



## Educational Case

# Educational Case: Pseudomembranous colitis attributable to *Clostridioides difficile*

Joseph L. Maniaci, MD<sup>a</sup>, Robin D. LeGallo, MD<sup>b,\*</sup>

<sup>a</sup> University of North Carolina Department of Pathology, Chapel Hill, NC, USA

<sup>b</sup> University of Virginia Department of Pathology, Charlottesville, VA, USA

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see <https://www.journals.elsevier.com/academic-pathology/news/pathology-competencies-for-medical-education-pcme>.<sup>1</sup>

**Keywords:** Bowel infections, *Clostridioides difficile*, Diarrhea, Gastrointestinal tract, Organ system pathology, Pathology competencies, Pseudomembranous colitis

## Primary objective

Objective GT7.1: Bowel Infections. Compare the underlying mechanism and clinicopathologic features of GI tract involvement by common bacterial, fungal, and parasitic pathogens.

Competency 2: Organ System Pathology, Topic GT: Gastrointestinal Tract; Learning Goal 7: Bowel Infections.

## Secondary objectives

Objective FECT1.1: Host Barrier. Explain the human host barrier to infection and describe how organisms spread within the body once the barrier is broken.

Competency 1: Disease Mechanisms and Processes, Topic FECT: Infectious Mechanisms; Learning Goal 1: Mechanisms of Infection.

Objective FECT2.6: Tissue Response to Bacterial Infection. Describe the histologic patterns of tissue response to bacterial infection as a function of differences in the organisms involved, the specific organ affected, and the manner by which the bacterium enters the organ.

Competency 1: Disease Mechanisms and Processes, Topic FECT: Infectious Mechanisms; Learning Goal 2: Pathogenic Mechanism of Infection.

## Patient presentation

A 72-year-old woman presents to her physician with sudden onset watery diarrhea. She has been experiencing left lower quadrant cramping

and has counted 6 episodes of liquid, formless, non-bloody stool in the past 24 hours. She is nauseated and has vomited twice in the past 24 hours.

## Diagnostic findings, Part 1

The patient is febrile at 39 C. All other vital signs are normal. Physical exam reveals a soft but diffusely tender abdomen without rebound or guarding.

## Question/discussion points, Part 1

### ***What is the initial differential diagnosis and what further information should be obtained?***

The differential diagnosis of acute onset diarrhea is governed primarily by the circumstances surrounding the patient's presentation: food poisoning, recent travel, sick contacts, past medical history, and medications could all play a role. Thus, it is essential to get a good patient history, including the time course of diarrhea and exposure to risk factors. Additional findings which would point us to an inflammatory diarrhea would be if the patient repeatedly woke up at night to have bowel movements, or if the patient's bowel movements were not strictly related to consumption of food. A short time course of watery diarrhea points most clearly to infectious causes and prompts us to think about *Bacillus cereus* (classically reheated rice food poisoning), *Staphylococcus aureus* preformed enterotoxin (classically cream-based foods at a picnic), *Salmonella enteritidis* (raw egg food poisoning), *Vibrio cholerae* (rice water

\* Corresponding author. University of Virginia Department of Pathology, 1215 Lee Street, Charlottesville, VA, USA.

E-mail address: [RDL3S@hscmail.mcc.virginia.edu](mailto:RDL3S@hscmail.mcc.virginia.edu) (R.D. LeGallo).

stools), enterotoxigenic *Escherichia coli* (toxin-mediated watery diarrhea), *Clostridioides difficile* (antibiotic-associated colitis), early *Campylobacter jejuni* (poultry-associated food poisoning), norovirus (classically cruise ship-associated food poisoning), rotavirus (classically daycare-associated diarrhea), or giardiasis (parasitic infection classically associated with camping or freshwater).<sup>2</sup>

## Diagnostic findings, Part 2

A patient interview reveals that she was discharged two days ago from the hospital following successful inpatient treatment of osteomyelitis of the right femur. She was receiving 20 mg oral prednisone twice daily for pain management and oral ciprofloxacin 500 mg twice per day for the past four days to combat the infection. Her hospital course had progressed uneventfully and she was doing well at home until the diarrhea began. The patient denies sick contacts and recent travel outside of the country and does not attribute her diarrhea to food poisoning. She was not able to get a good night's sleep last night due to several episodes of diarrhea and cramping in her lower left abdomen.

## Questions/discussion points, Part 2

### How does this history change the differential diagnosis?

*Clostridioides difficile* (*C. difficile*) colitis is the clear frontrunner in light of the patient history. *C. difficile* is a common nosocomial pathogen causing watery diarrhea in hospitalized patients.<sup>3</sup> Although originally known as *Clostridium difficile*, the name has since been changed to *Clostridioides difficile* due to recent phylogenetic insights gained by sequencing of the 16S rRNA subunit in *C. difficile* and its relatives.<sup>4,5</sup> *C. difficile* is passed from person to person via ingestion of spores, which are common in healthcare facilities and cannot be easily decontaminated through heat inactivation or alcohol-based hand sanitizer.<sup>3</sup> Although spores can also be found in the community, community or non-hospital acquired *C. difficile* colitis is far less common.<sup>3,6</sup>

### What is the role of antibiotic therapy in the pathogenesis of *C. difficile* colitis?

Although *C. difficile* can be a member of the normal gut flora, the use of oral antibiotics for the treatment of other infections can wipe out a large portion of the more dominant but less resilient resident bacteria, creating an open niche which *C. difficile* can fill. Importantly, *C. difficile* does not invade colonocytes and cause damage. Instead, it colonizes the lumen, leading to a robust inflammatory response and the accumulation of inflammatory and necrotic debris which is known as a pseudomembrane.<sup>7</sup> Once it has colonized the colon, *C. difficile* produces two exotoxins, toxin A (TcdA) and toxin B (TcdB), which moderate pathogenic activity by disabling Rho GTPases within colonocytes.<sup>3</sup> While both toxins are independently able to interrupt cell-cell adherence junctions and induce apoptosis of colonocytes, toxin A is additionally able to trigger the formation of radical oxygen molecules and recruit an acute inflammatory response.<sup>8</sup> Toxin A also upregulates production of substance P within neurons of the gut wall.<sup>8</sup> Substance P is a neurotransmitter involved in the sensation of pain, among other things.

### What is the differential diagnosis of pseudomembranous colitis?

Although pseudomembranous colitis is most commonly associated with *C. difficile* infection, it is important to understand that, as a finding, colonic pseudomembranes are not pathognomonic for *C. difficile* infection. There are a diverse set of pathologies that can lead to colonic pseudomembranes. Vascular injury can lead to pseudomembrane formation—sudden revascularization following ischemic insult incites an influx of inflammatory cells and cytokines which can aggregate in the lumen and form pseudomembranes.<sup>7</sup> There are case reports of pseudomembranous disease

associated with microscopic colitis and inflammatory bowel disease flares.<sup>7,9–11</sup> Additionally, pseudomembrane formation has been reported to accompany a wide variety of infections other than *C. difficile*,<sup>7</sup> including cytomegalovirus,<sup>12–14</sup> *Clostridioides ramosum*,<sup>15</sup> enterohemorrhagic *Escherichia coli* O157–H7,<sup>16</sup> *Salmonella enterica*,<sup>17</sup> *Yersinia enterocolitica*,<sup>18</sup> and *Shigella dysenteriae*,<sup>19</sup> *Entamoeba histolytica*,<sup>20,21</sup> *Schistosoma mansoni*,<sup>22</sup> and *Strongyloides stercoralis*,<sup>23</sup> among others. At this time, fungal organisms have not been reported to cause pseudomembranous colitis. Careful consideration of each patient's history and risk factors is necessary in order to ensure efficient and accurate diagnosis of the culprit pathology.

### What assays should be ordered to confirm the diagnosis?

Patients should be tested for pseudomembranous colitis when one of two conditions is met: either abdominal imaging showing toxic megacolon or ileus or a new onset episode of three or more loose stools per day in the absence of laxative use, especially in a hospitalized patient.<sup>24</sup> Several testing options are available. A nucleic acid amplification test (NAAT) for the gene encoding toxin B, *tcdB*, provides a sensitive test for the presence of *C. difficile*.<sup>25</sup> However, recent studies indicate that *C. difficile* can be a minority member of the gut flora without producing symptoms in 8.7–15% of the population.<sup>26,27</sup> Because NAAT will be positive if a toxigenic strain of *C. difficile* is present in the colon even if it is not actively producing exotoxins, specific follow-up testing is recommended. A stool antigen test (enzyme immunoassay) for exotoxins A and B allows for confirmation of pathogenic behavior from *C. difficile* and secures the diagnosis.<sup>25</sup>

## Diagnostic findings, Part 3

An enzyme immunoassay for both TcdA and TcdB is performed on a stool sample and is positive for both toxins.

## Questions/discussion points, Part 3

### What is the appropriate management of this patient?

First, if the patient is an inpatient, contact precautions should be taken to minimize the possibility of spore transmission to staff. If possible, the patient should be moved to an isolation room and given access to a private bathroom to minimize the possibility of fecal-oral transmission of *C. difficile* spores between patients. Once the suspicion of *C. difficile* colitis has been confirmed, it is essential to discontinue the *C. difficile*-promoting antibiotic and prescribe a drug that can combat the infection. Stable patients can be treated on an outpatient basis with proper education on how to minimize the spread of disease, such as frequent hand-washing with soap and water and not sharing a bathroom if possible.<sup>28,29</sup> Although the traditional choice for treatment was oral metronidazole, oral vancomycin has been shown to be superior.<sup>25</sup> In severe cases where the patient is suffering from ileus, oral vancomycin can be combined with a vancomycin retention enema.<sup>25</sup> Anti-diarrheal drugs are not recommended.<sup>30</sup>

### When is lower endoscopy indicated?

Lower endoscopy is not indicated as a primary diagnostic tool for pseudomembranous colitis, as enzyme immunoassay for stool toxins or nucleic acid amplification testing both provide reliable and non-invasive means to make the diagnosis. However, colonoscopy can be appropriate on a case-by-case basis if there is suspicion of multiple concurrent colonic pathologies or a patient is worsening despite appropriate management.<sup>31</sup>

## Diagnostic findings, Part 4

The patient's ciprofloxacin regimen is stopped and she is started on oral vancomycin. Although she improves over the next three days, she

wakes up on the fourth day to worsened abdominal pain and has 11 episodes of unformed, watery diarrhea throughout the day. Her practitioner starts her on a second course of oral vancomycin, and although she briefly recovers while on the medication, she recurs again after the prescribed course is completed.

#### Questions/discussion points, Part 4

##### **What are the risk factors for recurrent infection with *C. difficile*?**

Several factors govern recurrence risk for *C. difficile* colitis, including advanced age (older age is associated with higher risk), number of episodes of diarrhea over the past day at the time of their presentation (higher number of episodes is associated with a higher risk), and history of previous pseudomembranous colitis (positive history is associated with higher risk).<sup>32</sup> Up to 30% of patients have at least one episode of recurrent *C. difficile* following appropriate medical management.<sup>32</sup>

##### **What is the appropriate management of recurrent *C. difficile* colitis?**

Patients experiencing recurrent pseudomembranous colitis can receive a fecal microbiota transplant by the manner of a frozen stool capsule from a donor with a normal gut flora. A recent meta-analysis<sup>33</sup> showed an overall 87% success rate for the resolution of pseudomembranous colitis via stool transplant, with the best results coming when the infection is localized to the ileocecal junction and ascending colon. Another recent study showed that introduction of kefir, a cultured probiotic yogurt, while simultaneously weaning off antibiotics may work comparably to stool transplant from a healthy donor.<sup>34</sup> Both mechanisms allow displacement of *C. difficile* from its majority position in the microbiome by other, more desirable microbes. In the case of disease refractory to medical therapy, the risks and benefits of partial or total abdominal colectomy should be weighed.<sup>35,36</sup>

#### Diagnostic findings, Part 5

The patient receives a fecal microbiota transplant from a healthy donor and recovers without further complications as an outpatient.

#### Questions/discussion points, Part 5

##### **What are the risks and benefits of surgical management for pseudomembranous colitis?**

Colectomy will eliminate the possibility for further recurrence of pseudomembranous colitis but offers its own set of short and long-term risks. The short-term risks associated with surgery include the risk of peri-procedural hemorrhage or infection, while long-term sequelae may include chronic diarrhea due to reduced water absorption from stool or urinary, sexual, and defecatory dysfunction due to surgical disruption of the autonomic nervous system.<sup>37</sup>

##### **What are the characteristic gross and histopathologic features of pseudomembranous colitis?**

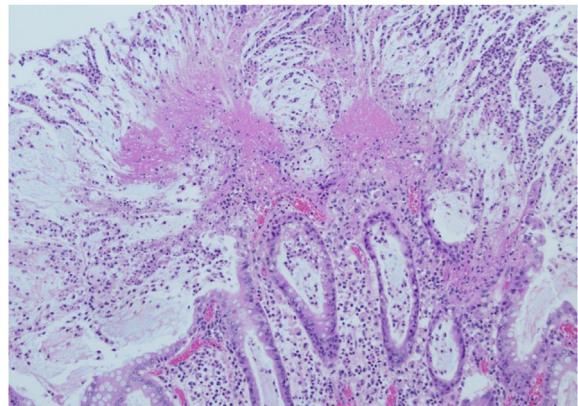
Pseudomembranous colitis has several distinguishing features on gross and microscopic exam. Examination of a colectomy specimen for pseudomembranous colitis will typically reveal discrete yellow-green plaques adherent to underlying edematous bowel tissue with hyperemic to dusky mucosa, indicative of bowel necrosis. In severe cases, the plaques may become confluent as more and more of the bowel necroses—it is important to note that a confluent yellow-green pseudomembrane can also be associated with severe inflammatory bowel disease, so microscopic examination is necessary to confirm the diagnosis.<sup>38</sup> A representative gross photo of a total

colectomy specimen for fulminant pseudomembranous colitis is shown in Fig. 1.

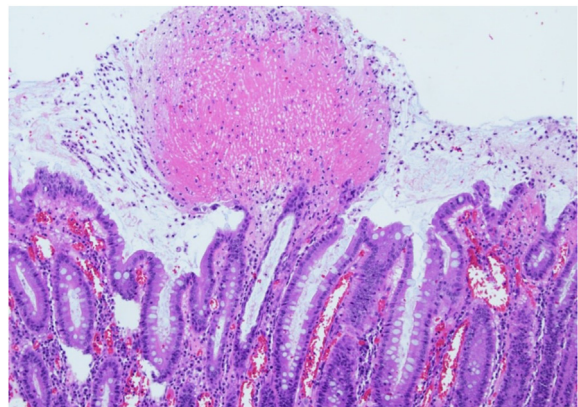
Microscopically, pseudomembranous colitis is defined by a prominent pseudomembrane composed of neutrophils and karyorrhectic debris overlying the epithelial surface with dense purulent exudate arising out of infected crypts (Fig. 2, Fig. 3). The eruption of the inflammatory exudate out of the deep crypts is a distinct feature of pseudomembranous



**Fig. 1.** A gross photograph of a total colectomy specimen for fulminant pseudomembranous colitis, which displays the characteristic hyperemic mucosa with yellow-green stuck-on exudate.



**Fig. 2.** Photomicrograph at 200× magnification which shows the characteristic histopathologic features of pseudomembranous colitis. Note the surface pseudomembrane composed of neutrophils and karyorrhectic debris, which is clearly visible at the luminal surface. Also appreciate the columnar neutrophilic infiltrate with mucoid and fibrotic debris, which is characteristic of this entity.



**Fig. 3.** Photomicrograph at 200× magnification which highlights prominent microcapillaries within the lamina propria of the affected bowel. An abundant dense purulent exudate erupts out of the affected crypts.



colitis, as opposed to inflammatory exudate involving the luminal surface but not the crypts. Note the characteristic columnar pattern of neutrophils with mucoid and fibrotic debris in Fig. 2.<sup>38</sup> There is also a brisk acute inflammatory response in the lamina propria. Affected tissue can also display dilated microcapillaries with microthrombi in the lamina propria, as inflammatory cytokines induce vasodilation and platelet aggregation.<sup>39</sup> Severe cases may demonstrate crypt necrosis.<sup>38</sup>

## Teaching points

- *Clostridioides difficile* is the primary causative agent of pseudomembranous colitis, a condition characterized by multiple episodes of watery diarrhea with abdominal cramping, usually in the setting of a hospitalized patient receiving antibiotics for a prior condition.
- Pseudomembranes are not pathognomonic for *C. difficile* infection. Vascular disease, inflammatory conditions, and other infectious agents can also lead to pseudomembrane formation, so clinico-pathologic correlation is required.
- The usage of antibiotics predisposes to *C. difficile* colitis by killing off a large portion of the healthy gut microbiota. *C. difficile*, a normal member of the gut flora, is then able to grow free from the hindrance of competing species.
- Production of toxins A and B by *C. difficile* is the mechanism of pathogenicity in pseudomembranous colitis. The toxins damage colonocytes despite the fact that *C. difficile* organisms are themselves non-invasive.
- In the right clinical setting, stool antigen testing via enzyme immuno-fluorescence or nucleic acid amplification testing allow for the diagnosis of pseudomembranous colitis. *C. difficile* can be a normal member of the gut microbiota, so testing should only be performed when there is a high degree of clinical suspicion.
- Colonoscopy can confirm pseudomembranous colitis via gross observation of pseudomembranes in the colon but is not indicated unless the diagnosis is uncertain.
- Pseudomembranous colitis is characterized microscopically by the presence of a prominent pseudomembrane overlying the epithelial surface composed of neutrophils and karyorrhectic debris which erupts out of the colonic crypts. Dilated capillaries and microthrombi are often present in the lamina propria.
- Oral vancomycin is the preferred first-choice therapeutic and is more effective than oral metronidazole.
- Recurrence is common and occurs in up to 30% of cases. Risk factors include age, severity of initial disease, and history of previous *C. difficile* infection.
- Recurrent *C. difficile* infection can be treated effectively with fecal microbiota transplant prepared from a healthy stool sample from a donor. There may be an emerging role for probiotics as well.
- Fulminant and medically refractory pseudomembranous colitis may warrant colectomy.

## Declaration of competing interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The article processing fee for this article was funded by an Open Access Award given by the Society of '67, which supports the mission of the Association of Pathology Chairs to produce the next generation of outstanding investigators and educational scholars in the field of pathology. This award helps to promote the publication of high-quality original scholarship in *Academic Pathology* by authors at an early stage of academic development.

## References

1. Knollmann-Ritschel BEC, Regula DP, Borowitz MJ, Conran R, Prystowsky MB. Pathology competencies for medical education and educational cases. *Acad Pathol*. 2017;4. doi:10.1177/2374289517715040
2. Shane AL, Mody RK, Crump JA, et al. Infectious diseases society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. *Clin Infect Dis*. 2017;65(12):e45–e80. doi:10.1093/cid/cix669
3. Leffler DA, Lamont JT. Clostridium difficile infection. *N Engl J Med*. 2015;372(16):1539–1548. doi:10.1056/NEJMra1403772
4. Nagy E. What do we know about the diagnostics, treatment and epidemiology of Clostridioides (Clostridium) difficile infection in Europe? *J Infect Chemother*. 2018;24(3):164–170. doi:10.1016/j.jiac.2017.12.003
5. Lawson PA, Citron DM, Tyrrell KL, Finegold SM. Reclassification of Clostridium difficile as Clostridioides difficile (Hall and O'toole 1935) prévot 1938. *Anaerobe*. 2016;40:95–99. doi:10.1016/j.anaerobe.2016.06.008
6. Slimings C, Riley TV. Antibiotics and hospital-acquired Clostridium difficile infection: update of systematic review and meta-analysis. *J Antimicrob Chemother*. 2014;69(4):881–891. doi:10.1093/jac/dkt477
7. Farooq PD, Urrunaga NH, Tang DM, von Rosenving EC. Pseudomembranous Colitis. *Dis-Mon DM*. 2015;61(5):181–206. doi:10.1016/j.disamonth.2015.01.006
8. Voth DE, Ballard JD. Clostridium difficile toxins: mechanism of action and role in disease. *Clin Microbiol Rev*. 2005;18(2):247–263. doi:10.1128/CMR.18.2.247-263.2005
9. Buchman AL, Rao S. Pseudomembranous collagenous colitis. *Dig Dis Sci*. 2004;49(11-12):1763–1767. doi:10.1007/s10620-004-9566-3
10. Yuan S, Reyes V, Bronner MP. Pseudomembranous collagenous colitis. *Am J Surg Pathol*. 2003;27(10):1375–1379. doi:10.1097/0000478-200310000-00010
11. Killinçalp S, Altınbaş A, Başar O, Deveci M, Yüksel O. A case of ulcerative colitis co-existing with pseudo-membranous enterocolitis. *J Crohns Colitis*. 2011;5(5):506–507. doi:10.1016/j.crohns.2011.06.012
12. Battaglino MP, Rockey DC. Cytomegalovirus colitis presenting with the endoscopic appearance of pseudomembranous colitis. *Gastrointest Endosc*. 1999;50(5):697–700. doi:10.1016/s0016-5107(99)80025-x
13. Olofinlade O, Chiang C. Cytomegalovirus infection as a cause of pseudomembrane colitis: a report of four cases. *J Clin Gastroenterol*. 2001;32(1):82–84. doi:10.1097/00004836-200101000-00019
14. Seo TH, Kim JH, Ko SY, et al. Cytomegalovirus colitis in immunocompetent patients: a clinical and endoscopic study. *Hepato-Gastroenterology*. 2012;59(119):2137–2141. doi:10.5754/hge10825
15. Alcalde-Vargas A, Trigo-Salado C, Leo Carnerero E, De-la-Cruz-Ramírez D, Herrera-Justiniño JM. Pseudomembranous colitis and bacteremia in an immune competent patient associated with a rare specie of Clostridium (*C. ramosum*). *Rev Espanola Enfermedades Dig Organo Of Soc Espanola Patol Dig*. 2012;104(9):498–499. doi:10.4321/s1130-01082012000900011
16. Uc A, Mitros FA, Kao SC, Sanders KD. Pseudomembranous colitis with Escherichia coli O157:H7. *J Pediatr Gastroenterol Nutr*. 1997;24(5):590–593. doi:10.1097/00005176-199705000-00017
17. Mönkemüller K, Patasiute I, Walther F, Peitz U, Fry LC, Malferteiner P. Pseudomembranous colitis due to Salmonella enterica serotype infantis. *Endoscopy*. 2006;38(5):546. doi:10.1055/s-2006-925343
18. Brown R, Tedesco FJ, Assad RT, Rao R. Yersinia colitis masquerading as pseudomembranous colitis. *Dig Dis Sci*. 1986;31(5):548–551. doi:10.1007/BF01320324
19. Kelber M, Ament ME. Shigella dysenteriae I: a forgotten cause of pseudomembranous colitis. *J Pediatr*. 1976;89(4):595–596. doi:10.1016/s0022-3476(76)80394-0
20. Chun D, Chandrasoma P, Kiyabu M. Fulminant amebic colitis. A morphologic study of four cases. *Dis Colon Rectum*. 1994;37(6):535–539. doi:10.1007/BF02050986
21. Koo JS, Choi WS, Park DW. Fulminant amebic colitis mimicking pseudomembranous colitis. *Gastrointest Endosc*. 2010;71(2):400–401. doi:10.1016/j.gie.2009.09.009 ; discussion 401.
22. Neves J, Raso P, Pinto D de M, da Silva SP, Alvarenga RJ. Ischaemic colitis (necrotizing colitis, pseudomembranous colitis) in acute schistosomiasis mansoni: report of two cases. *Trans R Soc Trop Med Hyg*. 1993;87(4):449–452. doi:10.1016/0035-9203(93)90031-k
23. Janvier J, Kuhn S, Church D. Not all pseudomembranous colitis is caused by Clostridium difficile. *Can J Infect Dis Med Microbiol J Can Mal Infect Microbiol Medecale*. 2008;19(3):256–257. doi:10.1155/2008/613573
24. Bagdasarjan N, Rao K, Malani PN. Diagnosis and treatment of Clostridium difficile in adults: a systematic review. *JAMA*. 2015;313(4):398–408. doi:10.1001/jama.2014.17103
25. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the infectious diseases society of America (IDSA) and society for healthcare epidemiology of America (SHEA). *Clin Infect Dis*. 2018;66(7):e1–e48. doi:10.1093/cid/cix1085
26. Espiritu K, Vernon M, Schora D, Peterson L, Singh K. Asymptomatic carriage of Clostridioides difficile and risk of subsequent infection. *Open Forum Infect Dis*. 2018;5(suppl\_1):S38. doi:10.1093/ofid/ofy209.088, 972.
27. Alasmari F, Seiler SM, Hink T, Burnham CAD, Dubberke ER. Prevalence and risk factors for asymptomatic Clostridium difficile carriage. *Clin Infect Dis*. 2014;59(2):216–222. doi:10.1093/cid/ciu258
28. Mounsey A, Smith KL, Reddy VC, Nickolich S. Clostridioides difficile infection: update on management. *Am Fam Physician*. 2020;101(3):168–175.

29. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the infectious diseases society of America (IDSA) and society for healthcare epidemiology of America (SHEA). *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2018;66(7):e1–e48. doi: [10.1093/cid/cix1085](https://doi.org/10.1093/cid/cix1085)
30. Elbeddini A, Gerochi R. Treatment of Clostridium difficile infection in community teaching hospital: a retrospective study. *J Pharm Policy Pract*. 2021;14(1):19. doi: [10.1186/s40545-020-00289-1](https://doi.org/10.1186/s40545-020-00289-1)
31. Burkart NE, Kwaan MR, Shepela C, et al. Indications and relative utility of lower endoscopy in the management of Clostridium difficile infection. *Gastroenterol Res Pract*. 2011;2011, e626582. doi: [10.1155/2011/626582](https://doi.org/10.1155/2011/626582)
32. D'Agostino RB, Collins SH, Pencina KM, Kean Y, Gorbach S. Risk estimation for recurrent Clostridium difficile infection based on clinical factors. *Clin Infect Dis*. 2014; 58(10):1386–1393. doi: [10.1093/cid/ciu107](https://doi.org/10.1093/cid/ciu107)
33. Cammarota G, Ianaro G, Gasbarrini A. Fecal microbiota transplantation for the treatment of Clostridium difficile infection: a systematic review. *J Clin Gastroenterol*. 2014;48(8):693–702. doi: [10.1097/MCG.0000000000000046](https://doi.org/10.1097/MCG.0000000000000046)
34. Bakken JS. Staggered and tapered antibiotic withdrawal with administration of kefir for recurrent Clostridium difficile infection. *Clin Infect Dis*. 2014;59(6):858–861. doi: [10.1093/cid/ciu429](https://doi.org/10.1093/cid/ciu429)
35. Seltman AK. Surgical management of Clostridium difficile colitis. *Clin Colon Rectal Surg*. 2012;25(4):204–209. doi: [10.1055/s-0032-1329390](https://doi.org/10.1055/s-0032-1329390)
36. Pevrah D, Chiu AS, Jean RA, Pei KY. Comparison of outcomes between total abdominal and partial colectomy for the management of severe, complicated Clostridium difficile infection. *J Am Coll Surg*. 2019;228(6):925–930. doi: [10.1016/j.jamcollsurg.2018.11.015](https://doi.org/10.1016/j.jamcollsurg.2018.11.015)
37. Giglia MD, Stein SL. Overlooked long-term complications of colorectal surgery. *Clin Colon Rectal Surg*. 2019;32(3):204–211. doi: [10.1055/s-0038-1677027](https://doi.org/10.1055/s-0038-1677027)
38. Price AB, Davies DR. Pseudomembranous colitis. *J Clin Pathol*. 1977;30(1):1–12. doi: [10.1136/jcp.30.1.1](https://doi.org/10.1136/jcp.30.1.1)
39. Beristain-Covarrubias N, Perez-Toledo M, Thomas MR, Henderson IR, Watson SP, Cunningham AF. Understanding infection-induced thrombosis: lessons learned from animal models. *Front Immunol*. 2019;10:2569. doi: [10.3389/fimmu.2019.02569](https://doi.org/10.3389/fimmu.2019.02569)