

Physical, Laboratory, Radiographic, and Endoscopic Workup for *Clostridium difficile* Colitis

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Abstract

Clostridium (reclassified as “*Clostridioides*”) *difficile* colitis is a common nosocomial infection associated with increased morbidity and mortality. Like many clinical encounters, a focused history and physical examination will help to guide initial management. Further laboratory testing will assist with diagnosis through stool studies, and blood tests, such as white blood cell counts and serum creatinine, can help to stratify patients into illness severity groups for treatment decisions. Radiographic evaluation can be helpful in patients with severe disease and concern for complicated colitis. Endoscopic evaluation should be carefully considered in patients with suspected mucosal injury secondary to infections and plays a role when an alternative diagnosis is suspected. Treatment options depend on the clinical presentation and can range from antibiotic therapy to emergent surgery to fecal transplantation for recurrent episodes. Care for these patients is often challenging, but through a systemic workup the appropriate treatment may be delivered.

Keywords

- ▶ *Clostridium difficile*
- ▶ *C. difficile*
- ▶ pseudomembranous colitis
- ▶ endoscopy

Clostridium difficile^a is a toxin forming, gram-positive, anaerobic bacillus bacteria that colonizes the gastrointestinal tract when the gut flora has been disturbed.^{1,2} *C. difficile* produces two toxins that make it particularly virulent. Toxin A is an exotoxin that binds to the brush border of the intestine disrupting the integrity of the intestinal lining^{3–5} and toxin B is a cytotoxin that destroys cytoskeletal structure of the enterocytes leading to the pathologic findings of pseudomembranes.^{6–8} The route of transmission for colonization is fecal-oral, and *C. difficile* infectious colitis is classically associated with a recent course of antibiotic therapy.^{1,2}

Certain patient populations are considered more high-risk for both initial and recurrent *C. difficile* colitis.⁹ Older age, long-term facility residence, recent hospitalizations, or prolonged lengths of stay, all predispose patients to increased risk.^{9–11} Other high-risk populations include patients undergoing immunosuppression therapy,¹² chronic kidney disease,¹³ cirrhosis,¹⁴ use of gastric acid suppressive medications,¹³ or inflammatory bowel disease.^{15,16} Just one dose of antibiotics

can be the inciting factor for *C. difficile* colitis; risk of infection increases with prolonged use of antibiotics and use of multiple antibiotic therapies.^{9–13}

C. difficile colitis can manifest in a spectrum of disease presentations from an asymptomatic carrier to fulminant colitis with toxic megacolon.^{1,13,17} When evaluating patients with suspected *C. difficile* infections, the patient history should focus on identifying offending medication(s), such as antibiotics, and high-risk patient features.¹³ Additionally, the history should focus on determining the severity of the disease and whether the presentation is an initial or a recurrent infection.¹⁷ The classification of disease severity is paramount to patient care because it will determine initial treatment.^{17–19}

In addition to the history, all patients, suspected of a *C. difficile* colitis infection, will require a focused abdominal exam, basic serum and stool laboratory testing, and potential radiographic evaluation; however, the indication(s) for further advanced testing depend on the clinical manifestations of the patient.^{1,17–19} For the remainder of this article, the authors will describe the physical examination findings,

^a The genus name “*Clostridium*” was reclassified as “*Clostridioides*” in 2016.

laboratory data, and the radiographic and endoscopic evaluation of patients with mild-to-moderate colitis, severe colitis, and fulminate colitis. These distinct classifications for disease severity are based on expert opinion; prospective scoring systems and predictive models are lacking.¹

Mild-to-Moderate Colitis

Patients determined to have mild-to-moderate colitis, typically endorse diarrhea without signs of systemic infection and have less laboratory derangements.^{1,17} Risk factors for this group, as mentioned previously, include the following: (1) antibiotic use, (2) recent hospitalization, (3) prolonged length of stay, (4) chemotherapy/immunosuppression, and (5) multiple comorbidities.^{13,17} Patients with enteral access who receive enteral feeds are also at an increased risk.¹⁷

Physical Examination

Patients with mild-to-moderate colitis are hemodynamically normal and stable. These patients may be febrile and usually present with abdominal discomfort and cramping. Diarrhea containing mucus and occult blood can be present, but patients with mild-to-moderate colitis typically do not present with frank hematochezia or melena.^{1,13,17} Their abdominal exam may be relatively benign or demonstrate some diffuse tenderness to palpation. Patients with mild-to-moderate colitis should not exhibit signs of guarding, rebound tenderness, or peritonitis.

Laboratory Data

Laboratory data for mild-to-moderate colitis include a mildly elevated white blood cell (WBC) count of 15,000 cells/mL or less. Patients also do not exhibit evidence of end-organ dysfunction and have a normal serum creatinine or one less than 1.5 mg/dL.^{13,17} Patients will have positive stool tests for *C. difficile* bacteria or toxins.^{1,13,17}

There are a variety of diagnostic tests available for *C. difficile* toxin testing in the stool and these should only be collected in patients with clinically significant diarrhea.²⁰ All of these tests require liquid stool. For patients with suspected *C. difficile* with an ileus and low liquid stool formation, a rectal swab may be used.^{21–23} There is no role for testing of asymptomatic patients nor is there a role for repeat testing within the episode of infection to indicate a test for a cure. Patients may continue to test positive throughout treatment and recovery.^{20,23–26}

The available types of diagnostic tests to be used alone or in combination for the detection of *C. difficile* infection include the following: nucleic acid amplification test (NAAT), enzyme immunoassay (EIA) for *C. difficile* glutamate dehydrogenase (GDH), EIA for *C. difficile* toxins A and B, cell culture cytotoxicity assay, and selective anaerobic culture.^{1,27–29} NAAT uses polymerase chain reaction (PCR) to detect gene specific to toxic strains of *C. difficile*. It is very sensitive and specific and results are available within an hour.^{27–29} However, there can be a false positive result with patients whose samples are delayed in processing or who have received empiric antibiotic treatment.^{29,30} NAAT

can also lead to overtreatment and over diagnosis, as it only detects the toxin genes but does not test for active toxin production.³¹ Therefore, this test should only be ordered on patients where it is clinically indicated to avoid overtreatment and identification of asymptomatic carriers.^{1,13,17,19,27} EIA testing for GDH and for toxins A and B are typically used in combination. EIA for *C. difficile* GDH has high sensitivity and the results are available in less than an hour.^{27–29} This assay tests for an enzyme present in both virulent and nonvirulent strains of *C. difficile*; therefore, its sensitivity and specificity are improved when used in combination with EIA for *C. difficile* toxins.^{27–29} EIA for *C. difficile* toxins A and B is specific to virulent strains but carries a high–false negative rate given the large amount of toxin needed for a positive test.^{27–29,32} Because of these limitations and low sensitivity at approximately 75%, it is used in combination with the EIA GDH testing.^{1,13,17,27,28} Algorithms for testing will vary by site, but a helpful guide to use of EIA GDH and toxin testing is shown in ►Fig. 1.³³ NAAT testing is used when discordant results are obtained.^{28,33} Selective anaerobic culture and cell culture cytotoxicity assay are both very sensitive and specific; however, the disadvantage to this testing is the amount of time needed before results can be reported.^{28,29,34} These studies are useful in patients with suspected *C. difficile* colitis and ileus or in epidemiologic testing and studies of outbreaks.³⁴

Radiographic and Endoscopic Evaluation

In patients with a classic presentation of mild to moderate disease, positive stool tests, and/or improvement with empiric antibiotic treatment, additional radiographic evaluation is not warranted.³⁵ If an abdominal radiograph or computed tomography (CT) scan is obtained in patients with these criteria, the findings would be generally benign and nonspecific, possibly showing signs of colonic inflammation. In patients with this disease presentation, endoscopic evaluation is not indicated.³⁵

Severe Colitis and Fulminate Colitis

Patients with severe colitis exhibit multiple bouts of diarrhea with evidence of systemic illness and evidence of laboratory derangement/end organ dysfunction. Risk factors for severe colitis include those for mild-to-moderate colitis plus advanced age (>65 years), history of chronic obstructive pulmonary disease, history of renal failure, and infection with the hypervirulent strain B1/NAP1/027.^{13,17,36}

Fulminate colitis is also known as severe, complicated colitis. Patients with fulminate colitis have multiple bouts of diarrhea with evidence of systemic infection, such as hypotension and shock, with concern for bowel distention, such as megacolon.^{13,17} Risk factors for fulminate colitis include those for mild-to-moderate colitis and severe colitis plus history of a recent abdominal operation, diagnosis of inflammatory bowel disease, or intravenous immunoglobulin therapy.^{1,13,17,36} These patients may present with an ileus or toxic megacolon and therefore with signs and symptoms of obstruction instead of diarrhea.

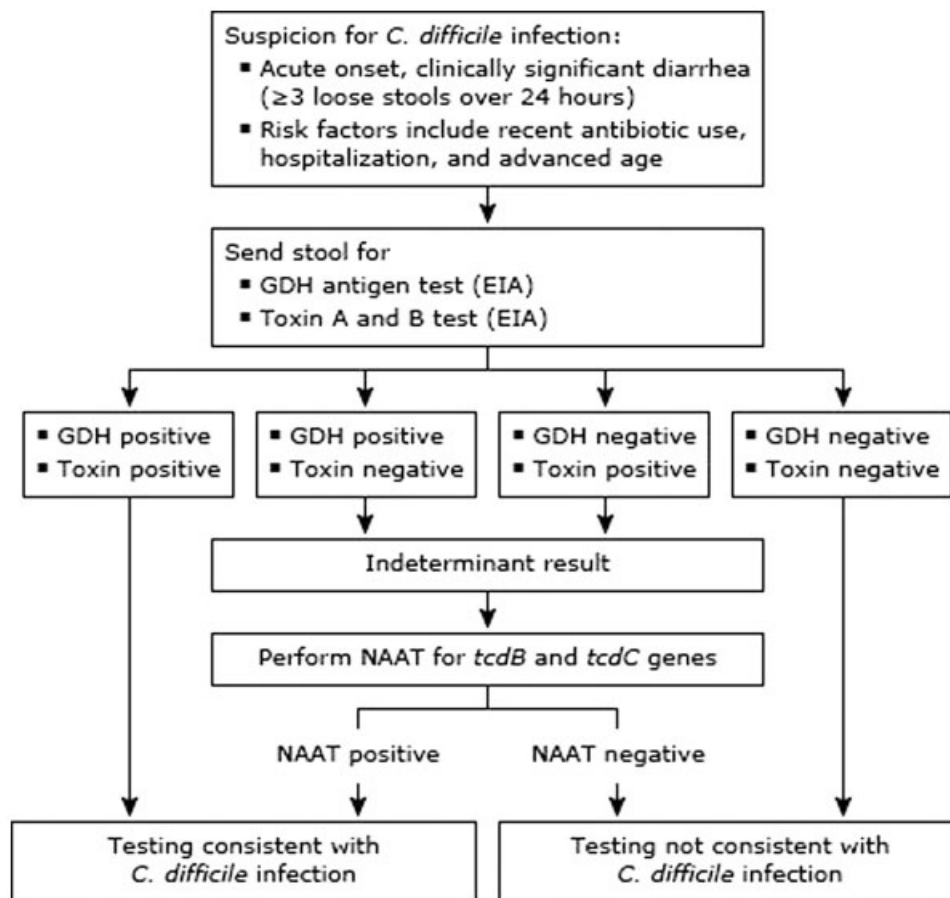


Fig. 1 UpToDate Algorithm for laboratory workup and diagnostic approach to *C. difficile*. EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; NAAT, nucleic acid amplification test.

Physical Examination

Patients with severe colitis may be hemodynamically unstable and should be given antibiotics, supportive care, resuscitation, and consideration for admission to an intensive care setting. These patients are typically febrile and complain of diffuse abdominal pain, discomfort, and distention. Patient can also exhibit exam findings consistent with hypovolemia, such as dry mucus membranes and decreased skin turgor.^{1,13,17,19,36} Abdominal exam will reveal diffuse tenderness, distention, and high-pitched bowel sounds. Patients may have some voluntary guarding secondary to pain but should not have rebound tenderness or peritonitis.

It is important to mention that patients with acute *C. difficile* colitis may present with an ileus and therefore will not endorse the classic symptoms of watery diarrhea.^{1,36} In these patients, the diagnosis of *C. difficile* may be overlooked. Even if these patients present with a more benign exam, they can rapidly progress to severe colitis and even fulminate colitis with evidence of toxic megacolon or perforation.^{1,36}

Patients with fulminant colitis are hemodynamically unstable with profound hypotension and shock.¹³ These patients require immediate administration of antibiotics and resuscitation in an intensive care setting. These patients are typically febrile and if not obtunded will complain of diffuse abdominal pain, discomfort, and distention. Abdom-

inal exam will reveal diffuse tenderness, distention, and possibly diminished sounds, or a rigid abdomen.^{13,17} Patients may also exhibit guarding, rebound tenderness, and peritonitis.³⁵ These exam findings should heighten the suspicion for perforation or impending perforation.

Laboratory Data

Laboratory data for severe colitis include WBC counts >15,000 cells/mL and evidence of end organ dysfunction with creatinine levels >1.5 mg/dL or greater than 1.5-times with a baseline creatine.¹⁷ These patients can also have electrolyte derangements consistent with hypovolemia, evidence of lactic acidosis, and hypoalbuminemia.^{17,36} Patients will also have positive stool tests for *C. difficile* bacteria or toxins.

Laboratory data for fulminate colitis is similar to severe colitis with evidence of leukocytosis (or leukopenia) and an elevated serum creatine.^{17,36} These patients can also have electrolyte derangements consistent with hypovolemia and evidence of lactic acidosis. They will also exhibit evidence of systemic inflammation, such as hypoalbuminemia.³⁶ Given the profound hypotension seen with fulminate colitis, there can also be evidence of end-organ dysfunction secondary to hypoperfusion, such as elevated liver enzymes. Patients will also have positive stool tests for *C. difficile* bacteria or toxins.

Radiographic and Endoscopic Evaluation

In patients who are found to have severe disease manifestations, additional radiographic evaluation of the abdomen, and pelvis may be warranted. Additional imaging can be helpful to evaluate for small bowel or colonic dilation, bowel wall thickening, air/fluid levels, or evidence of perforation. CT scan of the abdomen and pelvis with intravenous (IV) and by mouth (“per OS” PO) PO contrast is the ideal radiologic testing modality; plain films may be useful in circumstances when CT is unavailable.³⁵ Plain abdominal X-rays may show dilated small and large bowel loops that are less than 7 cm. CT scans can show some classic signs for colonic bowel wall inflammation and edema, such as “thumb printing” and “target signs.” CT findings suggestive of pseudomembranous colitis include the accordion sign, which results from oral contrast trapped between edematous large bowel haustra with areas of bright contrast alternating with edematous bowel to resemble an accordion.^{35–39} Patients with fulminate colitis show evidence of free air indicating perforation or colonic distention indicating toxic megacolon which can be seen on either abdominal X-ray or CT scan.³⁵ Toxic megacolon can be diagnosed based on radiographic evaluations showing dilated small bowel with air/fluid levels mimicking an obstruction or dilated colon up to 7 cm along in the setting of an infectious or inflammatory colitis.³⁵

Endoscopic evaluation of patients with colitis is undertaken in certain circumstances when an alternative diagnosis is considered and/or there is the need for direct mucosal inspection and biopsy. Endoscopy can also be considered in patients with an ileus and suspected *C. difficile* infections, since stool tests will be less useful and visualization of the pseudomembranes will help to make the diagnosis. Patients with *C. difficile* exhibit these pseudomembranes on endoscopy (→Fig. 2) due to the toxins produced by the bacteria causing ulcerations in the mucosal surface.⁶ These are described as yellow/white plaques and their distribution can be continuous or patchy.^{6,35} Patients undergoing endoscopy would also undergo mucosal biopsy and *C. difficile* testing.

The absence of pseudomembranes does not rule out *C. difficile* colitis, and conversely, while pseudomembranes on endoscopy can help to diagnose patients with *C. difficile* colitis, they are not exclusive to that diagnosis.²⁹ For example, several other infections and disease processes cause pseudomembranes in the setting of negative *C. difficile* testing, such as ischemic colitis, inflammatory bowel disease,

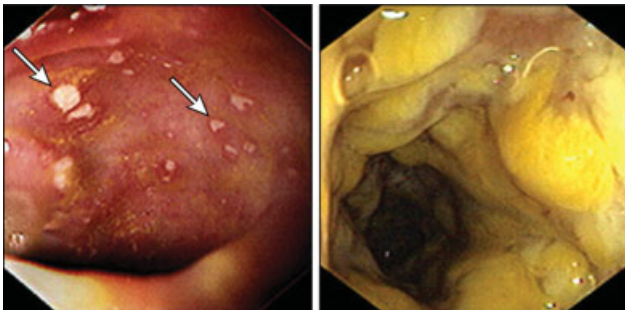


Fig. 2 Picture of pseudomembranous colitis on endoscopy. Arrows pointing at pseudomembranes.

viral infections like cytomegalovirus, and parasitic infections with *Entamoeba histolytica*.²⁹

If endoscopy is pursued, then limited flexible sigmoidoscopy should be considered to theoretically decrease the risk of perforation with little or no insufflation. Unfortunately, some patients may only show evidence of pseudomembranous colitis in the right colon or cecum area.^{35,40} However, for any case in which endoscopy is considered, one should proceed with caution. These evaluations should be performed at specialized centers under the care of experts. Patients who present with fulminate colitis and evidence of perforation or physical exam findings consistent with an acute abdomen warrant prompt surgical evaluation without the need for further endoscopic workup.

Conclusion

The treatment plan for patients with *C. difficile* colitis depends on the following factors: the severity of the disease at presentation, initial versus recurrent infection, and the overall clinical picture.^{13,17–19} The history, physical exam, and laboratory testing should all be used to aid in the workup and diagnosis of *C. difficile* colitis. Stool testing should follow protocols to ensure the highest specificity and sensitivity while remaining practical and time sensitive. Depending on patient presentation, radiographic and endoscopic testing can complement the workup to determine the most appropriate and effective treatment plan. Treatment options range from oral antibiotics therapy to urgent versus emergent surgery to consideration of fecal transplantation; these decisions are often made in combination with other medical professionals and services including surgery, critical care, gastroenterology, and infectious disease.

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Conflict of Interest

None declared.

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