Non-IBD Colitis

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Diagnosing Colitis

Classic symptoms of colitis are diarrhea, usually bloody, and abdominal pain. Possible accompanying symptoms include fever, cramps, malaise, nausea, vomiting, chills, and myalgia. The most frequent differential diagnosis of colitis is between acute self-limited colitis (i.e. ASLC or infectious colitis) and first attacks of idiopathic inflammatory bowel disease (IBD). In addition, there are multiple other causes of colitis.

TYPES OF COLITIS

I. Distinguishing Acute Self-Limited Colitis from Idiopathic Inflammatory Bowel Disease

**History and Physical Exam.** Acute onset suggests infectious colitis, inflammatory bowel disease is usually a chronic illness with a more indolent onset. Fever does favor infectious colitis but the symptoms are otherwise nonspecific. Physical exam is noncontributory. Laboratory evaluation is helpful if the stool culture is positive but this is positive in only 40-60% of patients with acute self-limited colitis. The most common pathogens are *Campylobacter, Salmonella, Shigella* and *E. coli* 0157:H7 (Shiga toxin E. coli). Laboratory evaluation is usually nonspecific. Anemia and elevated sed rate (ESR) favor inflammatory bowel disease. Fecal leukocytes are insensitive because they can be seen in both IBD and infectious colitis.

**Appearance of the colonic mucosa.** The appearance suggesting infectious colitis is focal changes, hemorrhage with focal edema and erythema. However, this does not differentiate one infection from another nor is it specific for infectious colitis.

Mucosal biopsy can be very helpful in distinguishing between inflammatory bowel disease, especially ulcerative colitis, and acute self-limiting colitis, because crypt distortion which is a hallmark of the former is rare in infectious colitis. The mucosa in ulcerative colitis shows branched or forked crypts, present even with an early presentation suggesting that crypt changes may precede the development of symptoms. In addition to branched glands, distortion of architecture can include a villous surface and crypt atrophy (sparse crypts which are shortened and do not reach the muscularis mucosae). In contrast, in acute self-limited colitis, crypt architecture remains normal, both during the disease and after healing has occurred. There may be some exceptions to this general rule.

Other histologic clues which help distinguish acute self-limited colitis from inflammatory bowel disease include the nature of the lamina propria inflammation, the presence or absence of granulomas, and the location of isolated giant cells.

The inflammatory infiltrate in acute self-limited colitis is often predominantly acute, i.e. polymorphonuclear cells but an increase in chronic cells can be present, and may be most prominent in the upper half of the mucosa. In contrast, in inflammatory bowel disease, the inflammation consists of both acute and chronic inflammatory cells (polymorphonuclears as well as plasma cells and lymphocytes). It should be noted that the normal lamina propria cells include plasma cells and lymphocytes but not polymorphonuclears; thus an increase in polymorphonuclear cells is easy to detect, but an increase in “chronic cells” should only be called abnormal if their numbers obviously clearly increased. There may also be an increase in plasma cells near the crypt bases, described as “basilar plamacytosis.” This is an area where plasma cells are normally sparse so that an increase can be more easily detected. Basilar lymphoid aggregates are increased in ulcerative colitis (2 or more per average sized biopsy is abnormal). Crypt abscesses are a nonspecific indication of inflammation, and do not indicate a specific diagnosis. Similarly, goblet cell mucin depletion is probably a response to intense inflammation, rather than a specific diagnostic clue for ulcerative colitis.
The histologic characteristics of ulcerative colitis are nonspecific but include crypt distortion which consists of crypt atrophy, a villous surface, and distorted or branched glands, more than one per biopsy. In addition, lamina propria inflammation is diffuse and mucosal, rarely submucosal, and consists of an increase in both acute and chronic inflammatory cells. Crypt abscesses are frequent but these are nonspecific and can be seen in colitis of other etiologies, including various infections. Basal inflammation including basal plasmacytosis and basal lymphoid hyperplasia are characteristic of ulcerative colitis.

Crohn’s disease is characterized by focal rather than diffuse inflammation. Focal inflammation consists of small collections of polymorphonuclear cells and/or chronic inflammatory cells. Crypt abscesses may or may not be present. The diagnostic hallmark is the epithelioid granuloma which can be found in up to 25% of biopsies when serial sections are made. In Crohn’s disease, the inflammation is segmental, but may be transmural (thus submucosal inflammation can be present in biopsies) which can result in the complications of fistula and abscess formation.

**Infectious Colitis.** Rectal biopsy is also useful in diagnosing infections. Infectious colitis is characterized by normal crypt architecture and acute lamina propria inflammation. This contrasts with IBD, where crypt distortion are common and basal inflammatory changes especially in ulcerative colitis. Specific diagnostic features suggesting specific infections include the presence of parasites, such as amebae which can be seen in micro ulcers over lymphoid nodules or in the mucus on the surface of the biopsy. The amoeba trophozoites are larger than a lymphocyte and thus can be easily recognized by an experienced technician. Specific fungi can cause colitis, although this is usually seen only in significantly immunosuppressed individuals. Bacterial colitis usually has no specific histologic features. Similarly at colonoscopy, the findings may be of a patchy mucosal erythema and superficial ulceration which contrasts somewhat with the more diffuse changes seen in ulcerative colitis and with the discrete linear ulcerations or the segmental colitis characteristic of Crohn’s disease. There are no histologic features which can distinguish inflammatory bowel disease with a bacterial superinfection. When pseudomembranes are present, they are usually easily recognized grossly on the colonic mucosa as creamy yellow-white plaques with mucosal bleeding when they are removed. The histologic features are characteristic with superficial edema and a pseudomembrane arising from relatively uninflamed mucosa with normal architecture. The pseudomembrane consists of fibrin and polymorphonuclear cells and erupts in a volcano-like fashion from the mucosa.

Pseudomembranous colitis is usually easily diagnosed with flexible sigmoidoscopy. Although 20% of patients may have an isolated right-sided colitis. Thus in difficult cases where diagnosis is obscure, a total colonoscopy may be necessary.

Two infections which may have an ischemic-like appearance in the mucosal biopsies are *E. coli* 0175:H7 and *C. difficile*. Both of these can cause histologic features such as pseudomembrane formation and an ischemic look. Both organisms act by toxin production. *E. coli* 0157:H7 produces a vero-like toxin, causing acute colitis often right-sided and can be complicated by hemolytic uremic syndrome and thrombocytopenic purpura. *Clostridium difficile* is well-recognized as a nosocomial pathogen which causes pseudomembranous colitis. Diagnosis is usually made by finding *C. difficile* toxin in the stool. Typical findings should be easily recognized grossly and histology can be helpful as an adjunct if endoscopic findings are equivocal.

Intranuclear viral inclusions are seen with Herpes Simples Virus Type II which causes a distal proctitis, in immunocompetent and immunodeficient individuals. Other histologic features of Herpes include ground glass nuclei and multinucleate giant cells. Typically, intranuclear and
cytoplasmic inclusions are diagnostic of cytomegalovirus which usually occurs in immunodeficient individuals but can occasionally cause a self-limited colitis in the immunocompetent individual. Parasites are diagnostic when seen in biopsy and these include amebiasis and shistosomiasis. Granulomas which usually indicate Crohn’s disease can also be seen in some infections such as Yersinia, tuberculosis, Chlamydia trachomatis, and syphilitic proctitis. The latter two are usually sexually transmitted.

II. Colitis of Other Causes (See Table 1)

A. Ischemic colopathy. Ischemic colopathy is usually a disease of the elderly who are susceptible to decrease in blood flow but can occur in young people in certain settings such as women taking oral contraceptive pills, marathon or long-distance runners, ergot, cocaine, vasopressin or associated with cardiovascular disease such as after the repair of aortic aneurysm. Colonoscopic appearance classically includes rectal sparing and discrete ulcers which can suggest Crohn’s disease. Clinical presentation of abdominal pain with bloody diarrhea or hematochezia, fever or leukocytosis may be present and x-rays may show a thumb printing of mucosa due to submucosal hemorrhage. Colonoscopic appearance may be characteristic when dusky blue purple mucosa can be seen at flexible sigmoidoscopy. It is important not to use excessive air inflation at sigmoidoscopy. Histology shows architecture remains but only ghosts of crypts with minimal inflammation and superficial necrosis.

B. Radiation Colopathy. Radiation-induced colitis most commonly follows radiation for cases with symptoms of diarrhea, rectal discharge, tenesmus and abdominal pain. The lesions usually involve the rectosigmoid colon with proctocolitis, ulcers, or loss of normal mucosal vascular pattern. Chronic radiation damage is due to ischemia and fibrosis which occur a result of obliterative arteritis. The histology resembles ischemia, with superficial necrosis. Specific histologic features include neovascularization and hyalinized blood vessel walls.

C. Solitary Rectal Ulcer Syndrome. Solitary rectal ulcer syndrome is a condition in which anterior rectal ulceration occurs, often associated with rectal prolapse. There is often a history of severe constipation. On digital exam, the ulcer may be so firm and indurated that it is mistaken for a rectal cancer. The histology is characteristic with mucosal fibrosis, hyperplasia of crypts, a prominent increase in collagen in the lamina propria, and buried glands present below the muscularis, called “colitis cystica profunda.” This latter finding may mislead an inexperienced pathologist into a false diagnosis of cancer. More commonly, the differential is with Crohn’s disease, but the unique histology should easily clarify this.

D. Microscopic Colitis
   a. Collagenous Colitis. This entity was first described in 1976 by Lindstrom and the first case remains a typical example. The illness occurs in middle aged women (4:1). Because the colonic mucosa looks normal grossly, it is unlikely to be confused with ulcerative colitis. Typically, these patients have chronic watery diarrhea, and an evaluation is normal. Biopsy is necessary to make the diagnosis. The histology is diagnostic, with a thickened subepithelial band of collagen, greater at least than 10 um. Normally, this layer is 0.4-4.6 um thick. Other histologic findings are a mild increase in lamina propria inflammatory cells (usually lymphocytes) and increased intra-epithelial lymphocytes.
   b. Lymphocytic Colitis. This entity was first described in 1982 in a small number of patients with chronic watery diarrhea in whom mild histologic changes in colonic
biopsies from normal appearing mucosa were noted (increased intraepithelial lymphocytes and a mild increase in lamina propria lymphocytes). As in collagenous colitis, other evaluation is negative and biopsy is necessary for diagnosis. Basically, the histology is the same as collagenous colitis, minus the diagnostic thickened collagen band. Colonic absorption is decreased. Microscopic colitis is 70-fold increase in patients with celiac disease.

While some feel that collagenous colitis and microscopic colitis may represent a spectrum, these entities are clearly distinct from inflammatory bowel disease, and do not develop it later. Treatment includes antidiarrheals, bismuth compounds, and budesonide. The best trial support budesonide 9 mg/day, with 80% rates of remission and NNT of 3. Many different therapies have been tried since there is no single effective remedy. The disease may resolve spontaneously in one-third of individuals.

E. Diversion Colitis. This is an inflammatory reaction which occurs in surgically defunctionalized segments of colon, and resolves when bowel continuity is restored. The mucosal changes of friable mucosa with ulcers in some cases can simulate ulcerative colitis or Crohn’s disease. Histology shows acute inflammatory changes, with crypt abscesses, mucin granulomas and lymphoid follicular hyperplasia. Histologic abnormalities can also include aphthous ulcers, crypt distortion and atrophy, all of which may mimic inflammatory bowel disease. Resolution of histologic abnormalities with short-chain fatty acid enemas suggests that the inflammation may be due to luminal nutritional deficiency.

F. Colitis with Systemic Disease (Vasculitis). Vasculitis that involves the intestine can involve medium-sized vessels (SLE, polyarteritis nodosa) or small vessels (Henoch-Schönlein purpura (HSP)), and Behcet’s disease. Medium-size vessel disease is more likely to cause transmural disease, and can lead to perforation. Small vessel disease causes mucosal ischemia. HSP is rare in adults; 90% of patients are under 10 years of age. Typical symptoms are colicky pain and bleeding. Any systemic vasculitis can affect the colon causing colitis, including polyarteritis nodosa and systemic lupus erythematosus. Colonscopic petechial lesions in the colon have been described in patients with Henoch-Schönlein purpura. These lesions resemble the skin lesions. Vasculitis has been demonstrated by biopsy.

Churg-Strauss Syndrome is a rare entity with asthma, hypereosinophilia, necrotizing vasculitis and extravascular granulomas. Colonic involvement is rare but multiple colonic ulcers can occur.

Behcet’s Syndrome consists of relapsing uveitis, and oral and genital ulcers. An associated colitis has been described which often involves the ileocecal area. Aphthous ulcers, skip areas and lymphocytic infiltrates may be present. For this reason, Crohn’s disease may be suspected. Some feel that the colitis of Behcet’s is indistinguishable from Crohn’s disease.

G. Other Causes of Colitis

a. Sarcoidosis. Gastrointestinal sarcoidosis can mimic Crohn’s when it causes a narrowed terminal ileum and granulomas in small and large bowel. Unlike Crohn’s disease, there is no transmural inflammation, lymphoid aggregates or strictures.
b. **Drugs.** Many drugs can cause colitis include aldomet, penicillamine, oral potassium supplements, and 5-flourouracil. Proctosigmoiditis in a teenager was associated with isotretinoin (Accutane); it resolved with removal of the drug but recurred after challenge. While series show an association with IBD, there is data to support its being the etiology. Colitis also occurs with gold therapy, but is rare. The endoscopic appearance is similar to ulcerative colitis; pseudomembranes have been reported. The illness usually resolves after gold is discontinued. A unique chemical colitis can occur in patients following colonoscopy. Such cases have usually been due to the contamination of the colonoscope cleaning channel with hydrogen peroxide (used during cleaning). White plaques can be mistaken for *C. difficile* colitis. Anthraquinone laxatives cause pseudomelanosis coli pigment in macrophages that causes discoloration of the colonic mucosa.

H. **NSAIDs.** Chronic nonsteroidal drug therapy can cause small intestinal and colonic injury, which can mimic Crohn’s disease. Small intestinal ulcers, strictures or perforations can occur in the jejunum or ileum, and can cause obstruction or hemorrhage. Although uncommon, the recognition of this entity is important. The distal intestinal strictures which simulate Crohn’s ileitis have a unique “membrane-like” narrowing, which may be missed by x-ray unless carefully searched for. Common symptoms are abdominal pain and bloody diarrhea. Focal colitis is common, both grossly and histologically. Flat colon ulcers may be seen. Histology can also look like ischemic colitis. NSAIDs can also exacerbate IBD.

a. **Neutropenic Colitis.** (Necrotizing enterocolitis in cancer patients: This is a complication of cytotoxic drug therapy often for leukemia or lymphoma. It is usually due to clostridial infection ([C. septicum or C. perfringens, C. paraperfringens]) whose toxins cause hemorrhagic necrosis. The abrupt onset abdominal pain, nausea and vomiting, diarrhea and fever progresses to peritonitis, septicemia and shock. The illness histologically resembles pseudomembranous colitis. There is a high-mortality.

b. **Graft-Versus Host Disease.** Graft-versus host disease occurs in the setting of bone marrow transplant. Both the skin and intestinal mucosa are targets for this syndrome. Diagnosis may be made by rectal biopsy which reveals focal proctitis, isolated injury to crypts and single-cell necrosis.

c. **Eosinophilic Colitis.** Eosinophilic gastroenteritis is rare, with eosinophils infiltrating the GI tract, most commonly stomach and small intestine. Allergy is a possible etiology. Eosinophils can infiltrate mucosa, muscle and/or submucosa. Symptoms depend on site of involvement. Small bowel disease causes abdominal pain, diarrhea and possible malabsorption. Diagnosis requires biopsy. Crypt distortion is uncommon, compared to Crohn’s disease. When ileoceleal involvement occurs, it may mimic Crohn’s disease. It can also be seen in ulcerative colitis. Drug hypersensitivity (rifampin, naproxen) is another cause. In children, it is often due to food allergy, usually resolving after age 5. Differential diagnosis includes parasites (Stronglyoides, Dientamoeba fragilis, and pinworm larvae). Symptoms are nonspecific but include abdominal pain and cramps, diarrhea and rectal bleeding. Biopsies show intense eosinophilic infiltration, more marked than the increase in lamina propria eosinophils which can be seen in inflammatory bowel disease.

I. **Diverticulitis.** Diverticulosis is present in 30-50% of individuals over 60. Most will be asymptomatic. Complications are diverticulitis (4%) and bleeding (5%). The most common symptoms of acute diverticulitis are abdominal pain (97%) and fever (90%). Less frequent symptoms are changes in bowel habits (40%) and urinary symptoms
(7%). Diagnosis made by classic presentation in a patient with known diverticulitis. Abdominal CT scan is the best diagnostic test for acute diverticulitis. Colonoscopy should be delayed for 6-8 weeks after acute attack of uncomplicated diverticulosis. Initial management is broad spectrum antibiotic, although this is now in question. It is complicated in 15% (abscess, perforation, fistula, obstruction) and bowel rest and a low-residue diet. Percutaneous drainage is indicated for abscesses over 4cm in size. Urgent surgical management is needed if there is a perforation, sepsis with failed medical therapy, obstruction or a large abscess that cannot be drained otherwise. Recurrence rate is 20% and is more common in younger patients (under 40). Elective surgery is indicated for fistula, chronic stricture and less commonly indicated for multiple recurrences.

J. **Segmental Colitis Associated with Diverticulitis (SCAD).** This is an inflammatory disorder that can mimic Crohn’s disease. It is most common in the sigmoid colon. Common symptoms are rectal bleeding, diarrhea and abdominal pain. It is most common in patients over age 40. Most respond to therapy with 5-ASA products, but in 20% there may be episodic recurrences.
Table 1. Differential Diagnosis of Colitis.

1. Idiopathic
   - IBD
     - Crohn’s Disease
     - Ulcerative Colitis
     - Indeterminate Colitis
   - Diversion Colitis
   - Collagenous Colitis
   - Microscopic (lymphocytic) Colitis
2. Infections (See section on Infectious Diarrhea)
   - Bacteria
   - Viruses
   - Parasites
   - Fungi
3. Ischemia
   - Mesenteric ischemia or thrombosis
   - Drug-induced (cocaine, oral contraceptives)
   - Proximal to mechanical obstruction
4. Physical Agents
   - Radiation
   - Solitary rectal ulcer syndrome (prolapse)
   - Glutaraldehyde/H₂O₂ (Endoscopic cleaning solutions)
   - Drug-induced
     - Gold – Isoretinoin – Laxatives – Allopurinol
     - Non-C. difficile antibiotic induced—i.e. ampicillin (usually right-sided colitis)
     - Chemotherapeutics (5FU)
     - NSAIDs
     - Aminophylline suppository
     - Hydrofluoric acid enemas
5. Immunologic
   - Mast cell disease
   - Allergic proctitis
   - Eosinophilic colitis
   - Graft vs. Host disease (GVHD)
   - Immunodeficiency syndromes
6. Associated with systemic vasculitis
   - Behcet’s disease
   - Sarcoidosis
   - Henoch-Schönlein purpura
   - Amyloidosis
7. Diverticular Disease:
   - Diverticulitis
   - Segmental Colitis associated with Diverticulitis
8. Miscellaneous
   - Endometriosis
QUESTIONS

Question 1. A previously healthy 53-year-old woman has had 3 months of watery diarrhea, up to 6 times a day, sometimes waking her at night. She has not lost weight. She has been taking ibuprofen for arthralgias for 3 months, and takes omeprazole daily for mild GERD. Colonoscopy is normal. The colon biopsy is below.

What is the next step?

A. Discontinuing the NSAIDs as this will result in immediate cessation of the diarrhea
B. Continue NSAIDs but add budesonide
C. Discontinue NSAIDs and start budesonide
D. No therapy is needed as this is likely functional

Answer C.

In several case reports, the evidence of association of NSAIDs with microscopic colitis is strong with onset soon after starting the drug and with resolution of symptoms several weeks to months after the drug is discontinued. It is best to stop the NSAIDs. In the meantime, treatment is indicated given moderately severe symptoms. Budesonide is reasonable.

**Question 2.** A 70-year-old woman with chronic kidney disease on dialysis has the sudden onset of left lower quadrant abdominal pain that doubles her over. The next day, she passes frank blood per rectum. In the ERC, she mild tenderness in the left lower quadrant, is afebrile, has a hematocrit of 29, a WBC of 12,000, normal electrolytes and lactate.

What is the best diagnostic test to order?

- A. Abdominal CT scan
- B. Mesenteric angiography
- C. Colonoscopy
- D. Bloodwork for hypercoagulable conditions

**Answer: A**

Abdominal CT scan with IV and PO contrast is the next best test. It showed focal colon wall thickening of the sigmoid and splenic flexure. At this point, colon ischemia is more likely than mesenteric ischemia. Most often, in older patients, this is not due to a hypercoagulable condition. Colonoscopy is indicated to confirm the diagnosis of ischemia but not if there is gangrene, and only to the area that is abnormal. A follow-up colonoscopy after recovery is indicated to evaluate the rest of the colon and confirm recovery.

Question 3. A 65-year-old woman presents with left lower-quadrant abdominal pain and constipation over the past 3 days. She has a history of hypertension and hyperlipidemia and is on simvastatin. On exam, she has focal tenderness and guarding in the left lower-quadrant. Labs show a WBC of 14,000 and elevated CRP.

What is the best diagnostic test?

A. Colonoscopy  
B. Small bowel enterography  
C. Abdominal CT scan  
D. CT colography

Answer: C
The presentation is consistent with acute diverticulitis, so colonoscopy is contraindicated. Abdominal CT is next best step but guidelines recommend colonoscopy at 6-8 weeks later if uncomplicated. The most common signs and symptoms are abdominal pain (97%), elevated CRP (90%), fever (90%), and elevated WBC (40%).

Question 4 – Case 3 Continued.
Management should include all EXCEPT ONE:
A. Broad spectrum antibiotics
B. Percutaneous draining of large abscesses
C. Bowel rest and low-residue diet
D. Segmental colectomy after recovery

Answer: D
Antibiotics, but this is now in question in mild cases.
Drain abscess if larger than 4 centimeters
Bowel rest, low-residue diet
Move is away from surgery for uncomplicated disease

Stollman et al. AGA guidelines Gastroenterol 2015.
Question 5 – Case Continued.
A colonoscopy is normal after she has recovered with antibiotics and bowel rest. A year later, she has a similar episode. A CT shows focal inflammation in the same area with a 2 cm abscess.

Which of the following is the best next step?
A. Antibiotics and bowel rest
B. IR for drainage of abscess
C. Segmental resection of sigmoid colon
D. Mesalamine

Answer: A
Treat symptomatically. Abscess does not need drainage if it is this small. No role for mesalamine in treatment of acute disease, and it is not clear if any role in prevention. Move is away from surgery for recurrences if mild.
**Question 6.** A 64-year-old man presented with a diverticular abscess with perforation. At urgent surgery, a diverting colostomy was made, with a Hartmann’s pouch. Several months later, prior to surgery for re-anastamosis, the surgeon asks for a colonoscopy to exclude colon cancer. The proximal colon is normal, but the rectum shows inflammation with ulcers and granulation tissue.

What is the best course of action?
- A. Further evaluation to rule out IBD is indicated
- B. Surgery should be delayed until rectal inflammation is controlled
- C. Broad spectrum antibiotics are indicated
- D. Surgery to re-anastomose is indicated

**Answer: C**
This represents diversion colitis. Inflammation is possibly due to alteration in fecal flora due to diversion, and has been shown to reverse with short chain fatty acids. The appropriate therapy is to reanastamose the colon, which will resolve the inflammation.

Question 7. A 32-year-old woman who is developmentally delayed presents with rectal bleeding. She is often constipated and occasionally manually disimpacts herself. On exam, there is a firm mass at 5 cm. on sigmoidoscopy retroflexed view shows a discrete ulcer with rolled edges. Biopsies show hyperplastic mucosa and the pathologist notes collagen in the lamina propria which is read as a desmoplastic reaction and raises a concern about malignancy.

Which is the most likely diagnosis?

A. Crohn’s disease  
B. Solitary Rectal Ulcer Syndrome  
C. Squamous cell carcinoma of the anus  
D. Adenocarcinoma of the rectum

Answer: B

The clinical presentation (constipation and rectal bleeding) with an ulcer strongly suggests SRUS. The histology showing hyperplastic mucosa is typical, the strands of collagen in the lamina propria are typical of SRUS, but an inexperienced pathologist can mistake them for the desmoplastic reaction seen in cancer. The most common differential diagnoses are Crohn’s disease and occasionally rectal cancer.

Saadah OI, Al-Hubayshi MS, Ghanem AT. Solitary rectal ulcer syndrome presenting as polypoid mass lesions in a young girl. World J Gastrointest Oncol 2010 2:332-334.