

# Gastrointestinal Bleeding in Children: An Overview of Conditions Requiring Nonoperative Management

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Gastrointestinal bleeding in infants and children is a common problem in the practice of general pediatrics. This report outlines the diagnosis and management of gastrointestinal bleeding in children that does not require surgical or invasive intervention. The spectrum of responsible entities are quite diverse and include a variety of immune-mediated diseases, peptic diseases, drug induced disorders, infections, and coagulation disorders. Through understanding the nature of the above-described problems, appropriate diagnostic and management principles can be applied.

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**G**ASTROINTESTINAL (GI) BLEEDING in infants and children is a fairly common problem in the practice of general pediatrics and it accounts for 10% to 15% of referrals to pediatric gastroenterologists. This chapter will try to provide a general outline and our opinion for the approach to the causes of GI bleeding, which usually do not require surgical or invasive intervention. The entities discussed (Tables 1 and 2) are, as a general rule, not associated with massive acute hemorrhage and do not lead to hemodynamic instability. They are, therefore, more commonly encountered in the general pediatric population than entities that produce major hemorrhage. These conditions should be considered after a careful history and physical examination when those entities that have the potential for major GI bleeding have been excluded. The etiology of GI bleeding, for the most part, can be established or at least clinically suspected in the majority of cases. Very often, particularly in young infants with suspected milk protein allergy or infectious enteritis, one must rely on circumstantial clinical evidence when offering an opinion of the etiology of the bleeding. In such instances, a clinical plan incorporating dietary changes and observation are the measures that usually are applied successfully.

## DIAGNOSTIC APPROACH

Experience has shown that in most children bleeding ceases spontaneously, regardless of source, before or early in their hospital course. In general, the etiologies are benign in children but extraordinarily varied.<sup>1</sup> The follow-

ing 3 points should be considered immediately when one evaluates a patient with GI bleeding.

(1) Is it really blood and is it coming from the gastrointestinal tract? Gastrointestinal bleeding in children can be acute and categorized by vomiting of either fresh blood or altered blood or by rectal evacuation of bright red blood or of melena. When the bleeding is less severe or chronic, the diagnosis is more difficult. It is important to remember that a number of substances such as food coloring, vegetables such as beets, Kool-Aid, gelatin dessert, ampicillin, and phenobarbital may simulate hematochezia. In a similar fashion, melena may be mimicked by iron or bismuth preparations, spinach, dark chocolate, blueberries, grape juice, or licorice-flavored ice cream. The confirmation of the presence of blood on stool specimen or finger-cot specimen should be performed. To confirm the blood in vomited material or gastric aspirate, Gastrocult (Smith and Kline Diagnostics) is preferred because of unreliability of the hemocult in acidic environment.

(2) How much has the child bled, and what is color and character of the gastric contents and stool? A rough estimate of the quantity and a description of color and character of blood are important for sorting out diagnostic possibilities. The following general guideline may assist the physician in localizing the source of blood: (a) Vomiting of bright red blood or of "coffee grounds" usually is associated with a lesion proximal to the ligament of Treitz. (b) Melena is indicative of a significant blood loss (over 2% of blood volume) most likely taking place proximal to the ligament of Treitz. In the event of massive bleeding from the upper tract, bright red rectal bleeding may occur in about 10% of cases. (c) Bright red or dark red blood in the stool usually is associated with lesion originating in the ileum or colon. (d) Blood streaks on the outside of a stool localize the lesion to anal canal or rectal ampulla.

(3) Is the child acutely or chronically bleeding? The most urgent part of the objective examination consists of evaluating the general condition of child with particular attention to presence of sign of anemia or shock. Pediatric patients can adapt to substantial blood loss because they do not suffer as often as adults from altered vital organ function. If bleeding is slow, as much as 15% of blood can be lost without any hemodynamic change. The loss of palmer crease erythema may be seen when the hand is hyperextended as a sign of 50% or more blood volume loss. A thorough physical examination should be per-

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Table 1. Upper Gastrointestinal Bleeding

Age Group	Common	Less Common
Neonates (0-30 days)	Swallowed maternal blood, gastritis, duodenitis	Coagulopathy, septicemia, vascular malformations
Infants (30 days-1 year)	Gastritis, esophagitis, duodenitis, trauma secondary to gastrostomy tubes	Foreign body, NSAIDs
Children (1-12 years)	Esophagitis, gastritis, Mallory-Weiss tear, nasopharyngeal bleeding, trauma secondary to gastrostomy tubes, eosinophilic gastroenteropathy, Munchausen by proxy	Foreign body, NSAIDs Thrombocytopenia, chemotherapy, NSAIDs
Adolescents (12 years-Adult)	Esophagitis, gastritis, trauma secondary to gastrostomy tubes, Mallory-Weiss tear	Thrombocytopenia, chemotherapy, NSAIDs

formed no matter how well the patient appears. The diagnosis may become apparent when the astute observer recognizes signs of portal hypertension, the presence of icterus, ascites, abdominal distension or masses, spider nevi, petechiae, purpura, ecchymoses, angiomas, telangiectasia, the mucosal pigmentation of Peutz-Jeghers, or the soft tissue lesions or bone tumors of Gardner's syndrome. The anus should be inspected carefully for fissures (before digital examination is done). This is a very common cause of rectal bleeding and can be identified on external examination. The vagina also should be examined for menstrual blood; nasal passages should be checked for signs of recent epistaxis. Excoriation of perineum and buttocks associated with diaper dermatitis can lead to guaiac-positive stools.

(4) Is the patient still bleeding? The physiological effects of bleeding depend on both the amount of blood

lost and rapidity of the loss. Recording pulse, blood pressure, and respiratory rate frequently is essential to assess ongoing bleeding.

#### Laboratory Evaluation

A prompt complete blood count with mean corpuscular volume of red blood cells will help to establish if the patient has previously bled. Thereafter, serial hemoglobin levels and hematocrit readings should be taken. Reductions in plasma and red cell volume are proportionate, and hematocrit level falls only after extravascular fluid enters the vascular space through reabsorption. Thus, a significant drop in hematocrit may take 24 hours. To rule out a bleeding diathesis, clotting studies are performed. Routine chemistry should include liver and renal function tests. Normal creatinine in the presence of high blood urea nitrogen (BUN) indicates that blood has accumulated in the small intestine. It results from volume depletion and absorbed proteins.

**Nasogastric intubation.** An important diagnostic tool for upper and lower bleeding site diagnosis is nasogastric intubation. A bloody aspirate confirms an upper gastrointestinal source. However, clear gastric aspirates may be seen in up to 10% of bleeding duodenal ulcers when duodeno-pyloric regurgitation is absent. A 16% false-negative aspirate rate is expected, and the sensitivity for assessing active bleeding is about 80%. The suspicion of varices does not preclude nasogastric intubation.

**Esophagogastroduodenoscopy.** Identifying the site of bleeding must wait until the child has been hemodynamically stabilized. The source of upper gastrointestinal bleeding can be determined in 90% of cases if endoscopy is performed within the first 24 hours. It is especially helpful in diagnosing esophagitis, gastritis, stress ulcer, inflammation caused by nonsteroidal antiinflammatory agents (NSAIDs), Menetrier's disease, and Mallory-Weiss tears.

Upper GI endoscopy is the investigation of choice for the diagnosis of gastritis and peptic ulcer disease. It has been shown to be both safe and effective even in small children. Single contrast barium meal is not a sensitive method in the identification of peptic ulcer disease. Definitive diagnosis is made with gastroscopy, which can confirm or exclude the presence of an ulcer. The endoscopic appearance of the stomach often correlates poorly with the presence or absence of gastritis. Nodularity of the antral mucosa is seen in association with *Helicobacter pylori* gastritis with or without duodenal ulcer. The appearance of a peptic ulcer depends on the stage of disease. Florid, active ulcers usually are round or oval with a wide base composed of debris or fibrin. The ulcer border may be hyperemic and elevated. Duodenal ulcers often are associated with spasm of the pylorus. The causes of ulcer disease and gastritis often can be differen-

Table 2. Lower Gastrointestinal Bleeding

Age Group	Common	Less Common
Infants (30 days-1 year)	Anorectal lesion, infectious diarrhea, milk protein allergy, eosinophilic gastroenteropathy	Acquired thrombocytopenia
Children (1-12 years)	Infectious diarrhea, anal fissure, eosinophilic gastroenteropathy, nodular lymphoid hyperplasia	Henoch-Schonlein purpura, hemolytic-uremic syndrome, vasculitis
Adolescents (12 years-Adult)	Anal fissure, infectious diarrhea	Henoch-Schonlein purpura

tiated by endoscopic examination and by biopsies of appropriate areas of the stomach.

**Colonoscopy.** Colonoscopy can identify the source of lower gastrointestinal bleeding with more accuracy than barium enema. It is sensitive for identifying the cause of bleeding in 80% of cases. In older children with chronic bleeding, colonoscopy has elicited the diagnosis in 40% of patients. Lesions such as juvenile, adenomatous, or hamartomatous polyps; vascular malformations of the colon; varices; lymphoid nodular hyperplasia; mucosal ulcerations; and the adenocarcinoma complicating either ulcerative colitis or Gardner's syndrome are identified readily by colonoscopy. The colonoscopy procedure should be timed for a setting when the child is stable and when blood and feces will not obscure visualization. It should ideally be performed after cessation of bleeding or after appropriate bowel preparation. The use of Golytely (Braintree Laboratories, Braintree, MA) as a bowel-cleansing preparation even in patients with active bleeding may allow for adequate visualization. Intraoperative enterocolonoscopy is reserved for instances of recurrent or persistent bleeding in which no site of hemorrhage is found.

#### ENTITIES RESPONSIBLE FOR GASTROINTESTINAL BLEEDING IN INFANTS AND CHILDREN

Fortunately, the most common causes of GI bleeding in normal healthy neonates tend to be benign and self-limited and rarely require invasive procedures to establish the diagnosis. For example, lower GI tract bleeding in neonates usually relates to anorectal trauma or fissures. Although the lesion may not be readily discernible on inspection of the anus, the history of blood coating the stool suggests this diagnosis.

##### *Swallowed Maternal Blood*

Hematemesis during the first few days of life may result from the fetus swallowing blood during delivery. This possibility can be excluded rapidly by the performance of Apt test, in which blood from stomach is placed on filter paper and mixed with 1% sodium hydroxide. Maternal adult hemoglobin will be reduced from a rusty brown to yellow color. Fetal hemoglobin is resistant to reduction and will retain a pink or bright red color. Absence of fetal hemoglobin should eliminate concern about acute GI bleeding. The test should be limited to bright red blood and cannot be applied to denatured blood found in melena or coffee-ground material.

##### *Milk Protein Allergy*

Cow milk allergy can produce either occult blood loss or even gross bleeding associated with colitis as an adverse immune reaction to the offending antigen. It is the most common allergy seen in infancy and a very

common cause for rectal bleeding in infancy. Associated symptoms may include irritability and poor feeding, diarrhea, vomiting, and failure to thrive. The diagnosis also should be suspected in infants presenting with bleeding, even those who are exclusively breast fed, because the condition can be indirectly induced through the passage of antigens to the infant from breast milk. Implicated antigens include lactoglobulin, casein, bovine serum albumin, and lactalbumin. Several immunologic mechanisms may be involved: immediate anaphylactic hypersensitivity involving IgE antibodies, antibody-dependent cytotoxic hypersensitivity involving IgM or IgG antibodies, immune complex hypersensitivity, and cell-mediated hypersensitivity.

In a similar manner, allergic responses to other protein formulas are not rare. About 40% to 50% of infants who are sensitive to milk protein also are sensitive to soy protein. In addition, some infants are sensitive to the small peptides in protein hydrolysate formulas such as nutramigen, pregestimil and alimentum. Peptide sensitivity must be considered whenever an infant suspected of milk protein sensitivity persists with symptoms after change to these formulas. These latter infants usually respond well to amino acid formulas such as neocate or vivonex.

Gastrointestinal manifestations that occur with or without the involvement of skin or respiratory symptoms usually dominate the clinical picture of protein or peptide hypersensitivity. Any region of the gastrointestinal tract may be affected. Intra-gastric antigens may provoke an edematous inflammation in the gastric mucosa. Acute vomiting caused by immediate hypersensitivity can occur in infants and usually is associated with watery or even bloody diarrhea. In a most fulminant form, glottic swelling or fatal anaphylactic shock may occur. Small intestinal involvement manifests in 3 ways. Acute watery diarrhea occurs as an immediate response to antigen ingestion with or without vomiting or abdominal cramps. Chronic diarrhea and failure to thrive may follow after the ingestion of milk because it induces a patchy villous atrophy in the small intestine. Excessive intestinal protein and blood loss may lead to hypoproteinemia and iron deficiency often without obvious intestinal symptoms. This latter presentation form occurs in infants who are fed fresh whole cow milk early in life and presents with edema, hypoproteinemia, and occult blood loss in the stools. The anemia develops chronically and while being profound, hemodynamic stability is preserved.

The eosinophil may provide support for the suspected diagnosis of milk protein allergy. Peripheral blood eosinophilia may be present. Stools may contain eosinophils, and biopsy specimens from the colon, esophagus, and small intestine may exhibit prominent content of eosinophils. In this regard, however, although eosinophils

detected in the esophagus have been considered to be a specific marker of reflux esophagitis, their presence has been ascribed recently to protein allergy. Children with symptoms attributable to intractable gastroesophageal reflux unresponsive to standard medical management have shown improvement with elemental formulas. Open food challenges with either milk, soy, egg, or peanut reproduce symptoms within a median of 1 hour suggesting specific protein reaction as the etiology of the problem.

Diagnosis of cow milk allergy is clinical. Acute symptoms subside within 48 hours and chronic symptoms within 2 weeks after complete withdrawal of milk. Eosinophilia, as stated above, may support the diagnosis. An elevated eosinophil cationic protein, or alpha-1-antitrypsin activity in the feces also supports the diagnosis. Great care must be exercised in rechallenging these patients. If an acute response is expected, the challenge should be carried out under observation in the emergency room beginning with small doses of formula. In older children with chronic symptoms, mucosal biopsy may be taken to evaluate the response to challenge. Manifestations should resolve completely once cow milk is stopped. Breast feeding mothers should be advised a milk elimination diet. With continuation of symptoms, proctosigmoidoscopy or endoscopy with biopsy should be considered as well as a therapeutic and diagnostic trial of amino acid formula in those with persistent symptoms unresponsive to hydrolysate formulas. Reports exist attesting to the benefit of oral cromolyn for this condition.

#### *Eosinophilic Gastroenteropathy*

Eosinophilic gastroenteropathy is a chronic relapsing disorder in which the eosinophil constitutes the major cell type of the inflammatory infiltrate in gastrointestinal tract. It may even represent several distinct diseases that have eosinophilic infiltration as the unifying feature. Clinical presentation correlates with the extent of eosinophilic infiltration (diffuse v circumscribed) and the depth of eosinophilic reaction (mucosal, muscularis, and serosal). It may involve the whole GI tract, but stomach and small intestine are more commonly involved. Mucosal involvement is most common and produces either bleeding or protein loss. Muscularis infiltration may produce stricture and obstruction, and serosal activity leads to eosinophilic ascities.

The prevalence of allergic histories varies widely in different series from 0 to 70%. Food sensitivity may play a role, but the exact etiologic basis of this condition is unknown. IgE-mediated and IgE-independent hypersensitivity are possibilities. Manifestation of this entity may include vomiting, abdominal pain, growth failure, diarrhea with or without rectal bleeding, peripheral edema, anemia, and hypoproteinemia.<sup>3</sup>

Results of radiographic studies may show narrowing

and nodularity of the gastric antrum and duodenum or thickened mucosal folds in the intestine. Endoscopy is often contributory, because it may show erythema, nodularity, friability erosions, and ulceration's in the affected areas, but it affords the ability to perform mucosal biopsies. Proof of diagnosis depends on finding of excessive eosinophils in biopsy specimens or resected tissue specimens assuming that other common causes of eosinophilic infiltrates like lymphoma, Crohn's disease, parasitism, vasculitis, and chronic granulomatous disease of childhood have been excluded.

When food provokes characteristic symptoms, dietary elimination circumvents the problem. When symptoms persist, corticosteroids (1 to 2 mg/kg/d), and oral disodium cromoglycate (50 to 200 mg per dose given 4 times per day) may help control the symptoms. Surgery usually is not required except in cases of intractable strictures.

#### *Esophageal or Gastric Lacerations*

Esophageal laceration may result from vigorous use of oropharyngeal suction, the passage of nasogastric tube or endoscopic trauma. One also needs to consider the local traumatic effects that button gastrostomy tubes may exert on the gastric mucosa. These range from small to significant tears. Treatment is dependent upon the degree of bleeding. Most can be managed conservatively with application of carafate and antacids as well as acid suppressive medications.

Children with Mallory-Weiss tear present with history of one or more episodes of vomiting over several days followed by emesis of bright red blood. Mostly, bleeding is painless. Generally the laceration is located at the esophagogastric junction, but it may be confined to proximal stomach or lower esophagus.

#### *Henoch-Schonlein Purpura*

Henoch-Schonlein purpura is a multisystem vascular disorder characterized by purpura, colicky abdominal and gastrointestinal bleeding, and hematuria. Obvious lower GI bleeding occurs in 25% of cases. Endoscopic examination may show mucosal edema, patchy erythema, and multiple gastric erosions. These lesions are more severe in duodenal bulb and second portion of duodenum. Rectosigmoid examination may show shallow ulcers. Biopsy findings exhibit neutrophil infiltrate in lamina propria, predominantly around blood vessels.

#### *Esophagitis*

Peptic esophagitis is the most common form of esophagitis. It is caused by gastroesophageal reflux. In infants, in addition to regurgitation as a symptom, it may present with pain on swallowing, dysphasia leading to food aversion, and failure to thrive. The inflammatory process

may be quite extensive and be responsible for hematemesis.

Viral esophagitis may be caused by herpes simplex virus (HSV), cytomegalovirus (CMV), and occasionally varicella zoster. Of these, only HSV is common in immunocompetent host. Severe odynophagia and dysphagia are the main symptoms. Complications of viral esophagitis include hemorrhage, fistula formation, dissemination, perforation, and superinfection. More than 90% of AIDS patients have evidence of CMV dissemination at autopsy, and 10% of liver and kidney transplant patients get herpes or CMV.

An esophogram can be a useful first step in evaluation. It can identify any mechanical problems and may suggest that a patient has an esophagitis.<sup>4</sup> Nuclear medicine scintiscan and pH probes are very helpful in the diagnosis of gastroesophageal reflux. Endoscopy is the best way to make a definitive diagnosis of viral esophagitis by obtaining brushing and biopsy specimens for cultures.

Peptic esophagitis may be treated with proton pump inhibitors such as prilosec and propulsive agents such as reglan or cisapride.<sup>5</sup> Viral esophagitis in the immunocompetent host requires no specific antiviral treatment. Symptomatic therapy with antacid and analgesic usually suffices. The immunocompromised patient needs specific medications. Acyclovir is very successful in HSV, whereas gancyclovir is the preferred drug for CMV infections.

#### Gastritis and Duodenitis

Peptic disorders account for less than 5% of children who present with abdominal pain, and are far less prevalent in pediatrics than in the practice of adult gastroenterology. Symptoms of gastritis, peptic ulcer, and duodenitis may be similar, and in school-aged children they may be similar to those in adults. Being awakened from sleep by epigastric pain is a typical symptom of peptic ulcer disease in children. As many as 90% of children with biopsy-proven ulcers have abdominal pain. Most peptic ulcers occur in children between 7 and 16 years of age.<sup>6</sup> Acute episodes of hematemesis in association with abdominal pain may indicate primary or secondary ulcer disease. On physical examination epigastric tenderness is an unreliable sign of gastritis or ulcer disease. Perforation and penetration are less common complications in children than adults.

Gastritis and peptic ulcer disease were previously considered as distinct entities, but over the past 10 years we have come to understand that these two conditions are closely related. Both entities can be divided into primary and secondary categories based on the underlying etiology. Primary gastritis and primary ulcer disease are associated with *H pylori* infection. Secondary gastritis and ulcer disease occur in association with severe stress in dealing with systemic illnesses such as burns, head

injuries, Crohn's disease, and NSAID usage. Gastritis is defined as microscopic evidence of inflammation affecting gastric mucosa. It is purely a histological diagnosis made by either targeted or random endoscopic biopsies. Peptic ulcer disease is described as a discontinuity in the gastric or duodenal mucosa exposed to acid or pepsin. Peptic erosions are superficial mucosal lesions, whereas duodenal ulcers are deep mucosal lesions that disrupt the muscular coat of gastric or duodenal wall.

In children, *H pylori* is the most common cause of gastritis. Typically, it is solely an antral gastritis, although occasionally the entire gastric body may be involved.<sup>7</sup> *H pylori* gastritis without an ulcer is accompanied by a striking nodularity of the antrum in about 50% of cases. In children when *H pylori* gastritis is associated with duodenal ulcer, the nodularity is always present.<sup>8</sup> Because the antral mucosa appears normal on endoscopy in about half of cases, tissue biopsy should always be performed regardless of endoscopic appearance. About 15% of children with duodenal ulcers have no serological or histological evidence of *H pylori*.<sup>9</sup> They do not appear to have greater acid secretion and at this time may be regarded as idiopathic ulcers. The diagnosis of *H pylori*-associated gastritis requires mucosal biopsies of gastric antrum. Colonization of antrum can be identified by rapid urease testing (CLO test) or urea breath test. The serum IgG antibody may be helpful in following the response to antimicrobial therapy, but it adds little to the acute diagnosis. When an *H pylori*-negative ulcer is diagnosed, a fasting plasma gastrin level should be obtained to exclude one of the G-cell disorders or Zollinger-Ellison syndrome, and a biopsy specimen should be examined carefully for signs of Crohn's disease.

NSAIDs such as acetylsalicylic acid, phenylbutazone, indomethacin, ibuprofen, and naproxin are known to cause both gastritis and mucosal ulceration. Early erosions and hemorrhages occur in the gastric body and antrum. The ulcerations associated with NSAIDs usually are gastric and occasionally duodenal, and it is these lesions that may perforate and bleed. Infants and young children treated with even small doses of aspirin for febrile illnesses may present with hematemesis and significant blood loss. The characteristic finding associated with NSAIDs is the presence of one or more ulcers on the incisura. NSAIDs are believed to inhibit mucosal bicarbonate production and cause a loss of the protective surface mucus thus impairing gastric mucosal defense mechanisms.

Stress gastropathy occurs in seriously ill children and is related to physiological stresses such as shock, acidosis, sepsis, burns, and head injuries. These result in mucosal ischemia. Early lesions predominate in the fundus and proximal body and spread to the antrum producing a diffuse erosive and hemorrhagic appearance.

Stress gastritis is treated by managing the underlying hypoxemia, acidosis sepsis, and by providing acid suppression and antacids.

Duodenitis is similar to gastritis in that it is diagnosed neither clinically nor radiologically. It may be diagnosed purely endoscopically or histologically, but usually it is both. Nonspecific duodenitis may be confined to the duodenal bulb and manifest as multiple duodenal erosions. Generalized inflammation may occur in this region as a part of the spectrum of duodenal ulcer disease. This pattern also may occur as a result of physiological stress or NSAIDs ingestion, usually with and occasionally without, a gastric component. Duodenitis also may occur in continuity with disorders of the rest of small bowel. Nonspecific lesions may be postinfectious or associated with celiac sprue or immunodeficiency states (eg, AIDS). Specific lesions are those of Crohn's disease, giardiasis, CMV, and graft-versus-host disease.

#### *Lymphoid Nodular Hyperplasia*

Lymphoid nodular hyperplasia is a benign condition that may represent an incidental normal finding in childhood. It is frequently attributed to be the cause of rectal bleeding in infants and children who have no identifiable cause of bleeding. Colonoscopic findings include raised mucosal elevations. The mucosal pattern of lymphoid nodular hyperplasia on double-contrast radiographs has a typical pattern consisting of a central umbilication, but the classical pattern may at times be atypical of this condition and suggest larger polyps such as in the case of familial polyposis syndromes. Colonoscopy results can easily distinguish the two conditions.

#### *Disorders of Coagulation*

Patients with coagulopathies and deficiencies in thrombocytes such as idiopathic thrombocytopenia, leukemia, and drug-induced thrombocytopenia have a low incidence of spontaneous gastrointestinal bleeding unless there is a coexisting underlying mucosal surface lesion. Each potential bleeding site would be expected to bleed more briskly and be more prolonged in duration in the setting of coagulation system disorders. Patients with severe factor VIII or IX deficiency carry a 10% to 25% incidence of GI hemorrhage usually related to peptic disease. Those with mild deficiencies do not appear to be at risk. Therefore, it appears that the degree of the deficiency and the presence of an underlying mucosal lesion are determining factors in the development of GI bleeding in these cases.

*Idiopathic thrombocytopenic purpura.* Idiopathic thrombocytopenic purpura (ITP) is the most common cause of purpuras in children that usually follows as acute viral infection. It is associated with petechiae, mucocutaneous bleeding, and occasionally hemorrhage into tissue.

It is caused by an antibody (IgG or IgM) that binds to platelet membrane and results in the splenic destruction of antibody-coated platelets. Rarely, it may be the presenting symptom of lupus. The onset typically is acute. Bruising and generalized petechiae occur 1 to 4 weeks after a viral infection. Hemorrhage in the mucus membranes may be prominent.<sup>10</sup> Significant adenopathy and hepatosplenomegaly are unusual, and red cell and white cell counts are normal. Diagnosis of ITP does not require a bone marrow examination. The presence of atypical findings require a bone marrow examination to rule out leukemia or aplastic anemia. Severe thrombocytopenia or clinical bleeding requires treatment with intravenous gamma globulin. Systemic steroids decrease the duration of severe thrombocytopenia but do not affect the longevity of the disease.

*Disseminated intravascular coagulation.* Disseminated intravascular coagulation (DIC) refers to a disorder in which a severely ill patient sustains widespread activation of coagulation mechanism usually associated with shock. Bleeding or clotting manifestations may be present. Normal hemostasis is a balance between hemorrhage and thrombosis. In DIC this balance is altered by severe illness so that patient has activation of both coagulation (thrombin) and fibrinolysis (plasmin). Coagulation factors, especially fibrinogen, and factor II, V, and VIII are consumed. The diagnosis of DIC is a clinical one sustained by laboratory findings. Prothrombin (PT) and partial thromboplastin (PTT) times are prolonged. Platelets, plasma fibrinogen, factors V and VIII are low, whereas fibrin degradation (split) products are elevated.

The treatment of DIC is problematic. The underlying disorder inducing DIC should be treated promptly and effectively. Depleted blood clotting factors, platelets, and anticoagulant proteins should be replaced.

#### *Bleeding Associated With Gastrointestinal Infections*

An evaluation for gastrointestinal infections should be performed in children presenting with lower gastrointestinal bleeding associated with altered bowel movements. It is important to remember that the clinical symptoms, endoscopic, radiographic, and histological findings of the enteric infections (Table 3) can be indistinguishable from

Table 3. Infectious Agents Associated With Hematochezia

<i>Clostridium difficile</i>
<i>Salmonella</i>
<i>Shigella</i>
<i>Compylobacter jejuni</i>
<i>Yersinia enterocolitica</i>
Enteroinvasive <i>Escherichia coli</i>
Enterohemorrhagic <i>E coli</i>
<i>Aeromonas hydrophilla</i>
<i>Entamoeba histolytica</i>
Cytomegalovirus

those of idiopathic inflammatory bowel disease (IBD). Also, enteric infections can coexist with IBD. Although viral infections usually produce nonbloody diarrhea in the immunocompromised host, viruses such as CMV can induce colitis with diarrhea. It is important to exclude enteric infections by appropriate stool examinations before the performance of invasive diagnostic procedures. Diarrhea is a common complication of antibiotic use and is usually benign, requires no investigation and usually subsides with discontinuation of the antibiotic. This self-limited antibiotic-associated diarrhea may be caused by a transient alteration of balance of colonic microbiological flora and does not lead to pseudomembrane formation. In contrast, antibiotic-associated pseudomembranous colitis (PMC) is a serious condition, characterized by the presence of discrete mucosal yellow plaques or pseudomembranes composed of an inflammatory exudate. It is caused by toxigenic *Clostridium difficile*, a spore-forming gram-positive noninvasive bacillus. This obligative anaerobic organism is part of the normal flora of 3% adults and a much higher percentage of neonate (50% to 70%) and infants (20% to 50%). Neonates and infants may remain asymptomatic because their intestinal epithelium may not express the toxin receptor.

Toxins account for the pathogenicity of the organism. About 25% of *C difficile* do not produce toxins and, therefore, are not considered causative agents for diarrhea or colitis. Colitis develops from toxin production within the intestinal lumen. *C difficile* produces 5 toxin factors, the most important of which are toxin A, an enterotoxin and toxin B, a cytotoxin. Toxin A binds to receptors on mucosal surfaces. Binding of toxin to the epithelial membrane microfilaments producing contraction, hemorrhage, necrosis, and inflammation. Toxin A is believed to be the major factor for virulence. Toxin B induces alteration in cell shape by acting on intracellular actin microfilaments.

The spectrum of disease induced by enteric *C difficile* varies widely. The severity of symptoms range from mild watery diarrhea with abdominal cramps to severe hemorrhagic colitis. It can present with protein-losing enteropathy, hypoalbuminemia, shock, fever, abdominal tenderness and distension, toxic megacolon, colonic, cecal perforation, peritonitis, secondary sepsis, and death. Symptoms usually appear during antibiotic therapy but may be delayed as long as 2 months after antibiotics have been discontinued.

Diagnosis of PMC is rapidly established by visualization of inflammation signifying colitis and by identifying pseudomembranes on sigmoidoscopy. Plain films of the abdomen and computed tomography (CT) scan may show a thickened bowel wall. Nonspecific laboratory findings that support the diagnosis in PMC include

leukocytosis, presence of fecal leukocytes, elevated erythrocyte sedimentation rate, and hypoproteinemia. Protein-losing enteropathy can be confirmed by the detection of elevated levels of fecal alpha-one-antitrypsin concentrations. Stool examination is the most sensitive test. Whereas the stool cell cytotoxicity assay (toxin B) is the most specific assay for maximal diagnostic sensitivity and specificity; performance of both tests is recommended. EIAs for toxin A are rapid but may be less sensitive as well as less specific than cell cytotoxin assays. The use of EIA in place of cytotoxin assay is recommended as an acceptable alternative to the cell cytotoxin assay.

Diarrhea will resolve in 15% to 23% with discontinuation of therapy. The rest will require specific antibiotic therapy. Metronidazole, vancomycin, teicoplanin, and fusidic acid are all effective therapeutic agents. Oral therapy with either metronidazole or vancomycin for 10 days is effective in 95% of the patients. Recommended doses for metronidazole and also vancomycin are 40 mg/kg/d divided 3 to 4 times daily. Vancomycin is considered a more specific therapy for this condition. Although most patients will be cured, 5% to 30% will have recurrent *C difficile* usually within 1 to 2 weeks after discontinuation of therapy. A variety of empirical approaches have been used to treat patients with recurrent *C difficile* including biotherapeutic measures. The rationale of such measures is to avoid further antibiotic therapy and allow normal flora to reestablish itself. Probiotics such as *Saccharomyces boulardii* or *Lactobacillus* species are given orally. Also, rectal infusion of feces or a synthetic fecal bacterial flora or even administration of nontoxigenic *C difficile* strain has been tried. Additional strategies have involved administration of vancomycin and rifampacin in combination, vancomycin in tapering doses, cholestyramine, and intravenous gamma-globulin. Whole-bowel irrigation with the use of polyethylene glycol solutions were described to be effective in some patients with recurrent infections. The many different therapies applied to cases of recurrent *C difficile* infection do emphasize the difficulty of the problem.

*Escherichia coli* are among the most common flora that inhabit the healthy colon. The organism is a gram-negative bacillus that is motile and may form chains. It can give rise to a variety of disease states. The *E coli*-causing diarrhea have been studied extensively and divided into classes and serotypes. Two of these can give rise to bloody diarrhea. Enteroinvasive *E coli* (EIEC) are nonmotile and unable to ferment lactose, the properties similar to those observed in with shigella. EIEC and shigella also share common virulence mechanisms. These organisms preferentially colonize the colon and invade and replicate within the epithelial cells where they cause cell death. Patients experience cramping

abdominal pain and tenesmus. Watery diarrhea occurs initially, progressing to stools mixed with mucus and leukocytes. Gross blood is not always present in stool, and bacteremia does not occur. The usual mode of spread is through contaminated food or water, but person to person transmission can also occur. Diagnosis depends on results of bioassay, serotyping, or enzyme-linked immunosorbent assay (ELISA). Treatment currently is limited to supportive measures, although ampicillin given systemically or oral bactrim have been associated with bacteriologic cure and clinical improvement.

Enterohemorrhagic *E coli* (EHEC) have been recognized to produce a syndrome of hemorrhagic colitis. In some studies this organism is found to be the most common cause of acute bloody diarrhea. In contrast to other forms of diarrhea-producing *E coli* strains, cattle, not humans, are the reservoir for EHEC. Data from fast food-associated outbreaks indicate that the incubation period is 3 to 4 days. Clinically, EHEC may produce a wide variety of symptoms from relatively mild watery diarrhea to potentially severe hemorrhagic colitis. Symptoms may persist for a few days to 2 weeks. Endoscopy findings may show diffuse mucosal edema, with areas of hemorrhage especially in proximal colon. Histological findings range from normal appearance to intense inflammation as well as the presence of pseudomembranes.

The 0157:H7 strain frequently is found in cases of hemolytic uremic syndrome, which usually manifests 1 week after the onset of diarrhea. Thrombotic thrombocytopenic purpura is another serious complication of *E coli* 0157:H7 infection.<sup>12</sup> Both of these complications are most common in young children and the elderly in developed countries but are rarely seen in the third-world setting. Diagnoses of EHEC may be established by serotyping for the serotype 0157:H7. Immunoassay and gene probe techniques also are available for diagnoses. Treatment currently is supportive.

Salmonellae are gram-negative, motile aerobic bacilli. The family is classified into three species: *S enteritidis*, *S typhi*, and *S choleraesuis*. *S enteritidis* is by far the largest *Salmonella* species. The usual incubation period is 12 to 72 hours, but it may be as long as 10 days. The peak incidence of disease occurs in early childhood and infancy. The organisms are acquired by ingesting contaminated food and drink. A typical episode of *Salmonella* gastroenteritis is accompanied by fever, nausea, and may be associated with bloody or watery diarrhea. Episodes are usually self-limited. Bacteremia is fairly common and occurs by invasion of lamina propria. Systemic complications are most common in youngest age groups and include meningitis, osteomyelitis, and pneumonia. The median duration of excretion of organisms is about 3 weeks, but may be more prolonged with antibiotic use. Standard stool culture techniques will isolate the *Salmo-*

*nella* organism, but the use of DNA probe specific to *Salmonella* can reduce the number of microbiological assays required to identify the organism. Treatment is recommended if there is bacteremia or if the patient is less than 3 months of age. Ampicillin, chloramphenicol, or ceftriaxone are the drugs of choice.

Shigellae are gram-negative rods that are divided into 4 major serologically distinct species: *S dysenteriae*, *S flexneri*, *S boydii*, and *S sonnei*. *S sonnei* accounts for majority of isolates in the United States, although the incidence is declining, whereas the numbers of *Campylobacter* and *Salmonella* infection are increasing. *Shigella* has been found to cause disease in only humans. The organisms are extremely potent, with as few as 10 organisms able to cause disease by invading epithelial cells. Its plasmid plays an important role in mediating invasiveness. Once within the enterocyte, *Shigella* multiplies and spreads to the adjacent cells. Invasion and multiplication are associated with an intense inflammatory response leading to cell death. Exotoxin (shiga toxin) elaborated by the *Shigella* organism, also is responsible for their virulence and has enterotoxic, cytotoxic, and neurotoxic effects. The patient infected with shigella may experience a mild self-limited watery diarrhea that is clinically indistinguishable from gastroenteritis caused by variety of other organisms. The more classical form of shigellosis, however, is bacillary dysentery. This illness usually begins with fever and malaise, followed by watery diarrhea and cramping abdominal pain. By the second day of illness, blood and mucus usually is present in the stools, and tenesmus has become a prominent symptom. At this point in half of the patients, stool volume decreases with only scant amounts of blood and mucus being passed. This pattern of bloody mucus-containing stools is referred to as dysentery. Bacteremia is an uncommon feature of this illness. Several other complications include seizures (in children), arthritis, purulent keratitis, and the hemolytic uremic syndrome. Stool cultures provide the only means to differentiate this organism from other invasive pathogens. Sigmoidoscopy or colonoscopy findings typically show friable mucosa with discrete ulcers. Antibiotic therapy is recommended for patients who are severely ill at the time of diagnosis or who remain ill at the time of identification of shigella in a stool culture. Currently, the agent of choice is trimethoprim-sulfamethoxazole (TMP 5 mg/kg, plus SMZ 25 mg/kg per dose) given every 12 hours orally or intravenously for 5 days. Ampicillin, cefixime, and ceftriaxone are other effective agents, but amoxicillin is ineffective against shigella.

*Campylobacter jejuni* is a gram-negative, motile curved or spiral shaped rod, exhibiting "seagull" appearance when identified in stained stool smears. It is recognized to be worldwide in distribution. In developing countries it

causes diarrhea in children younger than 2 years, whereas in older children it tends to be asymptomatic. In the industrialized world, most patients infected with *C jejuni* get symptoms. It may be spread by direct contact or through contaminated sources of food and water. Milk, meat, and eggs, especially if undercooked, have been implicated in outbreaks. It infects either the colon or distal small intestine and is presumed to be an invasive organism because it causes an inflammatory tissue response and can cause bacteremia. It also produces an enterotoxin similar to cholera toxin, but the biological relevance of the toxin is unclear.

Episodes usually begin with fever and malaise, followed by nausea, diarrhea, and abdominal pain. The diarrhea can be profuse and watery, and may contain blood and white blood cells. The episode may mimic appendicitis or inflammatory bowel disease. The symptoms usually resolve in less than 1 week. *Campylobacter* also is known to cause meningitis, abscesses, septic abortions, pancreatitis, and pneumonia. Guillain-Barre syndrome and Reiter's syndrome are documented to occur as sequelae of *Campylobacter* infection. After the resolution of symptoms, patients may continue to shed organisms for as long as 7 weeks.

*Campylobacter* can be recognized by microscopic examination of a gram-stained stool smear. Culture of the organism, the gold standard for diagnosis, can be routinely accomplished in most laboratories if selective media are used and cultures are incubated at 42°C. Because the disease usually is mild and self-limited, supportive treatment alone should suffice. In cases of

severe disease, erythromycin (10 mg/kg/dose given every 6 hours for 5 to 7 days) has been recommended. For cases of *Campylobacter* septicemia, gentamicin, chloramphenicol, or erythromycin are the drugs of choice.

*Aeromonas hydrophilia* and its closely related species are gram-negative motile bacilli that inhabit fresh and salt water and cause diarrhea in humans and animals. The usual vehicle of infection is water, sewage, animal feces, and contaminated food. The pathogenic mechanism is believed to be the production of cytotoxin and enterotoxin.

Clinical symptoms attributed to *Aeromonas* can be grouped into 3 groups: (1) acute watery diarrhea, the most common syndrome; (2) dysentery, which is usually self-limited; (3) persistent watery diarrhea. Cramping abdominal pain and vomiting also may occur.<sup>13</sup> Fecal leukocytes have been observed in some cases. It is important to note that symptoms may occasionally be severe, especially when dysentery is present, and may be incorrectly diagnosed as ulcerative colitis. In mild cases supportive treatment should suffice. In immunocompromised patients or patients with severe symptoms, treatment with antibiotics is recommended. Trimethoprim-sulfamethoxazole usually is as effective as tetracycline, chloramphenicol, and the aminoglycosides.

We have briefly presented a description of some of the commonly encountered causes of GI bleeding in infants and children. The responsible entities are quite varied and diverse. By understanding the nature of the above-described problems, appropriate diagnostic and management principles can be applied.

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