are at highest risk of NSAID-associated intestinal perforation
E. COX-2 inhibitors reduce the risk of mucosal damage, but are not effective in treating NSAID-associated dyspeptic symptoms in adults
F. Misoprostol, proton pump inhibitors, H2 blockers and nitrous oxide are used to counteract the ulcerogenic effects in the stomach and duodenum

V. Nonsteroidal Anti-Inflammatory Drug (NSAID) Strictures
A. Reported in adults only in the small intestine and colon after prolonged NSAID
B. Occurs in the absence of prior ulceration or perforation

VI. Nonsteroidal Anti-Inflammatory Drug Enteropathy
A. Poorly defined entity with variable disturbance of the small intestinal function in the absence of macroscopic lesions
B. Mechanism unclear, but inflammation and increase in intestinal permeability may be causative
C. Symptoms of NSAID enteropathy result from chronic blood loss, protein-losing enteropathy and lipid malabsorption

VII. Nonsteroidal Anti-Inflammatory Drug Colitis
A. Watery or bloody diarrhea associated with NSAID use >6 months
B. Colon biopsies may show eosinophilic, collagenous or pseudomembranous colitis
C. NSAIDs may activate inflammatory bowel disease, especially ulcerative colitis, possibly via inhibition of COX, which produces a shift in the arachidonic pathway toward the production of proinflammatory cytokines

VIII. Prostaglandin E1 (PG E1)
A. PG E1 is used to sustain circulation dependent on ductus arteriosus in neonates with heart disease
B. Causes diarrhea and antral hyperplasia without pyloric stenosis. Gastric outlet obstruction may occur

IX. Erythromycin
A. Erythromycin is a gastrointestinal prokinetic that stimulates motilin receptors, causing contractions of stomach and intestines
B. Erythromycin administration within the first 2 weeks of life increases the risk of pyloric stenosis by 7–10-fold
C. Maternal use of erythromycin during pregnancy or lactation does not increase the risk of pyloric stenosis
D. No other macrolide is linked to pyloric stenosis
E. Most common symptom associated with erythromycin is crampy abdominal pain

X. Dexamethasone
A. Associated with gastric and small intestinal perforation in premature infants
B. Dexamethasone used with indomethacin may increase the risk of intestinal perforation

XI. Antibiotic-associated diarrhea
A. Most antibiotic-associated diarrhea is watery, nonspecific and self-limited
B. *Clostridium difficile*
   1. Causes ~20% of antibiotic-associated diarrhea
   2. Onset from 4–18 days after first dose of antibiotic
   3. Bloody diarrhea with fever, leukocytosis, abdominal pain and, rarely, signs of peritonitis may occur
   4. Causative agents are cytotoxins A and B produced by this organism. Toxins A and B can be detected in stool by immunoassay or observation of cytotoxic effect on cultured cells. Organisms can be cultured from stool
   5. Colonoscopy shows patchy adherant plaques of white cells and fibrin with apparently normal intervening mucosa
   6. Histology shows cryptitis with microscopic volcano eruptions of white cells. Most likely mechanism is a change in bacterial flora caused by antibiotics or other drugs. Stasis caused by drugs or surgery is another risk factor
7. Mild pseudomembranous colitis resolves on discontinuing offending antibiotic. Severe cases require fluid resuscitation and intravenous metronidazole or oral vancomycin. Relapse occurs in up to 67% of cases.
8. Diarrhea with *Clostridium difficile* may be the first manifestation of underlying inflammatory bowel disease.
9. Infants under 12 months may have *Clostridium difficile* or its toxins in stool, but do not develop pseudomembranous colitis.

**XII. Drug-induced intestinal hypomotility**

A. Most common agents are vincristine, anticholinergics or drugs with anticholinergic properties (tricyclic antidepressants, opioids).
B. Symptoms of intestinal hypomotility – nausea, emesis, constipation, bloating occur within 2–3 days of therapy.
C. Vincristine causes hypomotility by damaging the myenteric plexus. The impact is aggravated by simultaneous use of itraconazole.
D. Anticholinergics cause hypomotility by interfering with nerve conduction in the bowel.
E. Discontinuation of drug usually effective within 2 weeks, but vincristine sometimes causes prolonged symptoms.

**XIII. Neutropenic enterocolitis: typhlitis and ileocecal syndrome**

A. Severe inflammation leading to necrosis in cecum, ascending colon and terminal ileum most commonly in oncology patients receiving chemotherapy.
B. Severe granulocytopenia, fever, nausea, vomiting, diarrhea and abdominal pain.
C. Perforation, peritonitis and sepsis can occur.
D. Imaging shows fluid-filled lumen, pneumatosis or cecal wall thickening.
E. Treatment: triple antibiotics, supportive measures and surgery in case of complications or perforation.

**Recommended Reading**


12L. Radiation-induced Injury

Ala Shaikhkhalil, MD
Brendan Boyle, MD

I. Overview/Epidemiology
A. Radiation therapy for abdominal malignancies in children is rarely used. Current indications include: leukemia, intracranial malignancy, Wilms tumor and preparation for bone marrow transplant
B. The incidence of radiation enteritis in adults receiving abdominal radiation therapy is 2.5%–25%
C. Children are more prone to the acute effects of radiation therapy because of actively growing tissues. In one study of children with total body irradiation and chemotherapy, 74% developed GI symptoms acutely and 36% developed GI symptoms chronically

II. Pathogenesis/Pathophysiology
A. Radiation induced injury is described as either acute or chronic
B. Intestinal injury is related to the physical characteristics of radiation exposure: dose rate, total dose and fractionation, field size and type of irradiation
C. Acute injury contributes to the chronic effects of radiotherapy by several mechanisms
   1. Radiation produces free radicals in tissue water disrupting DNA and causing cell death
   2. The earliest impact of radiation on gut epithelium is in crypt cells (most rapidly dividing cells)
   3. Cellular response to radiation is influenced by the phase of division cycle. Cells are most sensitive to radiation in mitotic (cell division) and G2 (DNA synthesis) phases
   4. Other modifiers of intestinal radiation injury are tissue perfusion (hypoxic cells are resistant), pancreatic secretions (exacerbate radiation-induced damage), cellular expression of different molecules (that can be cytoprotective against programmed cell death) and platelet adherence to vascular wall (resulting in occlusion of the vascular lumen)
D. Late complications of radiotherapy are related to vascular and connective tissue changes (these cells are less mitotically active and less radiosensitive, hence the later effects). Obliterative endarteritis causes ischemia. Vasculopathy causes progressive fibrosis leading to strictures
E. Microscopic abnormalities in radiation damaged bowel:
   1. Increased apoptotic bodies
   2. Decreased mitotic bodies
   3. Shortened villi with concomitant loss of disaccharidases
   4. Crypt abscesses (containing high eosinophils suggesting an allergic-type response)

III. Clinical features
A. Classified as early, chronic and very late
B. Location of radiation determines GI tract involvement
   1. Thoracic irradiation causes esophageal symptoms
   2. Abdominal irradiation causes small bowel involvement
   3. Pelvic irradiation leads to damage in distal small bowel and colon
C. Some chemotherapeutic agents increase the risk of enteritis
   1. 5-fluorouracil, methotrexate and actinomycin D
   2. These agents are generally avoided in current radiation therapy
D. Small bowel is relatively protected by its constant mobility. Intestinal damage is increased if bowel is fixed by adhesions or scars
E. Symptoms of acute radiation injury
   1. Symptoms and extent of tissue injury are dose related
   2. Mostly mild. Respond to supportive management
3. 30% of children develop electrolyte imbalances due to vomiting and diarrhea
4. Symptoms usually improve within 2 weeks of cessation of radiotherapy
5. Patients with severe early enteritis are at greater risk of chronic enteritis
6. Early injury symptoms may develop within hours of exposure but usually begin after 7–10 days

IV. Specific syndromes of radiation injury—Thoracic irradiation (esophageal injury)
   A. Esophageal epithelium is radiotherapy resistant; symptoms tend to be mild and reversible
   B. Proximal esophagus is most commonly affected
   C. Epithelial regeneration starts within 2 weeks after standard radiotherapy but complete epithelial recovery may take 3–24 months
      1. Symptoms typically start within 2 weeks and resolve in about 1 month of cessation of therapy
      2. Symptoms include odynophagia, dysphagia and chest pain
      3. Rare complications include tracheo-esophageal fistula, perforation or GI bleeding
      4. Radiographic findings in radiation-induced esophageal injury include abnormal esophageal motility, stricture and ulceration

V. Specific syndromes of radiation injury—Radiation-induced gastritis
   1. Uncommon in children
   2. Radiotherapy injures mucosal cells and disrupts normal gastric secretion
   3. Radiation-induced gastritis occurs within a week of radiotherapy with histological recovery usually 3 weeks after completing therapy
   4. In adults, even low-dose radiation is associated with long-term reduction in stomach acid production
   5. Acute symptoms include anorexia, nausea, fatigue and abdominal cramping and occur 3–4 weeks into standard radiotherapy
   6. With modern radiation techniques, the rate of severe gastric injury (ulceration) is about 5% in adults

VI. Specific syndromes of radiation injury—Abdominal irradiation (small bowel injury)
   A. Most patients receiving abdominal radiotherapy develop early symptoms consisting of vomiting, diarrhea and dehydration
   B. Diarrhea is caused by loss of absorptive capacity (inflammation, shortened villi, loss of disaccharidases and bile salt malabsorption)
   C. Vomiting and nausea are common. Radiotherapy stimulates 5-HT3 receptors centrally and peripherally. 5-HT3 receptor antagonists are used in treatment
   D. Radiation enteritis is rarely life-threatening, except during concomitant chemotherapy
   E. Majority of acute symptoms resolve 2–6 weeks after radiotherapy
   F. Acute radiation enteritis largely due to depletion of crypt epithelium, mucositis and damage to the mucosal barrier. There is dense infiltration of leukocyte and plasma cells, with shortened villi and decreased total surface area for absorption
   G. Acute changes are generally reversible but increase the risk of chronic radiation enteritis

VII. Specific syndromes of radiation injury—Pelvic irradiation (colon injury)
   A. Uncommon in pediatric population. Affects distal ileal loops and colon
   B. Proctosigmoiditis, mucoid rectal discharge, rectal bleeding and tenesmus
   C. Rectal bleeding is difficult to treat but is self-limiting in about 80% of adults. Need for transfusion is a poor prognostic indicator in adults

VIII. Specific syndromes of radiation injury—Chronic radiation enteritis
   A. Affects about 10% of children, usually appearing within 2 months of completion of radiotherapy
   B. Most patients have antecedent acute enteritis as well
   C. Symptoms—vomiting, diarrhea, abdominal distension, malabsorption, vitamin B₁₂ deficiency (terminal ileal involvement)
   D. Intestinal lesions—adhesions, fibrosis, obstruction, fistula, abscess
   E. Most cases affect both small and large intestine and damage is often more extended than expected
F. Chronic complications tend to progress over time.
G. Pathophysiology of delayed reactions is related to persistent villous atrophy, malabsorption, protein-losing enteropathy (lymphatic damage) and bacterial overgrowth.
H. Prognosis is poor; mortality is 10%.

IX. Very late effects of radiation therapy
A. Most delayed effects occur 6 months to 5 years after therapy, but may occur up to 20 years later.
B. Effects are dose related and affect anatomically fixed parts of the GI tract more often.
C. Esophageal symptoms: progressive dysphagia, stricture formation and abnormal motility.
D. Small intestinal symptoms: subacute small bowel obstruction, vomiting, abdominal pain, constipation, diarrhea, bleeding, anemia, anorexia, fatigue and wasting.
E. Most children have loose stools for years but it tends to not interfere with daily activities.
F. Colonic involvement is rare and manifests as proctosigmoiditis.
G. Secondary malignancy is rare.

X. Diagnosis of radiation injury
A. Early symptoms:
   1. Minor symptoms early in therapy do not require formal evaluation. Treat symptomatically.
   2. Endoscopy especially in pelvic irradiation is helpful shows hyperemia, friability, erosions and sometimes ulcerations of affected mucosa.
   3. Perforation risk is high in acute stage disease.
   4. Biopsies reveal villous atrophy and inflammatory changes.
   5. Imaging studies rarely helpful in acute injury.
B. Delayed symptoms:
   1. Barium upper or lower GI x-rays helpful in stricture formation, but localization is difficult in small bowel injury.
   2. CT and MRI are helpful for diagnosis of abscess and obstruction.
   3. CT enteroclysis may help diagnose site of obstruction or occult bleeding.
   4. Common radiographic findings are dilatation of bowel loops, wall edema and loss of normal motility.
   5. Endoscopy is rarely helpful in delayed symptoms, as involved areas are often outside the reach of the scope.
   6. Testing for malabsorption and bacterial overgrowth can be clinically helpful.

XI. Treatment
A. Most symptoms improve with supportive care and resolve within 2 weeks of cessation of radiotherapy.
B. Occasionally changes to the radiotherapy regimen are needed for severe symptoms.
C. Management of chronic radiation enteritis is challenging because of the progressive nature of the condition and the variation in the clinical manifestations.
D. Medications:
   1. Antispasmodic and anti-motility agents are used for abdominal cramping.
   2. Antidiarrheal agents—loperamide.
   3. Cholestyramine helpful in bile salt malabsorption–related diarrhea.
   4. Octreotide may be beneficial as an antidiarrheal agent in patients who fail to respond to other agents.
   5. 5HT3 receptor antagonists used for nausea, vomiting and might improve small bowel dysmotility.
   6. NSAIDs used for nausea, vomiting and diarrhea.
   7. Prokinetic agents, sucralfate, acid suppression, NSAIDs and local anesthetics are used empirically for radiation esophagitis. No controlled studies.
   8. Sulfasalazine may reduce acute radiation injury when given orally during radiation therapy. Proposed mechanism is reduced synthesis of eicosanoids (prostaglandins, leukotrienes, etc).
10. Antibiotics for treatment of bacterial overgrowth.
11. Methyl prednisone sometimes used in patients with chronic enteritis and malnutrition.
E. Dietary modifications:
   1. Assessment of nutritional status and nutritional support essential for all stages of radiation
   2. Lactose free, low fat diet commonly prescribed
   3. In severe acute or chronic enteritis, elemental diets and TPN sometimes used
      a. Lactose-free, gluten-free, and low-fat low-fiber diet is often helpful in children with chronic enteritis
   4. Dietary supplementation with fat-soluble vitamins and vitamin B₁₂ may be required
F. Surgical/endoscopic intervention:
   1. Surgery may be hazardous in an irradiated field; risk of postoperative fistula, perforation and abscess
   2. Resection of affected bowel is preferable to bypass due poor quality of anastomoses using irradiated bowel
   3. Low-grade strictures should be managed conservatively if possible
   4. Resection of the rectum may be needed for severe proctitis
   5. Factors that contribute to poor surgical outcome:
      a. Poor nutritional status
      b. Previous surgeries
      c. Interval of <12 months between radiation and surgery
   6. Argon plasma coagulation often used for hemorrhagic GI tract lesions
   7. Esophageal strictures may require repeat dilations
G. Other interventions:
   1. Cytokines such as filgrastim shorten the duration of associated neutropenia and may accelerate recovery
   2. Hyperbaric oxygen recently used in adults to create an O₂ gradient that stimulates new blood vessel growth and reduces ischemia. Dosage and administration remain unclear

XII. Prevention
   A. Highly focused therapy prevents widespread tissue injury
   B. Scale dose to size of child
   C. Use of elemental diet or TPN associated with decreased diarrhea during acute phase of abdominal radiation
   D. Prophylactic NSAIDs may ameliorate radiation enteritis. Sucralfate has been shown to reduce acute and chronic radiation side effects in patients receiving pelvic irradiation
   E. Amifostine is cytoprotective in adults against radiation mucositis; it is a prodrug that protects normal cells against ionizing radiation likely through scavenging free radicals
   F. In a large adult-based trial, amifostine failed to reduce the incidence or severity of esophagitis

Recommended Reading


I. Tubes for feeding are placed in both the stomach and the jejunum. The complications, advantages and disadvantages of the tubes differ.

II. Gastrostomy
   A. Insertion Methods
      1. Endoscopic: Percutaneous Endoscopic Gastrostomy (PEG)
      2. Radiological: with fluoroscopic guidance
      3. Surgical
   B. Advantages
      1. Allow long-term access and are easily cared for
      2. Can be easily replaced
      3. Bolus feeding and administration of medication are possible due to large caliber of the tube
   C. Disadvantages
      1. Can increase reflux by altering contour of stomach and allowing larger volume feedings
   D. Complications
      1. Aspiration, bleeding, tube occlusion, dislodgment, pneumoperitoneum, stomal leakage, tube deterioration, wound infection

III. Jejunostomy
   A. Insertion Methods
      1. Endoscopic
         a. Percutaneous Gastrojejunostomy (JET-PEG, jejunal extension through a PEG)—jejunal tube is placed via a matured gastrostomy site
         b. Primary Percutaneous Endoscopic Jejunostomy (PEJ)—tube placed with the PEG technique directly into the small intestine.
      2. Radiological—can insert a small feeding tube through the stomach and fluoroscopically guide it through the pylorus to the duodenojejunal flexure
      3. Open surgery
   B. Advantages
      1. Decrease the risk of tube feeding–related aspiration
      2. Early postoperative feeding is possible
   C. Disadvantages
      1. Infusion pump is required
      2. Administration of medication is dependent on the size of the tube
      3. Invasive procedures are required for placement
      4. Outside connectors are prone to break and may require replacement of the entire tube
      5. The tubes are difficult to replace unless a mature tract has developed
   D. Complications
      1. Pneumatosis intestinalis, bowel obstruction/intussusception, bleeding, tube occlusion, dislodgment, stomal leakage, tube deterioration, wound infection and volvulus
IV. Proper care for gastrostomy and jejunostomy tubes

A. Checking placement

1. For traditional gastrostomy and jejunostomy tubes, document the external length of the device to monitor for migration of the internal stabilizing balloon or other device
2. Gastrostomy tubes with internal bumpers ought to allow 360° of rotation. If this is not possible, a buried bumper may be developing
3. Low profile devices (LPD) should also be monitored daily. The tube should have some movement. LPDs should be gently pushed in approximately 0.5 inch and rotated 360° daily to prevent the balloon or internal bumper from adhering to the gastric wall

B. Care of exit site and tube

1. Check exit site for erythema, edema, warmth and exudate. Foul-smelling drainage is a sign of infection
2. Monitor site for skin breakdown, pressure necrosis, hypergranulation (keep site dry), gastric leakage (identify the cause)
3. A decrease in exterior length of G tube >1 inch in adults and >0.25 inches for infants and small children indicates possible tube migration
4. Immediate postplacement skin care. Clean the exit site with diluted hydrogen peroxide
5. After healing, clean the site daily with soap and water. Clean and inspect under external bumpers or disks to check for excessive pressure. External bumpers and disks should be just above skin level and not tight against the skin

C. Tube stabilization. Stabilizing a tube can reduce the risk of tube displacement, pain and enlargement of the tract

1. Sutures or T-fasteners may be used to secure gastrostomy or jejunostomy tubes. Most jejunostomy tubes require a secure suture
2. Anchoring devices can secure the tube and protect against stoma enlargement and protect the skin from trauma of frequent dressing changes
3. If the tube has a balloon, check the water in the balloon weekly

D. Maturation of the tract generally occurs in 2–3 weeks in the adult patient and 6 weeks in the pediatric patient. Longer for PEGs (up to 12 weeks)

1. If the tube is inadvertently removed, it should be replaced as soon as possible; the tract can close within hours of the incident

Recommended Reading
