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Pseudomembranous Colitis

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Abstract

Pseudomembranous colitis is an inflammatory condition of the colon characterized by elevated yellow-white plaques that coalesce to form pseudomembranes on the mucosa. Patients with the condition commonly present with abdominal pain, diarrhea, fever, and leukocytosis. Because pseudomembranous colitis is often associated with *C. difficile* infection, stool testing and empiric antibiotic treatment should be initiated when suspected. When results of *C. difficile* testing are negative and symptoms persist despite escalating empiric treatment, early gastroenterology consultation and lower endoscopy would be the next step in the appropriate clinical setting. If pseudomembranous colitis is confirmed endoscopically, colonic biopsies should be obtained, as histology can offer helpful clues to the underlying diagnosis. The less common non-*C. difficile* causes of pseudomembranous colitis should be entertained, as a number of etiologies can result in this condition. Examples include Behcet's disease, collagenous colitis, inflammatory bowel disease, ischemic colitis, other infections organisms (e.g. bacteria, parasites, viruses), and a handful of drugs and toxins. Pinpointing the correct underlying etiology would better direct patient care and disease management. Surgical specialists would be most helpful in colonic perforation, gangrenous colon, or severe disease.

Keywords

Clostridium difficile; pseudomembranous colitis

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Introduction

Pseudomembranous colitis (PMC) is a manifestation of severe colonic disease that is usually associated with *Clostridium difficile* infection, but can be caused by a number of different etiologies. Prior to the use of broad-spectrum antibiotics, PMC was more frequently related with ischemic disease, obstruction, sepsis, uremia, and heavy metal poisoning.[1] The list of associated etiologies is vast, although *Clostridium difficile* infection (CDI) is still the most common cause.

On endoscopic examination, PMC is characterized by elevated yellow-white nodules or plaques that form pseudomembranes on the mucosal surfaces of the colon (Figure 1).[2,3] Endothelial damage from the initial event or disease process causes small areas of necrosis in the surface epithelium. The eruption of neutrophils, nuclear debris, and other inflammatory elements from the lamina propria onto the epithelium then leads to pseudomembrane formation.[4,5] Pseudomembranes can be up to two centimeters in diameter, scattered among areas of normal or erythematous mucosa; however, confluent pseudomembranes that cover the entirety of the mucosa can be seen in severe disease.[4,6]

Classification of pseudomembranous lesions can be made based on the degree and depth of inflammatory changes, with grading of lesions from type 1 (“summit lesions”, focal surface epithelial inflammation or necrosis) to type 3 (complete mucosal necrosis and significant inflammatory debris).[1,6,7] Histologic examination of biopsy samples vary based on the underlying cause, disease severity, and time course of the disease, which can make identification of the inciting trigger challenging.

This article will review the many diverse etiologies of PMC (Table 1). Although CDI is the most common cause, other less common etiologies of PMC will be described. These include ischemic colitis, collagenous colitis, inflammatory bowel disease, viral infection with cytomegalovirus (CMV), numerous bacterial and parasitic organisms, and multiple drugs and toxins. The purpose of this comprehensive review is to aid the general practitioner in the diagnosis of both typical (*C. difficle*) and atypical (non-*C. difficile*) causes of PMC.

Clostridium difficile infection

Clostridium difficile was first described in 1935, but its association with antibiotics and PMC was not described until the 1970s, corresponding with an increased use of broad-spectrum antibiotics.[7] *C. difficile* is an obligate anaerobic organism and toxin-producing gram-positive rod with the ability to form spores.[8] This latter characteristic lends itself to acquisition from the environment, particularly in nosocomial settings. It has been identified as the causative agent in 15–30% of antibiotic-associated diarrhea and as the primary cause of antibiotic-associated colitis.[9]

The clinical presentation of CDI is highly variable, ranging from the asymptomatic carrier to the patient with PMC, fulminant colitis, and toxic megacolon.[5,10,11] Accompanying signs and symptoms include fever, leukocytosis, abdominal cramping, and non-specific radiographic findings of colitis or megacolon. Severe cases can present with profound leukocytosis (with reports of white blood cell counts up to 100,000/mm^3), hypovolemia,

hypotension, hypoalbuminemia/protein-losing enteropathy, renal dysfunction, and reactive arthritis.[3,9–12] It is estimated that 3–8% of patients with CDI develop fulminant infection, which includes severe ileus, toxic megacolon, colonic perforation with subsequent peritonitis, and septic shock; many of these patients require colectomy and have an overall high mortality.[13]

The pathophysiology of CDI has been studied extensively and appears to progress in a particular sequence. The common first step is the disruption of the normal colonic flora with subsequent *C. difficile* colonization. This is usually precipitated by the use of antibiotics, but can also follow the use of chemotherapeutic drugs and immunosuppressive therapy.[5,14]

Antibiotics, such as clindamycin, penicillins, fluoroquinolones, and cephalosporins, are typically associated with CDI, but disease can occur with almost any anti-bacterial agent, including vancomycin and metronidazole, which are commonly used for treatment.[5,7] Furthermore, fluoroquinolones have been linked with the highly resistant and virulent North American pulsed-field gel electrophoresis type 1, restriction endonuclease analysis group BI, polymerase chain reaction (PCR) ribotype 027 (NAP1/BI/027) strain of *C. difficile*, responsible for a number of highly morbid, nosocomial outbreaks in North America and Europe.[15,16] Various studies have estimated the median time from *C. difficile* exposure to CDI to be two to three days, although symptoms can be delayed by up to three months and can occur even after a single dose of an antimicrobial or chemotherapeutic agent.[9,14] Proton pump inhibitors have also been shown to increase the risk of acquiring CDI, although the relationship remains unclear.[17]

Following initial colonization, clinically significant infection is mediated by toxin production. Most disease-causing strains produce two large protein exotoxins, toxin A and toxin B.[5,15] Once released in the colon, the toxins bind to cell-surface receptors and are internalized within the targeted cells.[5] Inside the cell, they cause glycosylation of small proteins involved in cell signaling and regulating pathways. This, in turn, leads to cytoskeleton disruption, causing cell morphologic changes, cytokine activation, and eventual cell death.[8,10,15,18] In addition, tight junctions between neighboring colonic cells are affected, allowing infiltration by neutrophils and causing an inflammatory response characteristic of colitis.[8] Pseudomembranes form via this influx of neutrophils into the mucosa and further activation of the native immune system by the toxins. Activation of macrophages and monocytes causes the release of pro-inflammatory cytokines like interleukin (IL)-1, IL-8, tumor necrosis factor (TNF), and leukotriene B4, which lead to additional mucosal injury and focal microabscess and pseudomembrane formation.[19]

Toxin A was widely believed to be the main causative agent of CDI, as it possesses both enterotoxic and cytotoxic properties. Nonetheless, more recent studies have reported disease associated with toxin A-negative, toxin B-positive strains.[5,8] An *in vitro* disease study in 2009 using hamster models demonstrated that toxin B, not toxin A, was the essential virulence factor in CDI.[20] This was later refuted in another hamster model study published in 2010, where mutant strains of *C. difficile* producing either toxin A or B were found to be just as likely as wild-type strains to cause significant disease. In addition, double-mutant strains producing neither toxin were found to be avirulent.[21] Given the variability of

published findings, it is prudent to focus on diagnostic testing that can identify the presence of both toxins.

Endoscopy is not routinely recommended in patients with typical CDI symptoms and positive laboratory testing due to its inherent risks and cost. However, it can be valuable in patients with consistent symptoms and negative testing, failure of conventional CDI therapy, or inability to obtain stool samples due to ileus.[3] Endoscopy should be avoided when fulminant colitis or toxic megacolon is suspected, given the procedural risk of perforation and subsequent peritonitis.[2]

Endoscopic findings in the colon vary in CDI, although PMC appears to be the most commonly described finding. Pseudomembranes can develop very early in the course of CDI with only mild symptoms. A small, single-center prospective study published in 1985 identified 149 *C. difficile*-positive patients very early in the course of symptomatic disease. Of the endoscopic examinations performed in 96 of these patients, 39 patients (41%) had PMC.[22] Several patients only underwent flexible sigmoidoscopy, which may have underestimated the true incidence of PMC, since up to one-third of patients have disease limited to the right colon.[23] As a result, colonoscopy is preferred when endoscopy is needed for diagnosis.

In mild cases of CDI, only signs of non-specific colitis may be seen, including erythematous, inflamed, or friable mucosa. Pseudomembranes may be absent or too small for visualization by endoscopy. In such cases, where clinical suspicion for CDI is high, biopsy is indicated to seek characteristic histologic findings of PMC.[3,24] Focal pseudomembranes can also coalesce to involve large areas of mucosa as the disease progresses, although the interposing mucosa will usually appear normal or only mildly erythematous or inflamed.[7]

Radiographic studies can also be advantageous in the diagnosis of CDI, given the wide spectrum of findings and choice of radiologic tests. Plain radiography of the abdomen may show evidence of colonic ileus, small bowel ileus, ascites, nodular thickening, or “thumbprinting”, a finding of wide transverse bands associated with haustral thickening. Severe disease may be demonstrated by marked colonic dilatation, perforation, or pneumoperitoneum.[2,7] Computed tomography (CT) is more commonly used given the lower sensitivity of plain radiography. CT findings in CDI include colonic wall thickening and nodularity, bowel wall stranding and edema, ascites, the “accordion” sign (ingested oral contrast becomes trapped between thickened haustral folds), and the “double-halo” sign (submucosal edema indicated by two or three concentric rings in the large bowel seen on transverse imaging) [2,7,23,25] A single-center retrospective review comparing the CT scans of 54 *C. difficile*-positive and 56 *C. difficile*-negative patients, all with symptoms, found that CT imaging alone had a sensitivity of 52–70% and specificity of 93% in diagnosing *C. difficile* colitis. Sensitivity varied based on the criteria used for diagnosis and generally favored the combination of both colonic wall thickening and another sign. Of particular note was a positive predictive value of 88%, meaning that those with positive diagnostic criteria by CT had an 88% chance of testing positive on a stool assay. This raises the possibility of

CT imaging being used for rapid diagnosis in those awaiting the results of stool assay testing.[25]

Initial testing in patients with non-specific gastrointestinal (GI) and/or infectious symptoms often includes a complete blood count (CBC). As previously discussed, leukocytosis is a prominent feature of CDI. A retrospective study of 70 hospitalized patients found a significant difference in the white blood cell (WBC) counts of *C. difficile*-positive and *C. difficile*-negative patients (15,800/mm^3 vs. 7700/mm^3), demonstrating the utility of a frequently obtained lab marker in initial suspicion and subsequent diagnosis of CDI.[26,27]

Specific laboratory testing for CDI has evolved greatly since it was first discovered as the main causative agent in PMC. In general, only stools from patients with diarrhea should be tested for *C. difficile*; one caveat to this recommendation is that when CDI is suspected in a patient with ileus, either solid stool or rectal swabs can be submitted for testing.[28] The *C. difficile* cytotoxin neutralization assay (CCNA) and toxigenic culture (TC) have both been called gold standard tests, although TC has been shown to detect one-third more cases of CDI when compared to CCNA. CCNA detects the cytopathic effect of toxin B on cells (cell rounding) and then neutralization of the effect with anti-toxin. TC involves standard stool culture for *C. difficile* (this will identify both toxigenic and non-toxigenic strains), followed a confirmatory test to detect the presence of toxin genes or actual toxin proteins.[27] Recently, both methods have been abandoned in standard clinical practice because results are often not available for several days.[13,27] Nonetheless, because of their high sensitivities and specificities, they are still used in epidemiologic studies and in trials comparing the efficacy of newer testing methods.[28]

For many years, the most frequently used diagnostic tests were enzyme immunoassays (EIA) for toxins A and/or B; however, more recent evidence has questioned the utility of EIA in single-step testing algorithms. One prospective study in 1993 compared gold standard testing (cytotoxin assay and toxigenic culture) to three different commercially available EIA (one detected toxins A and B, and two detected monoclonal antibodies directed against toxin A) using 285 stool samples from patients with suspected CDI. The results showed excellent sensitivity and specificity for cytotoxin assay and toxigenic culture, but poor sensitivity (75.5% for EIA detecting toxin A and B, 65.4% for EIA only detecting toxin A) and excellent specificity (97.8–100%) for all three EIA.[29] As previously discussed, toxin A-only EIA is more likely to have a false-negative result given the existence of toxin A-negative, toxin B-positive disease-producing strains; consequently, the most commercial available EIA can now detect both toxins.[28,30] A systematic review of rapid toxin detection kits for both toxins A and B, including EIA and similar testing modalities, reported overall sensitivities and specificities as 75–95% and 83–98% respectively, when compared to CCNA.[30] Given these results, efforts have been made to standardize two- or three-step diagnostic algorithms or further the use of more accurate one-step tests.

Newer advances in the diagnosis of CDI include nucleic acid amplification tests (NAAT) such as polymerase chain reaction (PCR), and stool testing for glutamate dehydrogenase (GDH). NAAT appears to be much more sensitive than EIA (>90% vs. 40–80%) with high specificity, when compared against gold standard.[27] NAAT also appears to have a generally

high negative predictive value, further supporting its use as a single-step test.[11,28] In addition, NAAT results are readily available when compared to TC or CCNA. However, as with most molecular testing, NAAT detects genes associated with toxin production rather than the presence of actual toxin in the stool. Given the number of colonized, asymptomatic patients, especially in the nosocomial and long-term care settings, there is potential for false-positive results.[11,27] Finally, NAAT is expensive and there is only limited data to suggest that rapid diagnosis of CDI by an accurate test is more cost-effective in the long term.[27,31]

GDH is an enzyme produced by *C. difficile*, both in toxigenic and non-toxigenic strains. Thus, testing for GDH is sensitive, but not specific for CDI, with the potential for high false-positive rates but very high negative predictive value. This has made it a useful screening test in multiple-step testing sequences.[9,11,28,32] Examples include EIA for GDH, followed by EIA for toxins A and B, CCNA, or NAAT; such approaches can have sensitivities of 75–100% and very high specificities, with rapid time to results.[9,23,27,31] Further evaluation of these approaches, including head-to-head testing and cost-benefit analyses, will determine which, if any of these methods, will become the new gold standard in diagnosis.

Finally, numerous clinical practice guidelines have recommended against repeat testing during the same episode of illness after a negative result. Repeat testing after a negative result is positive in less than 5% of samples and greatly increases the chances of false positive results.[9,28] In addition, testing for cure after symptom resolution and treatment completion is not advised; stool can remain positive for both toxins and bacteria as long as 30 days after symptoms resolve.[9,11,28,32] Positive results during that period may lead to unnecessary CDI treatment and related complications.

Once diagnosis of CDI is confirmed, it is important to immediately identify responsible antibiotic or chemotherapy agents and discontinue these drugs as soon as possible. The next step is to individualize the agent of choice for each case. Fidaxomicin and oral vancomycin are the only agents approved by the U.S. Food and Drug Administration (FDA) for treatment of CDI, although metronidazole has been used as a first-line agent since the late 1970s to 1980s.[9,32] Numerous studies have demonstrated equal or near-equal efficacy of vancomycin and metronidazole when treating initial and/or mild-to-moderate episodes of CDI.[13]

To choose the correct treatment, it is important to classify the severity of disease. Mild-to-moderate disease is typically defined as CDI with diarrhea and other symptoms not consistent with severe illness; recommended treatment is oral metronidazole for 10–14 days or oral vancomycin for 10–14 days if the patient cannot tolerate or does not improve significantly while on metronidazole.[9,11,28,32] Important adverse reactions of metronidazole therapy include nausea, vomiting, taste disturbances, and dose-dependent neurotoxicity.[9] Of note, fidaxomicin, a macrolide antibiotic, was approved for the treatment of mild-moderate CDI in 2011. Two separately conducted phase III, randomized, double-blinded trials demonstrated non-inferiority when compared to oral vancomycin; further analysis proposed that fidaxomicin might be superior in preventing recurrences in non-NAP1/BI/027 strains, although the small number of trials and short duration of follow-up limits additional

conclusions. Moreover, fidaxomicin is much more expensive than vancomycin, and it is unclear if its proposed benefits outweigh the cost.[28,33–35]

Proposed criteria for severe disease include WBC count greater than 15,000/mm^3, elevated creatinine (greater than 1.5 times baseline), advanced age, and/or hypoalbuminemia (serum albumin less than 3.0 g/dl). Recommended treatment for severe disease is oral vancomycin (125 mg four times daily) for 10–14 days.[9,11,15,24,28] A prospective, randomized, double-blinded, placebo-controlled trial published in 2007 compared the efficacy of metronidazole and vancomycin in mild and severe CDI in 150 patients; there was no significant difference in treatment with metronidazole and vancomycin in mild disease, however, vancomycin was found to be superior in achieving cure for severe disease.[36]

Criteria used to define severe and complicated CDI have varied and have included admission to an intensive care unit, hypotension that may or may not require vasopressors, fever greater than 38.5°C, ileus, megacolon, altered mental status, severe leukocytosis (WBC count greater than 35,000/mm^3) or leukopenia (WBC count less than 2000/mm^3), elevated serum lactate, and/or end-organ damage. Recommended treatment is oral vancomycin (500 mg four times daily) in conjunction with intravenous metronidazole and rectal vancomycin enemas in cases of severe ileus.[9,11,24,28]

In fulminant CDI refractory to medical therapy or with complications (toxic megacolon, perforation with peritonitis, or septic shock), surgical intervention, including hemicolectomy or subtotal colectomy, may be necessary. Several retrospective cohort studies have found a survival benefit with early surgical intervention, particularly in patients undergoing total colectomy; nevertheless, overall morbidity and mortality in fulminant CDI is very high despite surgery, with mortality rates up to 80% reported.[9,28,37–40] In one retrospective observational cohort study of 165 patients with complicated or fulminant CDI, colectomy appeared more beneficial in patients meeting certain criteria, including age greater than 65 years, leukocytosis (WBC count greater than 20,000/mm^3), serum lactate level between 2.2 and 4.9 mmol/L, and immunocompetence. Independent predictive factors of 30-day mortality included severe leukocytosis (WBC count greater than 50,000/mm^3), serum lactate levels equal to or greater than 5 mmol/L, age equal to or greater than 75 years, immunosuppressed state, or septic shock requiring vasopressor support.[38] Early surgical consultation is advised in these settings.

Recurrent CDI is defined by the complete resolution of presenting symptoms on appropriate therapy, with subsequent relapse and return of symptoms after completion of treatment; this may be very difficult to distinguish from re-infection. Reported recurrence rates in small studies and review articles range from 5% to 66%, although 20–25% is often cited as an average rate.[9,17,41,42] Risk factors for recurrent disease include advanced age, female gender, additional courses of antibiotics and/or chemotherapy, the use of GI medications or procedures, prolonged hospital stays, and prior episodes of recurrent CDI. In patients with a history of one recurrence, the rate of additional recurrences increases to 40–65%.[13,17,41,42]

The first episode of recurrent CDI is typically treated with the same agent that was used initially, either with oral metronidazole or oral vancomycin. Exceptions to this

recommendation are markers of increasing disease severity, including leukocytosis (WBC count greater than 15,000/mm^3), rising serum creatinine or baseline renal insufficiency, or other signs of systemic illness. In this setting, treatment with oral vancomycin (500 mg/day) is recommended.[9,13,28,43] A subset analysis of one of two phase III clinical trials evaluating the use of fidaxomicin in treatment of CDI found that fidaxomicin was an effective therapy for recurrent CDI when compared to standard of care, oral vancomycin (500 mg/day) for 10 days. In addition, fidaxomicin was associated with a lower rate of further recurrence within 28 days of treatment completion when compared to oral vancomycin.[44] One proposed mechanism for this finding is the improved preservation of normal colonic flora in those treated with fidaxomicin, thereby preventing relapse from residual *C. difficile* spores (within 14 days of treatment completion). Recurrences secondary to suspected re-infection (after 14 days from time of therapy completion) did not appear to vary significantly.[44] As previously discussed, the high cost of fidaxomicin limits its widespread use in initial disease, although it should be considered in recurrent CDI.

For patients with a second recurrence of CDI, there are limited data for the optimal treatment regimen. Metronidazole should not be used after the first recurrent episode, given the risk for cumulative neurotoxicity with repeated therapy.[9,28] A case cohort study from the placebo arm of two trials evaluating the use of a probiotic in conjunction with standard treatment for CDI, found a significant reduction in further episodes of recurrent CDI with the use of tapered and pulsed dose regimens of oral vancomycin. Recurrence rates in patients receiving oral vancomycin for 10–14 days, tapered regimens, or pulsed-dose regimens were 54%, 31%, and 14%, respectively.[41] Consensus guidelines suggest a combined tapered/pulsed dose regimen of vancomycin 125 mg four times a day for 10–14 days, 125 mg two times a day for 7 days, 125 mg once a day for 7 days, and 125 mg once every 2–3 days for 2–8 weeks.[9] There are minimal data for the use of rifampin or rifaximin to treat recurrent CDI, further limited by evidence of increasing resistance to rifampin in certain strains of *C. difficile*.[9,28]

In a patient with three or more recurrences despite treatment with a tapered/pulsed dose oral vancomycin regimen, fecal microbiota transplant (FMT) should be considered.[9,28] FMT is the delivery of a liquid suspension of donor stool from a healthy individual to an infected recipient with the goal of restoring normal gut flora and clinical cure of recurrent CDI. Techniques for FMT delivery vary, with success described using retention enemas, colonoscopy, and nasogastric tube.[45] Two systematic reviews, published in 2011 and 2013, reported resolution rates after FMT of 89–92%, with the 2013 review reporting a non-significant difference favoring lower rather than upper GI delivery of stool.[46,47] A small, open-label, randomized, controlled trial of 43 patients, published in 2013, compared rates of resolution in recurrent CDI with three different treatment modalities – oral vancomycin (2 g/day) for four days followed by bowel lavage and FMT, oral vancomycin alone (2 g/day) for 14 days, and oral vancomycin (2 g/day) for 14 days with bowel lavage on day 4 or 5. The study was terminated early when results showed a cure rate of 81% in the donor feces infusion group after one infusion (94% overall after a second infusion in two patients achieved cure), compared to 31% in those receiving oral vancomycin alone and 23% of patients receiving oral vancomycin and bowel lavage. The significant difference between the

groups may be explained by failure of oral vancomycin (in standard, tapered, and pulses-dose regimens) in many of these patients prior to study inclusion or by the dramatic success of FMT.[48] A multi-center long-term follow-up study of 77 patients at five different U.S. medical centers found an overall cure rate of 91% within 90 days after FMT. Of the seven patients who failed FMT, six achieved symptom resolution with repeat FMT or oral vancomycin therapy, with a secondary cure rate of 98%.[49] FMT remains a viable option in patients with multiple relapses of CDI, although further studies are required to establish a more uniform protocol to optimize delivery method, amount of stool used, method and materials used in preparation, and time to repeat FMT.

Ischemic colitis

Previously recognized as gangrene, ischemic colitis (IC) was first described as reversible vascular occlusion of the colon in 1963.[50] IC encompasses a wide and heterogeneous spectrum of disease that includes mild and reversible colopathy, acute colitis (including PMC), chronic colitis, chronic disease with stricture, gangrenous bowel, and fulminant pan-colitis.[51–53] It is the most common form of GI ischemic disease, comprising 50–60% of reported episodes, and is also a common cause of lower GI bleeding, along with diverticulosis and angiodysplasias.[54,55] Non-gangrenous colitis is the most common form of IC, and appears to account for 80–85% of reported cases; approximately 50% of cases are transient and reversible. Chronic IC appears to occur in 30–40% of cases.[56] A systematic review of eight studies reported an estimated incidence of 4.5–44/100,000 person-years.[57] The true incidence of IC, however, remains unknown, as many patients experience mild, self-limited episodes and do not seek medical attention or diagnostic work-up.[52,53,58] Estimated mortality ranges from less than 10% to more than 50%; these rates frequently correlate with the overall severity of disease and vary based on the study population being reported.[51,59,60]

Symptoms at initial presentation can vary, but patients often present with an acute onset of mild to moderate, cramping, lower abdominal pain, followed by tenesmus and sudden urges to defecate, with the passage of bright red to maroon blood or bloody diarrhea within 24 hours. Total blood loss is usually minimal and does not typically require blood transfusion. Severe abdominal tenderness and peritoneal signs are not usually observed but could be an indicator of transmural colonic necrosis, colonic perforation, or fulminant/gangrenous IC.[51,54,58] Additional signs may include fever and leukocytosis.[61] Presentation may also be affected by the area and extent of bowel ischemia; in fact, isolated right-sided colonic ischemia (IRCI) is associated with more pronounced abdominal discomfort and decreased or absent hematochezia. Patients with IRCI appear to have a worse prognosis, with higher rates of surgical intervention and mortality.[51,59,60,62,63] This particular finding will be discussed further in the section on pathophysiology.

IC is caused by a mismatch between local blood flow, from acute or chronic compromise of the colonic vasculature, and metabolic demand of colonocytes.[56] The blood supply of the colon dictates which areas are involved in a particular episode. The superior mesenteric artery (SMA) and inferior mesenteric artery (IMA) supply blood to the colon; the SMA typically branches into four small arteries, the inferior pancreaticoduodenal, middle colic,

right colic, and ileocolic arteries. Although anatomy will differ in individual patients, typically the terminal ileum, cecum, and proximal ascending colon are supplied by the ileocolic artery, the distal ascending colon and hepatic flexure by the right colic artery, and the proximal transverse colon by the middle colic artery. The IMA usually branches into the left colic artery, multiple sigmoidal branches, and the superior rectal artery. The left colic artery supplies the remainder of the transverse colon and descending colon, the sigmoidal branches supply the sigmoid colon, and the superior rectal artery supplies the proximal rectum; the hypogastric artery, a branch of the intern iliac artery, supplies the distal rectum. Ischemia of the rectum is rare given its dual blood supply. Collateral blood supply exists between the SMA and IMA, as well as the IMA and internal iliac arteries. The splenic flexure and sigmoid colon, where these distinct circulations meet, are considered watershed areas and are more susceptible to ischemic damage. The marginal artery of Drummond is one of the collateral arteries that supplies the splenic flexure; patients who have atypical anatomy and lack this artery are at increased risk of ischemia.[56,58,64,65]

The pathophysiology of IC varies based on the underlying etiology. IC is typically seen in individuals older than 60 years of age, but can present in younger individuals with suggestive history. The list of risk factors for and causes of IC is extensive and includes advanced age, atherosclerosis, vascular occlusion (trauma, vascular surgery, thrombosis, or embolism), small-vessel disease (diabetes mellitus, rheumatoid arthritis, amyloidosis, radiation, systemic vasculitides), shock/low-flow states, numerous medications (estrogens/progesterones, ergotamine, sodium polystyrene, catecholamines/vasopressors, alosetron, digitalis, Danazol, gold-containing compounds, non-steroidal anti-inflammatory drugs, neuroleptic agents), illicit use of cocaine and amphetamines, sickle cell disease, hypercoagulable disorders, long-distance running, chronic renal failure/end-stage renal disease requiring hemodialysis, colonic obstruction (intrinsic and extrinsic), and endoscopic or other invasive GI procedures.[51,54,58,66]

In most cases, no definitive cause is identified; these episodes are often attributed to transient and localized nonocclusive ischemia. The colon is thought to be particularly vulnerable to ischemic injury because of its innately low blood flow and physiologic decrease in blood flow during functional activity.[51,58] Shock and other low-flow states, such as the intraoperative and perioperative stages of vascular and cardiac surgeries, can precipitate vasoconstriction and shunting of blood away from the circulation supplying the colon.[49,54] The incidence of IC after abdominal aortic surgery has been reported to be as high as 7%, with rates of up to 60% after repair of ruptured abdominal aortic aneurysms.[65] Etiologies that cause increased transmitted pressure to the bowel wall, either through intrinsic or extrinsic compression, can lead to mechanical ischemia. These include intra- and extraluminal obstructions, such as tumors, adhesions, stool impaction, rectal prolapse, volvulus, strictures, or insufflation of the colon during procedures.[54,58]

Endoscopic examination in IC is highly variable but appears to have clustered findings based on disease type: transient IC, severe/gangrenous IC, and chronic IC. A retrospective analysis of 85 patients with IC demonstrated a predominance of non-gangrenous disease (96%), of which nearly 93% were transient disease. Findings in milder and transient IC included edematous and friable mucosa, erythema, erosions, ulcerations, petechial

hemorrhage, hemorrhagic nodules, and sharply demarcated areas of involvement. Severe colonic ischemia appeared to be associated with dark, blue-black nodules and dusky mucosa, as well as pseudopolyps and pseudomembranes. Chronic IC was more often characterized by luminal strictures with transmural fibrosis, granular mucosa, and haustral changes. The incidence of pseudomembranes in this particular study was not reported. In addition, segmental colonic involvement appeared to be most common; 80% of patients had only left colon involvement while only 2.4% of patient had evidence of pancolitis. About 5% of the cases demonstrated involvement of the right colon.[67]

As discussed previously, IRCI has a worse prognosis than other forms of colonic ischemia. In a retrospective analysis of 60 inpatients with IC, right colonic involvement was independent predictor of disease severity and occurred more frequently in patients receiving hemodialysis.[59] In a larger retrospective study of 273 patients with biopsy-proven IC, outcomes were also worse for the 26% of patients with IRCI. Of those with IRCI, 59.2% had an unfavorable outcome (compared to 17.3% of patients with non-IRCI) and 54.5% required surgery (compared to 10.9%). In addition, the mortality rate in patients with IRCI was 22.5%, in contrast to 11.9% in the non-IRCI group.[62] A more recent retrospective analysis of 313 patients with biopsy-prove or biopsy-compatible IC, published in 2010, demonstrated similar results; patients with IRCI had significantly higher rates of atrial fibrillation, coronary artery disease, end-stage renal disease requiring hemodialysis, prolonged hospitalization, disease requiring surgical intervention, and overall mortality (20.3% compared to 9%).[63] Finally, a multi-center prospective trial of 364 patients also found greater rates of unfavorable outcomes, including gangrenous colitis, systemic signs of illness, and need for surgery, in patients IRCI.[60]

The pathogenesis underlying the worse prognosis in IRCI is not clear; it has been postulated that the right colon, typically supplied by the SMA, is more sensitive to non-occlusive ischemia, as there is little collateral circulation and the vasa recta that supply the right colon initiate closer to the left colon and have to travel further to reach the right side. Hemodialysis increases the risk of hypotensive or relative hypotensive episodes, putting this vulnerable area at further risk of ischemia. In addition, IRCI may a red flag of impending SMA occlusion; acute mesenteric ischemia in these patients may further explain their increased morbidity and mortality.[51,59,62,63]

Another retrospective study of 68 patients with IC demonstrated similar findings on endoscopy, but did not report any evidence of PMC. In this particular study, 35 of the patients underwent repeat colonoscopy after initial presentation; although time to first and repeat colonoscopies was highly variable, 13 of these patients had normal endoscopic examinations, indicative of rapid recovery in patients with transient IC.[61]

At a microscopic level, colonic ischemia occurs via a series of changes in the tissue following hypoxic or anoxic injury. As previously discussed, complete occlusive ischemia from thromboembolism is rare; much of what is described in IC is from non-occlusive disease. As the duration of bowel hypoxia increases, the amount and depth of ischemic damage increases as well. The mucosa, being the most superficial layer and most sensitive to ischemia, is affected first. This leads to neutrophil-rich edema and vascular congestion in

the lamina propria. Continued ischemic insult leads to necrosis of the affected mucosa with erosion and ulcer formation, and involvement of the submucosa and deeper layers of the bowel wall, leading outward to the serosa. Submucosal injury can lead to the formation of pseudopolyps. A second source of injury occurs with rapid reperfusion and subsequent inflammatory response; this influx of inflammatory cytokines, neutrophils, and oxygen free radicals leads to additional mucosal injury. In some cases, this can lead to the formation of pseudomembranes over the affected mucosal surface, formed by the expulsion of inflammatory infiltrate from the lamina propria onto the luminal surface. Finally, gut bacterial translocation during initial ischemia and reperfusion and endotoxin release can contribute to systemic symptoms. Overall outcome can be divided into three categories: total restoration of structure and function, partial restoration with fibrosis and stricture formation, or progressive ischemia with eventual transmural necrosis.[4,58,65,68]

On histologic exam, findings are variable and often correspond with endoscopic examination. In the previously described retrospective study of 85 patients with IC, histology of biopsies obtained by endoscopy showed mucosal infiltration by leukocytes and inflammatory milieus in all samples. Erosions and ulcerations secondary to mucosal necrosis were also common, as well as hemorrhage and hyalinization within the lamina propria, crypt destruction, and crypt abscesses. Mucosal atrophy and fibrotic tissue were also noted in chronic IC, with occasional pseudomembranes and pseudopolyps seen in more severe ischemia.[67]

Ischemia as a cause of PMC is not a novel concept, but it is often not recognized early in the course of disease, owing to the strong association of pseudomembranes with CDI. In a previously-cited, prospective, multi-center study of 364 patients, 13.1% of endoscopic biopsies and 24% of surgical biopsies in patients with IC showed ulcers with pseudomembranes; this finding appeared more commonly in the first 48 hours of presentation, a statistically significant finding.[60] Case reports have also demonstrated and exemplified the difficulty in diagnosing IC presenting with pseudomembranes.[69,70]

A randomized, retrospective analysis of 49 biopsies of PMC, 25 with clinical CDI and 24 with clinical IC, found hyalinization and hemorrhage of the lamina propria, atrophic micro-crypts, full-thickness mucosal necrosis and diffuse pseudomembranes (on biopsy sample) to be significantly more associated with ischemia. Diffuse pseudomembranes seen on endoscopy and localized pseudomembranes on histology were much more frequently seen in CDI, while pseudopolyps (secondary to submucosal edema) and localized affected area on endoscopy were more frequent in IC. Of all the findings, hyalinization of the lamina propria was most specific for IC. It is unclear why this particular finding is so characteristic of ischemia.[71] These particular studies highlight the importance of early endoscopy and biopsy when ischemic colitis is suspected. Care should be taken to avoid overinflation of the colon, which may precipitate further ischemia or iatrogenic perforation.

Radiographic studies can be helpful in work-up and diagnosis of IC. Plain abdominal films of the abdomen can show non-specific findings like “thumbprinting”, distended, air-filled loops of bowel, colonic wall thickening, and loss of haustral markings. In addition to being non-specific, plain abdominal radiography is not sensitive for identifying colonic

ischemia.[56] Barium enema can show early findings of colonic ischemia, which include "thumbprinting" and pseudopolyps/pseudotumors; however, colonoscopy is typically the test of choice given the ability to also sample affected areas. Barium enema should also be avoided when gangrenous bowel or perforation is suspected. Mesenteric angiography is typically not indicated, given the typical transient and non-occlusive nature of most cases of IC. However, angiography should be considered when concomitant acute mesenteric ischemia is suspected, as in IRCI and when symptoms are out of proportion to what is typically seen in IC.[53,56]

A retrospective study of CT findings in 54 patients with IC showed predominantly segmental involvement, with a mean length of involved colon of 19 cm. Colonic wall thickness ranged from 2 to 20 mm. Further findings were divided into three categories: heterogeneous enhancement with severe colonic edema, loss of haustral markings, and shaggy luminal contour in 61% of cases, mild concentric and mural thickening with homogeneous enhancement of the colon and smooth contour in 33% of patients, and intramural air consistent with pneumatosis coli in the remaining 6% of cases. Other observed findings included concentric rings, with both double-halo and target signs, in 24% of patients (all in the first group), free peritoneal fluid, and portal venous gas. CT findings and clinical course of disease could not be accurately correlated, although colonic wall thickening greater than 1 cm, pneumatosis coli, and segmental colonic involvement all appear to be more indicative of IC. Overall mortality in this study was reported to be 11%.[72] CT imaging remains a useful, but limited tool in the diagnosis of colonic ischemia given the non-specificity of many findings. Other newer imaging modalities, including ultrasound/sonography, color Doppler sonography, and scintigraphy, continue to be evaluated for potential use in diagnosing of IC. Ultrasound has shown early promise in identifying the extent of colonic involvement, bowel wall thickening, and the presence of extracolonic fluid in colonic ischemic disease.[56,73]

Management of IC varies based on the severity of disease. If there is no evidence of gangrene, perforation, or peritonitis, medical management and supportive care is usually advised. This includes bowel rest, decompression via nasogastric or rectal tube, intravenous fluid resuscitation, discontinuation of any precipitating drugs or therapies, and antibiotics targeted against gut bacteria to prevent translocation. No large trials or studies exist to support the routine use of antibiotics in IC, although it continues to be recommended in consensus statements and reviews.[51,53,58] Further randomized controlled studies are required to demonstrate the benefit of antibiotic therapy. Work-up of underlying cardiac conditions, such as coronary artery disease, dysrhythmias, and congestive heart failure, should be initiated if there is adequate clinical suspicion. Medical management and risk modification of identified diseases is advised.[56] In most cases of IC, signs and symptoms usually resolve within the first 48 hours, with complete remission of abnormal imaging and endoscopic findings within two weeks; patients with more severe initial insult may become asymptomatic quickly, but have persistently abnormal findings on imaging or endoscopy for up to 6 months.[58]

In gangrenous and/or fulminant IC, emergent surgery is typically the first line of treatment. In fact, a systematic review on the treatment of IC could only find a consensus in the

recommendation of surgery for suspected peritonitis and failure of standard management.[74] In a retrospective study of 73 patients with IC, 13 patients underwent emergent surgery for clinical concerns of peritonitis and systemic disease; the mortality rate in this group was 62%. In the initially non-surgical group, 1 patient died of septic shock, while 20 of the remaining 59 patients had delayed surgery, of which 30% died.[55] A 10-year longitudinal study of 115 patients who underwent colectomy for acute IC reported an overall in-hospital mortality rate of 37% and median survival of 4.9 months (43.6 months for patients who survived to discharge); 17 patients underwent end-ostomy reversal, of which 18% died and 35% were admitted to the intensive care unit (ICU).[75] Patients in both studies underwent partial or total colectomy with a variety of end-ostomy approaches; the extent of bowel resection was directly related to the extent of ischemic damage present. It is clear that severe colonic ischemia carries a high mortality rate and this is likely a combination of both the extent of disease itself and the innate risks of emergent and repeated surgery. Early surgical consultation in patients with systemic illness or failure of conventional therapy is recommended.

Inflammatory bowel disease

PMC has been reported in patients with Crohn's disease and ulcerative colitis. Pseudomembranes can be seen in patients with inflammatory bowel disease (IBD) during a flare that may be related or unrelated to coexistent infections like CDI or CMV.[76–78] A study included patients with IBD and CDI who underwent lower endoscopy. A total of 93 patients were identified. PMC was documented in 13% of the patients. The only factor associated with presence of pseudomembranes was fever at the time of admission.[79] Although there is low prevalence of PMC in patients with IBD and CDI, empiric treatment for CDI has been recommended because of the increasing rate of CDI, hospitalizations, and complications in patients with IBD. [76] Pseudomembranous colitis has been reported in a case of ulcerative colitis exacerbation in association with CMV antigenemia and positive CMV immunohistochemistry in colonic mucosa. Histology of the colon showed crypt abscesses suggestive of ulcerative colitis. *C. difficile* toxin in stool and stool culture were negative. Interestingly, the patient improved solely with sulfasalazine 3 g/day, and repeat colonoscopy after almost 8 weeks showed morphological remission.[78]

Microscopic Colitis (collagenous & lymphocytic colitis)

Collagenous colitis (CC) was first described in 1976 in a middle-aged woman with abdominal cramping and chronic watery diarrhea.[80] It is a chronic inflammatory condition of the colon that falls under the larger category of microscopic colitis (MC). MC, initially described in 1980, is characterized by the presence of grossly normal-appearing mucosa with abnormal biopsy findings of lymphocytic inflammatory infiltrate within the lamina propria.[81] Now expanded to include CC, it is differentiated from LC histologically by the presence or absence of thick subepithelial deposits of collagen.[82,83] MC appears to comprise 4–13% of patients undergoing work-up for chronic diarrhea and in Europe, the incidence and prevalence of CC have been estimated as 0.6–5.2/100,000 persons and 10–15.7/100,000 persons respectively.[82] A population-based cohort study in Olmstead County, Minnesota described an incidence rate of 3.1/100,000 persons and prevalence of 39.3/100,000 persons

for CC.[84] MC tends to affect older individuals, with average age at diagnosis of 53 to 69 years, although pediatric cases have been reported; there is also a female predilection, particularly in CC.[82,83,85]

The most typical feature in both CC and LC is frequent, watery, non-bloody diarrhea, with variable association of abdominal cramping, nausea, vomiting, flatulence, fecal incontinence, mucus-containing stools, fatigue, and weight loss.[83,85–87] MC is also characterized by the sudden onset of symptoms (which can mimic infectious causes) and a clinical course that is chronic and benign, with frequent relapses.[86] The severity of diarrhea in CC appears to be related to the degree of inflammatory response seen on biopsy, rather than the thickness of the collagen band seen in the subepithelium. Symptoms may be further explained by dysfunctions in electrolyte movement across the epithelium of the colon and tight junctions between colonic cells, and increased levels of nitric oxide and prostaglandins, which appear to cause increased secretion.[82,85,86]

Both subtypes of MC are associated with other autoimmune conditions, including thyroid disorders, rheumatoid arthritis, diabetes mellitus, inflammatory bowel disease, and celiac disease. It is estimated that one-third of patients with diagnosed celiac disease have concomitant histologic changes consistent with MC on colonic biopsy. Given the association with autoimmune diseases, there is great interest in the correlation between MC and human leukocyte antigen (HLA typing); however, data have been conflicting in establishing a relationship.[4,82,88]

On endoscopic examination of patients with MC, the colon usually appears normal or has only minimal changes, including mild erythema or pallor; occasionally, edema, mucosal friability, pinpoint hemorrhage, and hyperemia have been observed.[4,83] Although rare, several case reports and case series have demonstrated the presence of pseudomembranes in CC, both by endoscopy and histology, all with negative testing for *C. difficile*.[88–92] Histology of CC is typically characterized by preserved crypt architecture, a mixed inflammatory infiltrate extending into the lamina propria, and deposition of collagen in a band-like or irregular distribution below the epithelium.[4,89] In a case series of 10 patients with CC with evidence of pseudomembranes, 17 of 72 colonic biopsy samples were normal, demonstrating the often patchy nature of CC. Pseudomembranes were identified in 52.7% of abnormal biopsy samples, and were composed of neutrophils, inflammatory debris, fibrin, and sloughed epithelial cells. The subepithelial layer of collagen exceeded 10 μm and there was preserved crypt architecture in all cases, further supporting the diagnosis of CC with concomitant pseudomembrane formation.[89] Given the rarity of this clinical finding, it is difficult to understand what underlies pseudomembranous CC. One proposed mechanism is nonsteroidal anti-inflammatory drug (NSAID) and/or estrogen use causing local ischemic changes, as this particular history was obtained in a number of reported cases. It has also been postulated that innate toxic and/or ischemic mechanisms of CC can cause this finding, and that pseudomembranous CC is part of the natural disease spectrum.[88–90]

Many cases of MC resolve spontaneously, both clinically and histologically. However, given the chronic and relapsing nature of MC, treatment may be indicated. Of note, there are no significant differences in treatment strategies of CC and LC. The first step in the

management of MC usually entails discontinuation of offending agents, such as NSAIDs and diarrhea-promoting agents, likely caffeine, alcohol, and dairy products. Anti-diarrheal medications like loperamide and diphenoxylate/atropine can be effective in symptomatic management and are often first-line agents for milder cases of MC.[82,85,87] A multitude of other treatments have been utilized in the management of CC in particular, although only a few appear to be effective in randomized clinical trials. A Cochrane review published in 2009 for treatment of CC found that budesonide was effective in the induction and maintenance of symptom and histologic resolution, as well as improving quality of life. In particular, budesonide is preferred over other corticosteroids because its rapid hepatic metabolism minimizes systemic effects. Evidence for the use of bismuth salicylate and mesalamine (with or without cholestyramine) was weaker, but was overall promising and favored utilizing these agents in active CC. Other agents, like *Boswellia serrata* extract, prednisolone, and probiotics, did not show any evidence of symptom improvement or cure.[93]

Behcet's disease

Behcet's disease is a systemic vasculitis that can involve small, medium, and large vessels. It is characterized by the presence of mucocutaneous apthous ulcers and ocular inflammation. It can affect any organ including the central nervous system.[94] Clinical presentation includes fever, malaise, painful chronic or recurrent oral and urogenital ulcers, a great variety of cutaneous lesions (acneiform, papules, pustular, nodules, erythema nodosum, palpable purpura), ocular involvement (uveitis, hypopyon, retinal vasculitis), neurological involvement (myelopathy, encephalopathy, venous thrombosis), other thrombosis (pulmonary artery thrombosis, superior and inferior vena cava occlusion, Budd-Chiari syndrome), arthritis, renal disease (glomerulonephritis, interstitial nephritis), arthritis, and pericarditis.[95]

Behcet's disease can cause ulcerations in the GI tract. These ulcerations can be identified at any level but most commonly affect the ileocecal region and colon. The severity of ulcerations varies, but can cause intestinal perforation in severe cases. Differential diagnosis includes infectious colitis and inflammatory bowel disease.[94,96] The diagnosis of Behcet's disease is established based on clinical findings and inflammatory markers, although both can be nonspecific. Experts recommend the use of the diagnostic criteria like the International Criteria for Behcet's disease or the International Study Group (ISG) criteria, the latter of which is most widely accepted. The latter requires the presence of recurrent oral aphthae, at least three times in a year, plus two of the following: (1) recurrent genital ulcers or scarring, (2) eye lesions (uveitis, cell in vitreous, retinal vasculitis), (3) skin lesions (erythema nodosum, papulopustular lesions, acneiform nodules, pseudo-vasculitis), or (4) a positive pathergy test. Sensitivity and specificity of these criteria was reported as high as 95% and 100%, respectively.[97] Treatment involves glucocorticoids, azathioprine, cyclophosphamide, cyclosporine, and TNF alpha-inhibitors.

A case of pseudomembranous colitis due to Behcet's disease was reported in a 5-year-old boy. He presented with abdominal pain and bloody diarrhea associated with a vesicular skin rash, redness in the eyes, and fever. Colonoscopy revealed PMC. *C. difficile* toxin in stool

was negative multiple times. He also had negative studies for ova, parasites, and rotavirus. He became obtunded with right hemiparesis. Magnetic resonance imaging (MRI) of the brain showed hemorrhagic lesions in the caudate, left periventricular white matter and pons. He was evaluated by rheumatology and diagnosed with Behcet's disease. He was started on immunosuppressive therapy with slow but significant improvement within months.[94]

Drugs and toxins

Medications, drugs, and chemicals can cause PMC by localized ischemia and/or inflammation. Examples include alosetron, a selective serotonin antagonist used in the treatment of irritable bowel syndrome (IBS), cocaine, dextroamphetamine, gold, and glutaraldehyde, a disinfecting solution used to clean endoscopes.[4,66,98–101] An isolated case report of paraquat (herbicide) toxicity causing PMC was published in 1981, but it is unclear what testing was pursued to make the diagnosis. It was presumed that vascular injury played a role in the initial colonic injury.[102]

Glutaraldehyde is a chemical solution used to disinfect endoscopes after use, and its association with PMC is a well-described phenomenon that occurs after inadequate rinsing of the solution from cleaned endoscopes. Presenting symptoms often occur within 48 hours of initial colonoscopy, and include abdominal pain, tenesmus, mucoid or bloody diarrhea, and fever.[66,103–105] Multiple case reports and case series have demonstrated endoscopic findings of acute toxic colitis, including mucosal necrosis, friable and erythematous mucosa, and inflammatory fibrinous exudates; pseudomembrane formation is also reported. Histological examination reveals depletion of the protective mucin layer in the colon, breakdown of the epithelium extending into the luminal surface of the mucosa and glands, neutrophilic exudate, hyperemia and edema within the lamina propria, and mucosal erosions and ulcerations. These changes appear to be mediated by direct mucosal injury and resultant inflammatory response. Treatment is usually supportive due to self-limited symptoms, and resolution occurs within one week.[103–105]

NSAIDs are known to cause mucosal damage, most commonly manifesting as inflammation, stricturing disease, or ulcers, which can occur at any level of the GI tract. These agents, which are also weak acids, interfere with the cyclooxygenase pathways that produce prostaglandins and other protective factors. A decrease in the production of prostaglandins leads to a less effective mucus-bicarbonate GI barrier, reduced submucosal blood flow, and slower recovery in response to mucosal injury. Diclofenac and indomethacin, in particular, have been responsible for cases of non-CDI PMC.[106–108] Chemotherapeutic and anti-proliferative agents can injure the bowel mainly through free radical production and inflammatory cytokine upregulation. Reported examples are cisplatin, cyclosporine A, docetaxel, and 5-fluorouracil. [106,109–111] In one case, a pediatric patient with severe rheumatoid arthritis developed PMC as a result of cyclosporine A, indomethacin, or a combination of the two agents.

Viral infections

Cytomegalovirus colitis

CMV is a common human herpes viral pathogen, in which clinical disease can affect nearly all organ systems. Initial infection in healthy individuals is usually asymptomatic or mild, after which CMV typically enters a latency phase.[112] Clinically significant infection is often secondary to reactivation of latent disease. It is most frequently reported in immunocompromised patients, but illness due to reactivation or primary infection can also occur in otherwise immunocompetent individuals.[113]

CMV colitis is an important GI manifestation of this viral infection and is most commonly diagnosed in patients with acquired immune deficiency syndrome (AIDS), solid organ transplantation, malignancy, chronic corticosteroid use, and inflammatory bowel disease.[114] It is rarely seen in immunocompetent hosts; a recent meta-analysis demonstrated only 44 published cases from 1980 to 2003. Most of these patients were older (age greater than or equal to 55 years), male, and had other comorbidities; younger and otherwise healthy patients more often had complete resolution of symptoms.[115]

Colonic involvement often presents with non-specific symptoms, including fever, weight loss, malaise, abdominal discomfort, watery or bloody diarrhea, hematochezia, fecal urgency, and tenesmus.[114,116,117] Severe infection can be complicated by acute hemorrhage from large ulcerations, or toxic megacolon in AIDS patients or those with concomitant ulcerative colitis.[114] Initial evaluation should include stool bacterial culture, ova and parasite examination, and *C. difficile* testing. If negative, flexible sigmoidoscopy or colonoscopy with biopsy should be considered as the next step.

Endoscopic examination can vary greatly, with diffuse or focal ulcerative lesions most commonly reported; pseudopolyps and pseudomembranes are less common findings. In a prospective study of 59 human immunodeficiency virus (HIV)-infected patients with various lower GI symptoms undergoing endoscopy, findings varied greatly. Results demonstrated a predominance of ulcers and colitis (39%) or ulcers alone (38%); pseudomembranes were rare and only present in one patient (2%).[116] A more recent retrospective analysis of 12 immunocompetent patients with CMV colitis found pseudomembranes in three (25%), with ulcerative findings in the remainder.[118] Additional case reports have demonstrated PMC as the presenting feature of CMV colitis, all discovered in immunocompromised patients after testing for *C. difficile* was negative.[119,120]

Pathophysiology of pseudomembrane formation in CMV colitis is unclear, although poor tissue perfusion and anoxia, similar to ischemic colitis, have been suggested. CMV appears to infect endothelial cells, leading to local vascular compromise, which may also explain the typical ulcerative findings.[120] Laboratory testing is crucial to correctly identify CMV as the causative agent. The gold standard for diagnosis is tissue immunohistochemical staining specific to CMV antibodies. Traditional histologic examination with Papanicolaou or hematoxylin-eosin stains shows characteristic findings of large basophilic inclusion bodies (“owl’s eye”) in the nuclei and cytoplasm of giant cells.[112,121] Use of plasma or whole blood CMV DNA polymerase chain reaction (PCR) has become increasingly common to

identify viremia, but negative results cannot exclude GI disease. A retrospective study of 81 solid organ transplant patients, 20 of whom had biopsy-proven CMV GI disease, showed PCR to have 85% sensitivity and 95% specificity for detecting clinically-significant GI involvement. Three patients (15%) had undetectable CMV viral load despite disease established by gold standard testing.[122]

Recommendations for treatment were developed for infected HIV/AIDS patients but are frequently applied to other immunocompromised and immunocompetent patients. A randomized, double-blinded, placebo-controlled study in 1993 showed statistically significant improvement in viremia, constitutional symptoms, and endoscopic appearance of the colon in patients treated with 14 days of ganciclovir versus placebo for biopsy-proven CMV colitis. Ganciclovir toxicity, predominantly manifested as cytopenias, was uncommon and did not appear to outweigh the benefit of treatment.[123] The most recent consensus guidelines recommend treatment with intravenous ganciclovir, with transition to oral valganciclovir once oral therapy is tolerated and can be absorbed effectively; alternative therapy includes intravenous foscarnet for those with contraindications or resistance to ganciclovir.[124] Small prospective and randomized-controlled studies have demonstrated equivalent rates of endoscopic, histologic, and clinical improvement of GI CMV disease in patients treated with foscarnet when compared to ganciclovir.[125,126] Therapy should be continued for 21–42 days, with absolute duration determined by resolutions of signs and symptoms. Maintenance therapy can be considered in the setting of multiple relapses.[124]

Bacterial infections

Clostridium ramosum

Clostridium ramosum is a frequent enteric anaerobe that is usually a commensal organism in the GI tract but occasionally can be a pathogen. It is commonly isolated from stool samples of children but has been associated with infections in different systems and bacteremia.[127] There are reports of *C. ramosum* causing cerebellar abscess, acute otitis media, lung abscess, spondylodiscitis, and gas gangrene. Risks factors associated include immunosuppression and extremes of age, although it has been identified in immunocompetent patients.[127,128] For diagnosis, it is recommended to include anaerobic cultures. *C. ramosum* is usually resistant to penicillin (due to the presence of beta-lactamase), quinolones and clindamycin. In general, clostridia, especially *C. ramosum*, respond to treatment with chloramphenicol, piperacillin, metronidazole, imipenem, and combinations of beta-lactam drugs with beta-lactamase inhibitors. Only one patient with pseudomembranous colitis attributed to *C. ramosum* has been reported. The patient presented with watery diarrhea, fever, and abdominal pain with negative stool cultures and evaluation for *C. difficile* toxin. A lower endoscopy showed several ulcerations in the ascending colon with pseudomembranes. Biopsies were taken. Blood cultures were positive for *C. ramosum*.[129] The patient responded to metronidazole treatment for two weeks.

Enterohemorrhagic Escherichia coli O157:H7

Escherichia coli is a gram-negative, facultative-anaerobic, rod-shaped bacterium that is ubiquitous in the environment and in humans and is associated with a range of clinical

disease. Of particular importance is *E. coli* O157:H7, an enterohemorrhagic strain that was first described as a human GI pathogen in 1983.[130] It is strongly associated with outbreaks of hemorrhagic colitis, often linked to the consumption of undercooked ground beef. The spectrum of clinical disease with *E. coli* O157:H7 is broad and includes asymptomatic carriage, non-bloody diarrhea, hemorrhagic colitis with frank bloody diarrhea, severe colitis with pseudomembrane formation, hemolytic-uremic syndrome (HUS), and thrombotic thrombocytopenic purpura (TTP).[4,131,132] Enterohemorrhagic *E. coli* is able to cause clinical disease through the activity of specific enterotoxins, often called verotoxins or Shiga/Shiga-like toxins, because of their similarity to initially described *Shigella* toxins that cause hemorrhagic changes in the bowel mucosa.[131,133] Shiga toxins have been shown to possess neurotoxic properties and cause intestinal secretion, microangiopathic changes, and an inflammatory response with cytokine production.[134] Clinical presentation of *E. coli* O157:H7 varies greatly and can include abdominal pain, fever, vomiting, watery diarrhea, bloody diarrhea, and involvement of organ systems outside of the GI tract. Severe disease can be fatal.[131,134]

At least two cases (one pediatric and one adult) of pseudomembranous colitis caused by *E. coli* O157:H7 have been reported. Both patients tested negative for *C. difficile*; the pediatric patient had spontaneous resolution of symptoms while the adult patient required a total colectomy for diffuse necrotic changes. Pseudomembrane formation in these patients is postulated to occur from the innate ability of Shiga toxins to cause microvascular changes and endothelial damage in the colon. [132,135] Another case series published in 1990 reported four cases of PMC in patients with stool cultures positive for *E. coli* O157:H7; unfortunately, only one had a negative stool culture for *C. difficile*, as it was not obtained in the remaining three patients.[133] This highlights the importance of testing for CDI as the first step in the work-up of PMC. There are no consensus guidelines for the treatment of *E. coli* O157:H7 infection. Typical management is supportive and includes intravenous fluid repletion and nutrition. The use of antibiotics is controversial and it is unclear if there is any benefit; one systematic review published in 2006 demonstrated that there was insufficient evidence to make a recommendation for the use of antimicrobials, with the need for further randomized controlled trials.[136,137]

Klebsiella oxytoca

Klebsiella oxytoca is a non-motile, aerobic and facultatively anaerobic, gram-negative rod. *Klebsiella* infection can manifest in many ways, including pneumonia, meningitis, urinary tract infection, endophthalmitis, abscess, osteomyelitis, and hemorrhagic colitis.[138] In particular, *K. oxytoca* is associated with antibiotic-associated hemorrhagic colitis. It is postulated that the overgrowth of cytotoxin-producing strains of *K. oxytoca* in the colon during antibiotic therapy can cause direct mucosal damage and hemorrhagic changes. In a retrospective study of 22 patients, six patients had findings on endoscopy consistent with antibiotic-associated hemorrhagic colitis; of these six patients, five had positive cultures for *K. oxytoca*.[139] A single case of antibiotic-associated PMC caused by *K. oxytoca* (the patient was *C. difficile* negative) has been reported.[140] All reported cases appear to be have been diagnosed with selective stool culture and treatment is supportive.

Plesiomonas shigelloides

Plesiomonas shigelloides is a facultatively anaerobic, gram-negative, rod-shaped bacterium in the family *Enterobacteriaceae*, which also contains *Escherichia*, *Shigella*, *Salmonella*, and *Klebsiella*. It has been shown to cause gastroenteritis and diarrhea; severe disease can manifest as invasive colitis similar to shigellosis or voluminous secretory diarrhea. Symptoms include fever, abdominal pain, nausea, vomiting, watery or bloody diarrhea, and dehydration. The pathophysiology of infection with *P. shigelloides* remains unknown, although cytotoxin and enterotoxin-mediated damage has been proposed, and is still under investigation.[141,142] A case of PMC, presenting with six months of bloody diarrhea, and attributed to *P. shigelloides* has been reported; the patient was treated with oral tetracycline after multiple positive stool cultures and improved rapidly. Of note, testing for *C. difficile* was not obtained due to the patient's atypical symptoms.[143] Symptoms appear to last longer than in cases of infection caused by similar enteropathogenic organisms and antibiotic therapy may be indicated to decrease the duration of illness.[141]

Salmonella enterica

Salmonella enterica is a flagellated, facultatively anaerobic, gram-negative rod; it can be further divided into six different subspecies and thousands of serovars. Clinical disease can be classified into three general syndromes, including typhoid fever, enterocolitis/diarrhea, and bacteremia, as well as asymptomatic carriage.[144,145] In particular, GI disease is caused by bacterial colonization in the intestine, followed by invasion of the epithelial cells and activation of local inflammatory response, with resultant neutrophil infiltration, crypt abscess formation, localized mucosal necrosis, edema, and increased secretion of exudative fluid into the lumen.[144,146] Non-typhoidal *Salmonella* infection often presents with nausea, vomiting, abdominal discomfort, and watery or bloody diarrhea. Endoscopic examination often reveals evidence of acute colitis, with hyperemic and friable mucosa, ulcerations, erosions, fissures, and segmental/patchy areas of involvement.[4,145] At least one case of PMC secondary to *S. enterica* has been reported; the patient did not improve with empiric treatment for CDI, after which testing for *C. difficile* was found to be negative, with subsequent stool culture positive for *S. enterica* serotype *infantis*.[147] Symptoms usually resolve spontaneously with supportive care, including oral or intravenous rehydration therapy. Antibiotic therapy is not indicated for self-limited GI infection, although fluoroquinolones, third-generation cephalosporins, trimethoprim-sulfamethoxazole, and ampicillin can be used in severe disease or to prevent systemic manifestations.[144,145]

Shigella

Shigella is a genus of non-motile, facultatively anaerobic, gram-negative rod-shaped bacteria. Acute *Shigella* infection, also known as shigellosis, is no longer a common cause of infectious diarrhea in developed countries, but continues to cause severe disease and death in developing countries and vulnerable populations. Infection usually presents with fever, followed by a watery secretory diarrhea that progresses to invasive and hemorrhagic colitis, mediated by Shiga toxins. This is the same mechanism observed in *E.* coli O157:H7. Systemic manifestations can include electrolyte derangement, protein-losing enteropathy, and malnutrition. A retrospective study of 133 colonic biopsies from 81 patients with

culture-proven shigellosis demonstrated a wide range of histologic findings on biopsy and autopsy samples; 17 of 29 autopsy samples showed evidence of pseudomembrane formation.[148,149] A pediatric case report published in 1976 reported similar findings, with fulminant PMC requiring colectomy and confirmation of *Shigella dysenteriae* on stool culture, but this predated the recognition of CDI as a cause at the time.[150] Treatment of shigellosis is typically supportive, primarily by means of oral rehydration therapy, with frequent spontaneous resolution. However, antibiotic therapy can be used to alleviate symptoms, prevent further disease transmission, and reduce the risk of systemic complications. Fluoroquinolones are the antibiotic of choice in the treatment of shigellosis, although use is cautioned in the pediatric population given the risk of joint and cartilage rupture. There is increased concern for fluoroquinolone-resistant strains; these strains can typically be treated with macrolides or third-generation cephalosporins.[149]

Staphylococcus aureus

Staphylococcus aureus has been reported as the etiology of enterocolitis in hospitalized patients who received antibiotics. One study published in 1963 reported 155 patients, all of them with a stool culture positive for *S. aureus*. Most of the patients had diarrhea (153 in total), 31% of the patients died and nine patients were found to have pseudomembranous colitis at autopsy.[151] *C. difficile* was not identified as a cause of colitis and PMC until 1978. This raises the possibility that cases of colitis attributed to *S. aureus*, at times due to responsiveness to vancomycin despite negative stool culture, were in fact misdiagnosed cases of CDI.[152] *S. aureus* can colonize healthy humans with a prevalence of 30 to 50%. It is thought that 10% of colonized individuals will host *S. aureus* in the GI tract.[153] *S. aureus* enterocolitis is associated with prior use of antibiotics especially metronidazole and fluoroquinolones, immunosuppression, prior use of proton pump inhibitors, prior methicillin-resistant *S. aureus* (MRSA) colonization, and recent abdominal surgery.[154] Symptoms include fever, nausea, vomiting, inflammatory diarrhea, and abdominal pain.[155] Imaging is non-specific and can show bowel thickening, with various degrees of intestinal distention (including toxic megacolon) to bowel perforation.[155,156] If endoscopy is performed, areas of patchy erythema, ulcerations, and necrosis can be seen. *S. aureus* enterocolitis can present with pseudomembranes that can be loosely adherent and located in both the upper and lower GI tract.[153] This differs from pseudomembranes seen in CDI, which are tightly adherent, well-demarcated, and typically located only in the colon and ileocecal valve.[152] Pathology findings of *S. aureus* enterocolitis show pseudomembranes characterized by fibrin, necrotic areas with polymorphonuclear cells, and clusters of gram-positive cocci in the luminal border. Necrotizing disease of the bowel, including complete bowel necrosis and gangrene, has also been reported.[152] The diagnosis of *S. aureus* enterocolitis is made by excluding other etiologies, gram stain of pathology specimens, and stool culture positivity for *S. aureus*. Treatment with vancomycin is usually successful, but in severe cases with acute abdomen, bowel gangrene, toxic megacolon, or perforation, surgery is required.[155,156]

Yersinia enterocolitica

There are more than ten species of *Yersinia* but only three are important pathogens in humans. These include *Y. pestis*, which causes plague, and *Y. pseudotuberculosis* and *Y.*

enterocolitica, which cause yersiniosis, a condition characterized by GI symptoms such as diarrhea. Only *Y. enterocolitica* has been reported as a cause of PMC.[157] *Y. enterocolitica* lives in the oropharyngeal lymphoid system and the GI tract of several vertebrates, including pigs.[158] Transmission is typically foodborne (especially undercooked pork products) or waterborne, but transmission via blood transfusion has been reported.[159,160] Once *Y. enterocolitica* is ingested it can invade through the gastric mucosa and localize in the lymphoid tissue within the gastric wall and regional mesenteric lymph nodes. Clinically it can cause acute yersiniosis, pseudoappendicitis syndrome, and sepsis. Acute yersiniosis can present with diarrhea (acute or chronic), fever, abdominal pain, and sometimes nausea, vomiting, and sore throat are present. Acute yersiniosis can also mimic appendicitis.[161] Additionally it can cause severe colitis associated with bloody diarrhea, perforation, intussusception, toxic megacolon, ileus, necrotic small bowel, cholangitis and septicemia.[162] Extraintestinal manifestations have been reported including erythema nodosum, reactive arthritis, abscesses, and lymphadenitis.[163,164] One case of PMC secondary to *Y. enterocolitica* has been described. The 15-month-old patient presented with acute fever and diarrhea after antibiotic treatment for otitis. A sigmoidoscopy showed PMC and the patient was started on vancomycin without response. *C. difficile* toxin was negative in stool. Stool culture revealed *Y. enterocolitica.* [157] Diagnosis of *Y. enterocolitica* is by culture from stool samples, blood, lymph nodes or any infected tissue. Serologic tests like enzyme linked immunosorbent assays (ELISA) are available to identify IgG, IgA and IgM antibodies but careful interpretation is needed in areas with high prevalence of *Yersinia*.[158] Treatment options include fluoroquinolones, trimethoprim-sulfamethoxazole, doxycycline, and third-generation cephalosporins. Recommended length of treatment is from five days to three weeks based on the severity of the disease.[163]

Parasitic infections

Entamoeba histolytica

Entamoeba histolytica is an anaerobic parasitic protozoan that can be found worldwide but is endemic to a number of developing nations. *E. histolytica* has a relatively simple life cycle within the human host, existing as either infectious cysts or trophozoites, which form after cysts are ingested and have reached the terminal ileum or colon.[165,166] The spectrum of disease includes asymptomatic infection with or without eventual clearance, mild diarrhea, amebic colitis with occult-blood positive or frank bloody diarrhea, fulminant amebic colitis that may be complicated by necrotizing colitis or toxic megacolon, as well as liver and, rarely, brain abscesses. Amebic colitis often presents with fever, abdominal discomfort, weight loss, and watery or bloody diarrhea. It is caused by trophozoite invasion of the intestinal mucosa through the protective mucous layer of the colon. When the parasitic surface protein, also called lectin, binds to host cell surface *N*-acetyl-D-galactosamine, this results in an inflammatory cascade with activation of neutrophils, macrophages, and cytokines that mediate further damage and eventual cell death; the degree of damage determines the type and size of the lesions that are produced. On endoscopy and histologic exam, amebic colitis is characterized by mucosal thickening, edema, inflammation, ulcerations (classically flask-shaped), necrosis, and in severe cases, intestinal perforation.[165–168]

Two cases of fulminant amebic colitis with pseudomembrane formation have been reported, both of which required colectomy, with one patient dying two weeks after initial diagnosis.[169,170] Diagnosis of amebic colitis was previously made by direct microscopic examination of the stool; however, this method is limited by operator variability and difficulty in differentiating between *E. histolytica* and *E. dispar* (a common, but non-pathogenic species). ELISA stool essays are now more commonly used given their increased sensitivity, as well as biopsy during colonoscopy to look for trophozoites. Stool PCR remains an ongoing area of research.[165] Recommended treatment of amebic colitis are nitroimidazoles, typically metronidazole. In fulminant amebic colitis, broad-spectrum antibiotic coverage is suggested to provide adequate coverage of translocated gut bacteria.[165,167]

Schistosoma mansoni

There are five species of schistosoma that can infect humans. *Schistosoma mansoni* is most common in Africa and South America. Infection is common in freshwater areas where the snail *Biomphalaria* spp. resides, an intermediate host in the life cycle of schistosoma.[171] Infection can be chronic or acute, which is most commonly seen in travelers. Transmission occurs after contact with fresh water. Feces of the infected human or animal reservoir will seed eggs into the fresh water. The eggs will release miracidia that penetrate the snail. After two cycles of sporocysts, the snail will release cercariae into the water. The cercariae can infect humans by penetrating the skin and then later migrating to the blood vessels and finally to the liver where they mature into adults. From the portal circulation, adult schistosoma will reach the mesenteric veins of the colon and in one to three months the female worms will produce eggs. Adult worms can survive from five to 30 years.[171]

Acute symptoms include fever (known as “Katayama fever”), skin rash associated with itching (known as “swimmer’s itch”), malaise, arthralgias, headache, diarrhea and abdominal pain.[172] Chronic infection can be asymptomatic or associated with chronic diarrhea, abdominal pain, and intestinal obstruction (due to strictures, inflammatory mass or acute appendicitis).[173] Hepatosplenic schistosomiasis can present with splenomegaly, non-cirrhotic portal hypertension, nodular liver (due to periportal fibrosis) and GI varices.[174] Interestingly, liver function is not impaired. *S. mansoni* can also cause pulmonary symptoms especially if hepatosplenic disease is established. Dyspnea is common and eggs can invade the pulmonary arterioles causing a granulomatous reaction that can lead to pulmonary hypertension. Chest X-ray can show miliary nodules. Glomerular disease and neurological involvement have also been reported. Diagnosis is made via identification of eggs in the stool (gold standard); detection of antigen or deoxyribonucleic acid (DNA) in blood, stool or urine; or by serologic testing.[171] Biopsy of the rectum or intestinal polyps can demonstrate characteristic granulomas with eggs in the mucosa.[175] Treatment is praziquantel (one dose of 40 mg/kg).[171] Oxamniquine can be used for schistosomiasis resistant to praziquantel.

Two cases of ischemic necrosis of the sigmoid colon associated with pseudomembranous colitis due to *Schistosoma mansoni* in children have been reported. The patients developed acute abdomen and underwent laparotomy that showed necrosis of the bowel. Both patients underwent hemicolectomy with colostomy. Pathology was similar in both cases and showed

complete destruction of the mucosa and part of the submucosa with eggs of *S. mansoni* in the necrotic areas. Necrosis also involved the muscular layer and serosa in which granulomas were seen. Regional lymph nodes showed numerous eggs and granulomas. Both patients were treated with oxamniquine with good response.[176]

Strongyloides stercoralis

Strongyloides stercoralis is a human parasitic roundworm that is found in tropical, subtropical, and temperate regions; in particular, it is endemic to the southeastern United States, Africa, the West Indies, parts of southern Asia, and South America.[177,178] The life cycle of *Strongyloides* is intricate and allows for the organism to complete a full life cycle while residing in a human host. This causes recurrent autoinfection and persistent disease if left undiagnosed and untreated. Clinical disease can manifest in many ways, and includes asymptomatic parasitism, pruritic rash, pulmonary symptoms like cough, dyspnea, and wheezing, and GI symptoms of abdominal discomfort, nausea, vomiting and diarrhea.[177,178] The most severe presentations of *Strongyloides* infection are hyperinfection (caused by an increase in the total worm burden from recurrent autoinfection) and disseminated disease (spread of the parasite to organs other than the GI tract and lungs). Immunosuppressed individuals are at highest risk for these forms of infection.[178]

GI disease has been reported to involve the stomach, small intestine, and colon. A retrospective study of six patients with GI manifestations of *S. stercoralis* reported of findings on endoscopy of the colon, including friable and erythematous mucosa, mucosal edema, ulcers and erosions, white-yellow exudates, pseudopolyps, and loss of haustral markings.[179] At least two cases of colitis with pseudomembrane formation due to *S. stercoralis* infection have been reported; both patients suffered from chronic diseases that caused an immunosuppressed state and both were found to have evidence of hyperinfection.[180,181] It is unclear what triggered pseudomembrane formation, although *Strongyloides* appears to promote edema and inflammatory changes in the colon. Diagnosis typically begins with stool ova and parasite examination, although this is not always sensitive; ELISA testing can be used when there is high suspicion.[182] CBC should also be obtained to look for peripheral eosinophilia. Treatment of strongyloidiasis includes anti-helminthic agents like thiabendazole, ivermectin, and albendazole. Follow-up stool ova and parasite examination should be performed after treatment completion as a test of cure.[178]

Conclusion

PMC is an inflammatory condition of the colon that is most often a manifestation of CDI. If confirmed endoscopically and testing for CDI is negative, other less common etiologies should be entertained in order to identify the culprit. Ischemic colitis, inflammatory bowel disease, microscopic colitis, medications, chemicals, vasculitis, and multiple infectious pathogens can be responsible for non-*C. difficile* PMC. Repeat testing is not recommended when initial CDI testing is negative. Visualization of pseudomembranes on colonoscopy should be a cue for biopsy of unaffected and affected areas during the procedure. Histology varies significantly by underlying etiology and can establish the diagnosis. A careful and thorough history is crucial; quality and duration of symptoms, exposure history, chronic

medical problems (including conditions that cause an immunosuppressed state), and a current medication list will aid in narrowing the differential diagnosis. Treatment is specific to the underlying etiology and will be individualized. Consultation with a gastroenterologist should be considered early in the course of illness. In cases of suspected severe or fulminant colitis, early discussion with surgery consultants is also advised.

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Abbreviations

PMC	pseudomembranous colitis
CDI	*Clostridium difficile* infection
CMV	cytomegalovirus
IL	interleukin
TNF	tumor necrosis factor
PCR	polymerase chain reaction
CT	computed tomography
WBC	white blood cell
CCNA	cytotoxin neutralization assay
TC	toxigenic culture
EIA	enzyme immunoassays
NAAT	nucleic acid amplification tests
GDH	glutamate dehydrogenase
FDA	Food and Drug Administration
FMT	fecal microbiota transplant
IC	ischemic colitis
IRCI	isolated right-sided colonic ischemia
SMA	superior mesenteric artery
IMA	inferior mesenteric artery
ICU	intensive care unit
IBD	inflammatory bowel disease
CC	collagenous colitis

MC	microscopic colitis
LC	lymphocytic colitis
HLD	human leukocyte antigen
NSAID	nonsteroidal anti-inflammatory drug
GI	gastrointestinal
ISG	International Study Group
MRI	Magnetic Resonance Imaging
AIDS	acquired immune deficiency syndrome
HIV	human immunodeficiency virus
HUS	hemolytic-uremic syndrome
TTP	thrombotic thrombocytopenic purpura
MRSA	methicillin-resistant *Staphylococcus aureus*
ELISA	enzyme-linked immunosorbent assay
DNA	deoxyribonucleic acid
CBC	complete blood count
IBS	irritable bowel syndrome

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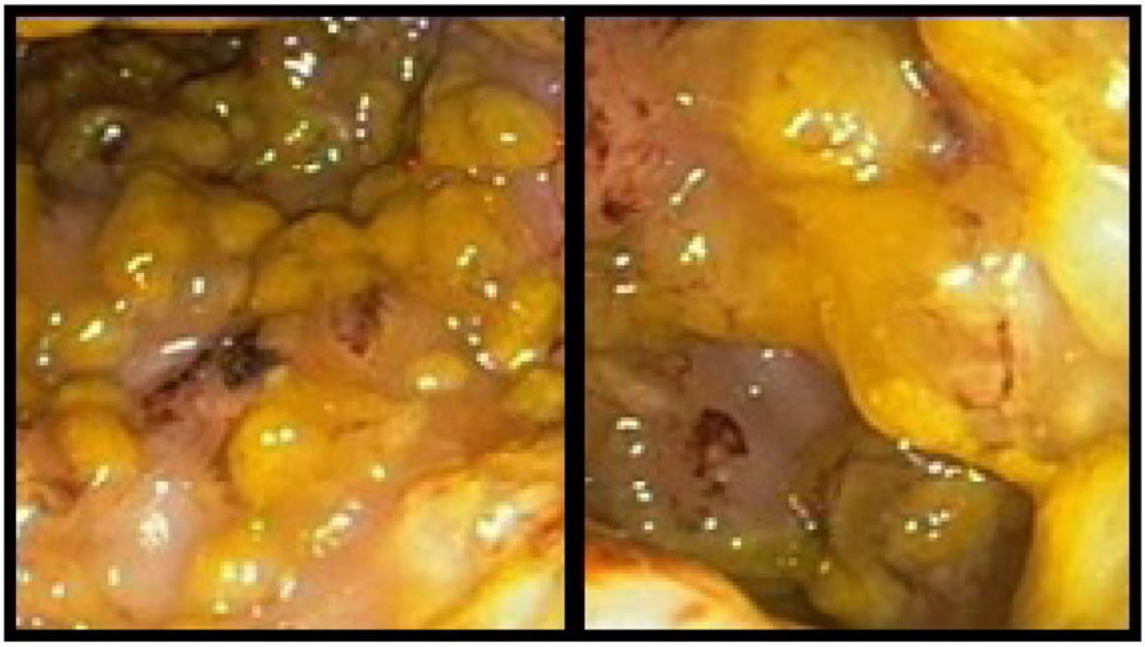

Figure 1.
Flexible sigmoidoscopy showing diffuse pseudomembranes covering severely edematous and friable mucosa in the rectosigmoid colon in a patient with *Clostridium difficile* infection.

Table 1

Causes of pseudomembranous colitis

Infectious etiologies
Bacterial
Clostridium difficile [1,71]
Clostridium ramosum [127]
Escherichia coli O157:H7[130,133]
Klebsiella oxytoca [138]
Plesiomonas shigelloides [141]
Salmonella enterica [145]
Shigella species [148]
Staphylococcus aureus [150,151]
Yersinia enterocolitica [155]
Parasitic
Entamoeba histolytica [167,168]
Schistosoma mansoni [174]
Strongyloides stercoralis [178,179]
Viral
Cytomegalovirus [117,118]
Other colitis
Behcet's disease [94]
Collagenous colitis [88–92]
Inflammatory bowel disease [77,78]
Ischemic colitis [69–71]
Medications/chemicals
Alosetron [98]
Cisplatin [111]
Cocaine [101]
Cyclosporine A [106]
Dextroamphetamine [99]
Docetaxel [110]
5-Fluorouracil [109]
Gold [100]
Glutaraldehyde [103–105]
NSAIDs [107,108]
Paraquat [102]