Clostridioides difficile infection in adults: Clinical manifestations and diagnosis

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INTRODUCTION

Clostridioides difficile is a spore-forming, toxin-producing, gram-positive anaerobic bacterium that causes antibiotic-associated colitis. It colonizes the human intestinal tract typically after the normal gut flora has been disrupted (frequently in association with antibiotic therapy). *C. difficile* infection (CDI) is one of the most common health care-associated infections and a significant cause of morbidity and mortality, especially among older adult hospitalized patients.

The clinical manifestations and diagnosis of CDI will be reviewed here. The treatment, epidemiology, and prevention of CDI are discussed separately. (See "*Clostridioides difficile* infection in adults: Treatment and prevention" and "*Clostridioides difficile* infection in adults: Epidemiology, microbiology, and pathophysiology" and "*Clostridioides difficile* infection: Prevention and control".)

CLINICAL MANIFESTATIONS

CDI can cause a spectrum of manifestations ranging from an asymptomatic carriage to fulminant disease with toxic megacolon [1-4]. The basis for this range of clinical manifestations is not fully understood but may be related to host and pathogen factors. (See "*Clostridioides difficile* infection in adults: Epidemiology, microbiology, and pathophysiology".)

Diarrhea with colitis — Patients with known or suspected CDI should be assessed for disease severity.

Nonsevere disease — Watery diarrhea (≥3 loose stools in 24 hours) is the cardinal symptom of CDI. Other manifestations include lower abdominal pain and cramping, low-grade fever, nausea, and anorexia [2,5]. Diarrhea may be associated with mucus or occult blood, but melena or hematochezia are rare. Fever is associated with CDI in about 15 percent of cases; temperature >38.5°C may occur in the setting of nonsevere or severe CDI.

Symptoms of CDI typically occur in the setting of antibiotic therapy. The antibiotics most frequently implicated in predisposition to CDI are fluoroquinolones, clindamycin, cephalosporins, and penicillins, though virtually any antibiotic can predispose to CDI (table 1). Symptoms of CDI may begin during or after antibiotic therapy, and most cases occur within two weeks of antibiotic therapy. Rarely, symptoms present as late as 10 weeks after cessation of antibiotic therapy [6]. However, a lack of antibiotic use does not rule out the possibility of CDI. In one study, about 30 percent of patients with community-acquired CDI had not been exposed to antibiotics [7]. Additional risk factors for CDI include age >65, recent hospitalization, and use of proton pump inhibitors. (See "*Clostridioides difficile* infection in adults: Epidemiology, microbiology, and pathophysiology", section on 'Risk factors'.)

Physical examination may demonstrate lower abdominal tenderness. Lower gastrointestinal endoscopy (flexible proctoscopy, sigmoidoscopy, or colonoscopy) examination may be normal or demonstrate a spectrum of findings, from patchy, mild erythema and friability to severe pseudomembranous colitis (severe inflammation of the inner lining of the bowel). (See 'Endoscopy' below.)

CDI is commonly associated with an average white blood cell count of up to 15,000 cells/microL [8]. Laboratory criteria proposed for nonsevere CDI (based on expert opinion) include white blood cell count ≤15,000 cells/microL and serum creatinine <1.5 mg/dL; prospectively validated severity scores for CDI are needed [1].

Unexplained leukocytosis in hospitalized patients (even in the absence of diarrhea) may reflect underlying CDI, although data are mixed. In a retrospective study of 248 hospitalized adults, white blood cell count ≥11,000 cells/microL was an independent risk factor for CDI (odds ratio 3.43, 95% CI 1.42-8.26) [9]. However, a retrospective, multicenter study of over 16,000 patients did not find any relationship between leukocytosis (white blood cell >15,000 cells/microL) and CDI in hospitalized patients [10]. Although there was an association between leukocytosis and CDI in outpatient and emergency room settings, accuracy was poor. In situations where

unexplained leukocytosis is due to CDI, diarrhea typically develops one to two days later. (See "Approach to the patient with neutrophilia", section on 'Infection'.)

Severe and fulminant colitis — Clinical manifestations of severe colitis include diarrhea, lower quadrant or diffuse abdominal pain, abdominal distention, fever, hypovolemia, lactic acidosis, hypoalbuminemia, elevated creatinine concentration, and marked leukocytosis (white blood cell count 40,000 cells/microL or higher) [8,11,12]. Criteria proposed for severe CDI (based on expert opinion) include white blood cell count >15,000 cells/microL or serum creatinine ≥1.5 mg/dL; prospectively validated severity scores for CDI are needed [1]. Peripheral eosinopenia has also been proposed as an indicator of CDI severity [13].

Fulminant colitis (previously referred to as severe, complicated CDI) may be characterized by hypotension or shock, ileus, or megacolon [1,14]:

- Severe hypotension progressing to multisystem organ failure may occur in the setting of fulminant CDI and/or in the setting of bowel perforation with peritonitis.
- Occasionally, CDI presents acutely as ileus, with little or no diarrhea. Diarrhea may be less prominent or absent due to pooling of secretions in a dilated, atonic colon. Such patients are usually severely ill, with colonic (and possibly small bowel) dilatation, often with colonic thickening, fever, and leukocytosis. In some cases, this presentation seems benign initially but progresses rapidly.
- Megacolon should be suspected in patients with severe systemic toxicity together with radiographic evidence of large bowel dilatation (>7 cm diameter in the colon and/or >12 cm diameter in the cecum). Megacolon may be complicated by bowel perforation; manifestations include abdominal rigidity, involuntary guarding, diminished bowel sounds, rebound tenderness, and severe localized tenderness in the left or right lower quadrants; abdominal radiographs may demonstrate free abdominal air. (See "Toxic megacolon".)

Patients with fulminant colitis warrant radiographic imaging (preferably computed tomography of the abdomen and pelvis) and prompt surgical evaluation. (See 'Radiographic imaging' below and "*Clostridioides difficile* infection in adults: Treatment and prevention".)

Recurrent disease — Recurrent CDI is defined by resolution of CDI symptoms while on appropriate therapy, followed by reappearance of symptoms within two to eight weeks after treatment has been stopped [1].

Up to 25 percent of patients experience recurrent *C. difficile* within 30 days of completing treatment [15]. Less commonly, recurrent CDI can occur as late as two months after discontinuation of treatment. Once patients have experienced one recurrence, they are at significantly increased risk for further recurrences. (See "*Clostridioides difficile* infection in adults: Epidemiology, microbiology, and pathophysiology", section on 'Recurrent infection'.)

Recurrent disease may be mild, severe, or fulminant [16]. One study including more than 1500 patients with CDI noted 34 percent of patients with recurrent infection needed hospital admission, 28 percent developed severe disease, and 4 percent developed fulminant colitis [17].

Risk factors for recurrence include age >65 years, severe underlying medical disorders, need for ongoing therapy with concomitant antibiotics during treatment for CDI, and lack of an antibody-mediated immune response to *C. difficile* toxins [18-22].

Recurrent symptoms may be due to relapse of the initial infecting strain or reinfection with a new strain [23-25]. Recurrent CDI often represents relapse rather than reinfection, regardless of the interval between episodes. Among 134 paired stool isolates from 102 patients with recurrent CDIs, isolates obtained 2 to 8 weeks apart were identical in 88 percent of cases; isolates obtained 8 weeks to 11 months apart were identical in 65 percent of cases [26].

Persistent diarrhea without resolution during initial therapy should prompt an evaluation for other causes and should not be considered recurrent disease. In the absence of an alternative diagnosis, such patients should be considered to have refractory CDI.

Patients with recurrent diarrhea, cramping, and bloating following treatment of CDI may have postinfectious irritable bowel syndrome or another inflammatory colitis. In atypical cases, colonoscopy should be considered to evaluate for evidence of CDI and to exclude other etiologies. (See 'Differential diagnosis' below.)

Asymptomatic carriage — Asymptomatic individuals do not warrant screening for *C. difficile* carriage, and individuals with asymptomatic carriage of *C. difficile* do not warrant treatment or contact precautions [1]. (See "*Clostridioides difficile* infection in adults: Epidemiology, microbiology, and pathophysiology" and "*Clostridioides difficile* infection: Prevention and control".)

Asymptomatic *C. difficile* carriage occurs in up to 20 percent of hospitalized adults; these patients shed *C. difficile* in stool but do not have diarrhea or other clinical symptoms [27-29]. In long-term care facilities, the rate of asymptomatic colonization may approach 50 percent. These individuals serve as a reservoir for environmental contamination [28,29]. An insufficient host immune response to *C. difficile* may play a role in determining asymptomatic carriage.

Unusual presentations — Unusual manifestations of *C. difficile* infection include protein-losing enteropathy and extracolonic involvement.

- Protein-losing enteropathy – Protein-losing enteropathy with hypoalbuminemia has been described in association with acute CDI in the absence of fulminant colitis [30,31]. Inflammation of the bowel wall allows leakage of albumin into the lumen, causing colonic loss of albumin with inadequate compensatory hepatic synthesis. As a result, serum albumin levels may drop below 2.0 g/dL (20 g/L). Ascites and peripheral edema may be observed. The protein-losing enteropathy responds to appropriate medical therapy of the infection. (See "Protein-losing gastroenteropathy" and "*Clostridioides difficile* infection in adults: Treatment and prevention".)

- Extracolonic involvement – Rare cases of *C. difficile* appendicitis, small bowel enteritis, and extraintestinal involvement have been described [32].

  - Appendicitis due to CDI has been described in a few case reports [33].

  - Small bowel involvement with *C. difficile* enteritis is rare but may occur in older adults and/or patients with multiple comorbidities [34-36]. In some cases, patients have had prior colectomy with ileostomy; manifestations may include increased ileostomy output, and it may be possible to visualize pseudomembranes (raised white or tan plaques attached to epithelium) on the exposed ileal mucosa at the stoma. Such patients may be at increased risk for fulminant disease with a high mortality rate [35,36].

  - Rare cases of *C. difficile* cellulitis, soft tissue infection, bacteremia, and reactive arthritis have been described [34,37,38].

DIAGNOSIS

When to suspect and test for C. difficile infection — The diagnosis of *C. difficile* infection should be suspected in patients with acute diarrhea (≥3 loose stools in 24 hours) with no obvious alternative explanation, particularly in the setting of relevant risk factors (including recent antibiotic use, hospitalization, and advanced age) [1]. Patients with suspected *C. difficile* infection should be placed on contact precautions preemptively pending diagnostic evaluation. (See "*Clostridioides difficile* infection: Prevention and control", section on 'Contact precautions'.)

The diagnosis of CDI is established via either a positive nucleic acid amplification test (NAAT) for *C. difficile* toxin gene or a positive stool test for *C. difficile* toxin(s). The diagnostic approach for

suspected recurrent *C. difficile* is the same as the approach for initial infection.

For patients with diarrhea and suspected CDI, only liquid stool should be sent for *C. difficile* testing. Diagnostic laboratory testing should be pursued only in patients with clinically significant diarrhea. Formed stool from asymptomatic patients should not be submitted for laboratory testing, since presence of *C. difficile* toxin gene does not distinguish between CDI and asymptomatic carriage (which does not warrant treatment) [39-42].

For patients with ileus and suspected CDI, laboratory diagnosis via rectal swab for toxin assay or anaerobic culture may be performed; the sensitivity of rectal swab for *C. difficile* culture in the setting of ileus is high (although test results take time) [39,43,44].

Diagnostic laboratory assays — Laboratory diagnosis of CDI requires demonstration of *C. difficile* toxin(s) or detection of toxigenic *C. difficile* organism(s) [45]. We favor use of NAATs for laboratory diagnosis of *C. difficile*, either alone or as part of an algorithm including initial EIA screening for glutamate dehydrogenase (GDH) antigen and toxins A and B (algorithm 1) [1,46,47].

A number of laboratory stool tests are available alone or in combination as part of a diagnostic algorithm:

- NAAT
- Enzyme immunoassay for *C. difficile* GDH
- Enzyme immunoassay for *C. difficile* toxins A and B
- Cell culture cytotoxicity assay
- Selective anaerobic culture

These tests are discussed in further detail below.

- NAAT – NAATs (which include polymerase chain reaction) detect one or more genes specific to toxigenic strains; the critical gene is *tcdB*, which encodes for toxin B. NAATs are highly sensitive [48-51]; their sensitivity is greater than EIA and comparable with cytotoxicity assay [52-56]. NAATs are specific for toxigenic strains but do not test for active toxin protein production and are capable of detecting asymptomatic carriers of *C. difficile*; therefore, only liquid stool samples from patients with ≥3 loose stools in 24 hours should be tested. Only a single stool sample should be tested. NAAT results can be available within as little as one hour. NAAT results may be falsely negative if stool specimen collection is delayed and the patient has been treated empirically for suspected CDI [57].

Given its high sensitivity and its inability to distinguish CDI from asymptomatic carriage, overdiagnosis of CDI has emerged as a risk of NAATs, resulting in antibiotic treatment of patients who may not require such therapy [58,59]. In a study of more than 1400 patients with suspected CDI, patients whose stool tested positive by NAAT but negative by immunoassay had a lower toxin load and less diarrhea than patients for whom both assays were positive [59]. For circumstances in which initial testing consisted of NAAT (with positive result), some favor subsequent testing with EIA for toxins A and B to bolster clinical specificity. It remains unclear whether a positive NAAT result along with a negative toxin EIA result is indicative of an active *C. difficile* infection. Although many patients with discrepant results can forego treatment without adverse outcomes [60], we treat patients who are severely ill and those who do not have an alternative explanation for the diarrhea because there is a lack of high-quality data establishing the safety of withholding treatment in these patient populations.

- EIA for *C. difficile* GDH antigen – GDH antigen is an essential enzyme produced constitutively by all *C. difficile* isolates; however, its detection cannot distinguish between toxigenic and nontoxigenic strains [61-63]. Therefore, testing for GDH antigen is useful as an initial screening step in a multistep approach, which also consists of subsequent testing with more specific assays such as toxin A and B EIA or NAAT on specimens that are GDH antigen positive [64]. GDH antigen testing has good sensitivity, and results are available in less than one hour.

- EIA for *C. difficile* toxins A and B – Most *C. difficile* strains produce both toxins A and B, although some strains produce only one toxin [65-70]. Testing for both toxins by EIA gives a higher sensitivity than testing for just one toxin [1,58]. Many inexpensive assays are commercially available, and test results are available within hours. The sensitivity of EIA for toxins A and B is on average about 75 percent, but the sensitivity varies depending on the specific assay used; the specificity is high (up to 99 percent) [71,72]. There is a relatively high false-negative rate since 100 to 1000 pg of toxin must be present for the test to be positive [73]. Hence, GDH antigen testing is often used together with toxin EIA. If the GDH is positive but the toxin EIA is negative, adjudication with NAAT is beneficial.

- Selective anaerobic culture – Selective anaerobic culture is seldom employed for clinical diagnosis as results take several days to finalize. Culture on selective medium with toxin testing of isolated *C. difficile* is a highly sensitive diagnostic method, although culture alone cannot distinguish toxin-producing strains from non-toxin-producing strains [74]. Use of a second test (EIA, cell culture cytotoxicity assay) is required to detect toxin production by cultured *C. difficile* strains. Treatment of stool with heat or alcohol to shock spores (to

increase vegetative growth and remove contaminants) is sometimes used to improve yield. Culture is useful for epidemiologic studies but is generally too slow and labor intensive for routine clinical use [71]. Rectal swab for toxin assay or anaerobic culture can be a useful diagnostic tool for patients with ileus and suspected CDI.

- Cell culture cytotoxicity assay – The cell culture cytotoxicity assay is sensitive and specific but resource intensive and time consuming; it is not a routine clinical diagnostic test. The assay was developed contemporaneously with the discovery of *C. difficile* and has been used as a gold standard test for diagnosis of *C. difficile*; it is more sensitive than enzyme immunoassay, although it is limited by lack of standardization, the requirement for a cell culture facility, and slow turnaround time (approximately two days) [74,75]. The cell culture cytotoxicity assay is performed by adding a prepared stool sample (diluted, buffered, and filtered) to a monolayer of cultured cells [45,76,77]. If *C. difficile* toxin is present, it exerts a cytopathic effect characterized by cell rounding; specificity of the cytotoxicity is demonstrated by neutralization of the cytopathic effect with specific antiserum.

It is important to note that *C. difficile* toxin degrades at room temperature and may be undetectable within two hours after collection; therefore, specimens for testing based on toxin detection (EIA for *C. difficile* toxins and cell culture cytotoxicity assay) should be kept at 4°C if delay in laboratory testing is anticipated. In addition, a suspected outbreak should prompt freezing of stool samples for later investigation.

Fecal leukocyte testing is not helpful for diagnosis of CDI [78].

Adjunctive diagnostic tools — Adjunctive diagnostic tools for evaluating patients with suspected CDI include radiographic imaging and endoscopy.

Radiographic imaging — Radiographic imaging of the abdomen and pelvis is warranted for patients with clinical manifestations of severe disease (severe abdominal pain, abdominal distention with apparent ileus, fever, hypovolemia, lactic acidosis, hypoalbuminemia, and/or marked leukocytosis) or fulminant colitis (characterized by hypotension or ileus) to evaluate for presence of toxic megacolon, bowel perforation, or other findings warranting surgical intervention. Computed tomography (CT) of the abdomen and pelvis with oral and intravenous contrast is the preferred imaging modality; plain films may be useful for circumstances in which CT is not readily available.

Radiographic evidence of colonic dilatation (>7 cm in diameter) in the clinical setting of severe CDI is diagnostic of toxic megacolon. Other radiographic findings consistent with toxic megacolon include small bowel dilatation, air-fluid levels (mimicking an intestinal obstruction or ischemia), and "thumb printing" (scalloping of the bowel wall) due to submucosal edema

(image 1 and image 2). In the setting of bowel perforation, free abdominal air may be observed. (See "Toxic megacolon".)

Other radiographic findings associated with *C. difficile* colitis include pronounced colonic wall thickening (image 3) and low-attenuation mural thickening, corresponding with mucosal and submucosal edema (which may be visible as a "target sign" or "double halo sign" consisting of two or three concentric rings of different attenuation) [79]. Pericolonic stranding and ascites may be seen but are not specific for CDI.

Findings consistent with pseudomembranous colitis (severe inflammation of the inner lining of the bowel) on radiographic examination are highly suggestive of CDI and should prompt laboratory testing if not already performed. The "accordion sign" is highly suggestive of pseudomembranous colitis; it consists of mucosal edema and inflammation involving the large bowel and is seen when orally administered contrast material becomes trapped between thickened haustral folds, giving the appearance of alternating bands of high attenuation (contrast material) and low attenuation (edematous haustra) [79-81]. (See 'When to suspect and test for C. difficile infection' above.)

Endoscopy — Lower gastrointestinal endoscopy is not warranted in patients with typical clinical manifestations of CDI, a positive laboratory test, and/or clinical response to empiric treatment. In general, endoscopy may be pursued for circumstances in which an alternative diagnosis is suspected that requires direct visualization and/or biopsy of the bowel mucosa. It may also be helpful for patients with ileus or fulminant colitis in the absence of diarrhea since it may allow visualization of pseudomembranes (severe inflammation of the inner lining of the bowel), a finding that is highly suggestive of CDI (picture 1). The decision to proceed with endoscopy should be made carefully; if pursued, limited flexible sigmoidoscopy is preferred with minimal or no air insufflation to avoid the risk of perforation of the inflamed colon.

Findings on lower gastrointestinal endoscopy in the setting of CDI include bowel wall edema, erythema, friability, and inflammation. The finding of pseudomembranes on the inflamed mucosal surface are highly suggestive of CDI and should prompt diagnostic laboratory confirmation if not already performed (via stool assay or, in the setting of ileus, a rectal swab for toxin assay or anaerobic culture) [82]. However, not all patients with CDI have pseudomembranes, particularly patients with mild or partially treated infection, and absence of pseudomembranes does not rule out CDI. Pseudomembranes are rarely observed in the setting of recurrent CDI or inflammatory bowel disease [83,84]. There are rare reports of other pathogens also capable of causing pseudomembranous colitis, and occasionally pseudomembranes are seen in patients with uremia or ischemic colitis. (See 'Differential diagnosis' below.)

Formation of pseudomembranes occurs following *C. difficile* toxin-induced ulcer formation on the mucosal surface of the intestine, which facilitates release of serum proteins, mucus, and inflammatory cells [85]. Pseudomembranes manifest as raised yellow or off-white plaques up to 2 cm in diameter scattered over the colonic mucosa (picture 1 and picture 2). Some patients with pseudomembranous colitis have scattered lesions with relatively normal-appearing intervening mucosa, while others have a confluent pseudomembrane covering the entire mucosa. Pseudomembranes may be absent in the rectosigmoid area but present more proximally, although colonoscopy for proximal evaluation of the colon is not warranted for diagnosis of *C. difficile* given potential bowel tissue friability and risk of perforation [82,86].

Biopsy is not needed for diagnosis of *C. difficile*. Biopsy may be warranted to establish an alternative diagnosis, particularly for patients who are not responding clinically to appropriate therapy for presumed CDI. (See 'Differential diagnosis' below.)

Repeating laboratory testing — There is no role for repeat laboratory testing (within seven days) during the same episode of diarrhea, and there is no indication to test for cure [1,87-93]. There is also no role for laboratory testing in asymptomatic patients or repeat testing of patients receiving treatment for acute CDI; stool assays may remain positive during or after clinical recovery. However, for patients with recurrent symptoms after initial resolution of diarrhea, repeat testing is warranted to evaluate for recurrent disease.

DIFFERENTIAL DIAGNOSIS

C. difficile must be distinguished from other infectious and noninfectious causes of diarrhea. Most antibiotic-associated diarrhea is not attributable to CDI (but rather to osmotic mechanisms), whereas antibiotic-associated diarrhea associated with colitis is nearly always due to CDI.

- Acute abdomen – CDI may present as abdominal distension mimicking small bowel ileus, Ogilvie's syndrome (colonic pseudo-obstruction), volvulus, or ischemia [94]. The approach to diagnosis varies by age, sex, and condition; tools include history and physical examination, surgical consultation, and radiographic imaging. (See "Evaluation of the adult with nontraumatic abdominal or flank pain in the emergency department".)

- Shock – Severe hypotension may occur in the setting of fulminant CDI and/or in the setting of bowel perforation with peritonitis. In addition, CDI may develop during antibiotic treatment for septic shock caused by a separate bacterial infection. Shock due to other causes (such as septic shock or cardiogenic shock) must be distinguished from severe

hypotension due to CDI via cardiac and hemodynamic assessment. (See "Evaluation of and initial approach to the adult patient with undifferentiated hypotension and shock".)

- Infectious diarrhea – Other organisms that have been implicated as causes of antibiotic-associated diarrhea include *Staphylococcus aureus*, *Klebsiella oxytoca*, *Clostridium perfringens*, and *Salmonella* spp [95-99]. The clinical manifestations are similar to those of CDI; the diagnosis is distinguished by stool culture and/or stool multiplex nucleic acid testing.

- Noninfectious diarrhea – Causes of noninfectious diarrhea that may mimic CDI include postinfectious irritable bowel syndrome, inflammatory bowel disease, celiac disease, and microscopic colitis. Differentiation of noninfectious antibiotic-associated diarrhea from CDI may be difficult, especially in patients who are asymptomatic *C. difficile* carriers; this is most relevant among patients in nursing homes or hospitals where the rate of asymptomatic carriage ranges from 10 to 50 percent (in community populations, the rate of asymptomatic carriage is ≤5 percent). Cessation of symptoms with discontinuation of oral intake is a distinguishing feature of osmotic diarrhea (figure 1). The presence of fever and leukocytosis favors *C. difficile* or other infectious etiology. (See "Approach to the adult with chronic diarrhea in resource-abundant settings".)

  - Postinfectious irritable bowel syndrome – Postinfectious irritable bowel syndrome occurs in about 10 percent of patients who have been successfully treated for an initial episode of *C. difficile*. These patients may have up to 10 watery stools per day; this must be distinguished from a relapse of the original CDI based on established criteria (table 2). (See "Clinical manifestations and diagnosis of irritable bowel syndrome in adults".)

  - Inflammatory bowel disease – Infection with *C. difficile* may complicate the course of inflammatory bowel disease (IBD) [100,101]. Enteric infections account for about 10 percent of symptomatic relapses in patients with IBD; *C. difficile* accounts for about half of these infections [102]. Rates of *C. difficile* among patients with IBD appear to be increasing [103,104]. The association between IBD and *C. difficile* may be due to a variety of factors, including dysbiosis associated with colitis or with antibiotic use for treatment of other gastrointestinal pathogens, and frequent hospitalization for management of IBD flares. Rarely, *C. difficile* can trigger an initial bout of IBD [102].

    CDI in patients with IBD requires prompt diagnosis and management, since failure to diagnose the infection can lead to inappropriate treatment with glucocorticoids or immunosuppressive therapy. Furthermore, *C. difficile* may be difficult to distinguish

from an IBD relapse given the similar symptoms of diarrhea, abdominal pain, and low-grade fever. Thus, a high index of suspicion is required when evaluating IBD patients with apparent flares, especially those who have recently received antibiotics and/or been hospitalized.

The diagnosis requires laboratory testing; endoscopy is usually not helpful because IBD patients generally do not develop pseudomembranes. Given preexisting colonic pathology, patients with IBD who develop *C. difficile* colitis require colectomy more frequently (20 percent in one series) [104].

There is a high prevalence of *C. difficile* carriage in patients with IBD. This was illustrated in a study of 122 patients with longstanding IBD in which the frequency of *C. difficile* carriage was higher in IBD patients than in healthy volunteers (8 versus 1 percent, respectively), in the absence of recent antibiotics or hospitalization [105]. Despite this observation, none developed symptomatic disease in the subsequent six months. The reason for this observation is not certain; possibilities include altered colonic microbial flora, mucosal inflammation, and impaired mucosal innate immunity.

- Microscopic colitis – Microscopic colitis is a chronic inflammatory disease of the colon characterized by chronic watery diarrhea. The diagnosis is established by histopathology following colonoscopy with biopsy. (See "Microscopic (lymphocytic and collagenous) colitis: Clinical manifestations, diagnosis, and management".)

- Celiac disease – Celiac disease is a small bowel disease associated with dietary gluten exposure intolerance; gastrointestinal symptoms including chronic or recurrent diarrhea, malabsorption, weight loss, and abdominal distension or bloating. The diagnosis is established via serology and/or biopsy. (See "Diagnosis of celiac disease in adults".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: *Clostridioides difficile* infection".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or email these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: *C. difficile* infection (The Basics)")
- Beyond the Basics topic (see "Patient education: Antibiotic-associated diarrhea caused by *Clostridioides difficile* (Beyond the Basics)")

SUMMARY

- **Risk factors for CDI** – *Clostridioides difficile* colonizes the human intestinal tract typically after the normal gut flora has been altered by antibiotic therapy and causes antibiotic-associated colitis. The antibiotics most frequently implicated in predisposition to *C. difficile* infection (CDI) are fluoroquinolones, clindamycin, cephalosporins, and penicillins (table 1). Additional risk factors include age >65 and recent hospitalization. (See 'Diarrhea with colitis' above.)
- **Clinical manifestations** – A spectrum of clinical manifestations is observed. (See 'Clinical manifestations' above.)
  - **Nonsevere CDI** – Clinical manifestations of nonsevere CDI include watery diarrhea (≥3 loose stools in 24 hours) with lower abdominal pain and cramping, low-grade fever, and leukocytosis. Criteria proposed for nonsevere CDI (based on expert opinion) include white blood cell count ≤15,000 cells/microL and serum creatinine <1.5 mg/dL; prospectively validated severity scores for CDI are needed. (See 'Diarrhea with colitis' above.)
  - **Severe CDI** – Clinical manifestations of severe CDI include diarrhea, severe lower quadrant or diffuse abdominal pain, abdominal distention, fever, hypovolemia, lactic

acidosis, hypoalbuminemia, and marked leukocytosis. Criteria proposed for severe CDI (based on expert opinion) include white blood cell count >15,000 cells/microL and/or serum creatinine ≥1.5 mg/dL. (See 'Severe and fulminant colitis' above.)

- **Fulminant colitis** – Fulminant colitis (previously referred to as severe, complicated CDI) may be characterized by hypotension or shock, ileus, or megacolon. (See 'Severe and fulminant colitis' above.)

- **Recurrent CDI** – Recurrent CDI is defined by resolution of CDI symptoms while on appropriate therapy, followed by reappearance of symptoms within two to eight weeks after treatment has been stopped. The clinical presentation may be similar to or more severe than the initial presentation. (See 'Recurrent disease' above.)

- **Diagnosis**

  - The diagnosis of CDI is established via a positive nucleic acid amplification test (NAAT) for *C. difficile* toxin gene or a positive stool test for *C. difficile* toxin(s). We favor use of NAAT for laboratory diagnosis of *C. difficile*, either alone or as part of an algorithm including initial enzyme immunoassay screening for glutamate dehydrogenase antigen and toxins A and B (algorithm 1). (See 'When to suspect and test for C. difficile infection' above.)

  - Laboratory testing should be pursued only in patients with clinically significant diarrhea, since testing cannot distinguish between CDI and asymptomatic carriage of *C. difficile* (which does not warrant treatment). For patients with ileus, laboratory diagnosis via perirectal swab for toxin assay or anaerobic culture may be performed. (See 'When to suspect and test for C. difficile infection' above.)

  - Radiographic imaging of the abdomen and pelvis is warranted for patients with clinical manifestations of severe illness or fulminant colitis to evaluate for presence of toxic megacolon, bowel perforation, or other findings warranting surgical intervention. (See 'When to suspect and test for C. difficile infection' above and 'Radiographic imaging' above.)

  - Lower gastrointestinal endoscopy is not warranted in patients with typical clinical manifestations of CDI, a positive laboratory test, and/or clinical response to empiric treatment. It may be helpful for patients with ileus or fulminant colitis in the absence of diarrhea since it may allow visualization of pseudomembranes (severe inflammation of the inner lining of the bowel), a finding that is highly suggestive of CDI. (See 'Endoscopy' above.)

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Topic 2699 Version 70.0

GRAPHICS

Antimicrobial agents that may induce *Clostridioides difficile* diarrhea and colitis

Frequently associated	Occasionally associated	Rarely associated
▪ Fluoroquinolones ▪ Clindamycin ▪ Penicillins and combinations (broad spectrum) ▪ Cephalosporins (2^{nd}/3^{rd}/4^{th} generation)* ▪ Carbapenems	▪ Macrolides ▪ Penicillins (narrow spectrum) ▪ Cephalosporins (1^{st} generation) ▪ Trimethoprim-sulfamethoxazole ▪ Sulfonamides	▪ Aminoglycosides ▪ Tetracyclines ▪ Tigecycline ▪ Chloramphenicol ▪ Metronidazole ▪ Vancomycin ▪ Nitrofurantoin

* Use of 1 to 2 doses of a first-generation cephalosporin for surgical antibiotic prophylaxis does not confer significant risk for *C. difficile* infection.

Data from:

1. *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; 66:987.*
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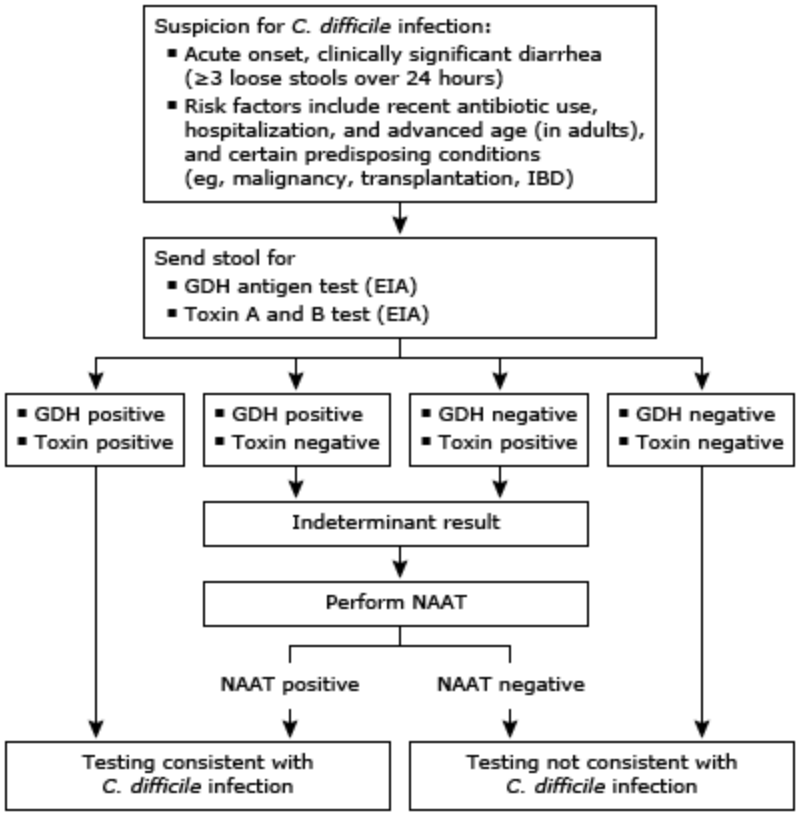
4. *Ge IY, Fevrier HB, Conell C, et al. Reducing risk of Clostridium difficile infection and overall use of antibiotic in the outpatient treatment of urinary tract infection. Ther Adv Urol 2018; 10:10.*

Graphic 55479 Version 14.0

A laboratory approach to diagnosis of *Clostridioides difficile*



- The laboratory approach to diagnosis of *C. difficile* infection consists of NAAT, either alone or as part of an algorithm, as summarized above. In laboratories that use the above approach, the steps are frequently performed reflexively.
- Only liquid stool samples from patients with ≥3 loose stools in 24 hours should be tested.
- The GDH antigen test uses antibodies to test for the presence of the GDH enzyme, a protein present in all *C. difficile* isolates. It is a useful screening test with good sensitivity, rapid turnaround time, and low cost. However, specificity is poor since this assay does not test for toxin production and cannot distinguish between toxigenic and nontoxigenic strains of *C. difficile*.
- The toxin test uses antibodies to detect the presence of *C. difficile* toxin A and/or toxin B; testing for both toxins is preferred. The toxin test has high specificity with rapid turnaround time and low cost. However, the sensitivity is low, so there is a high rate of false negatives.
- The NAAT tests for the presence of toxigenic *C. difficile* organisms in stool by amplifying one or more genes specific to toxigenic strains; the critical gene is *tcdB*, which encodes for toxin B. This test is specific for toxigenic strains but does not test for active

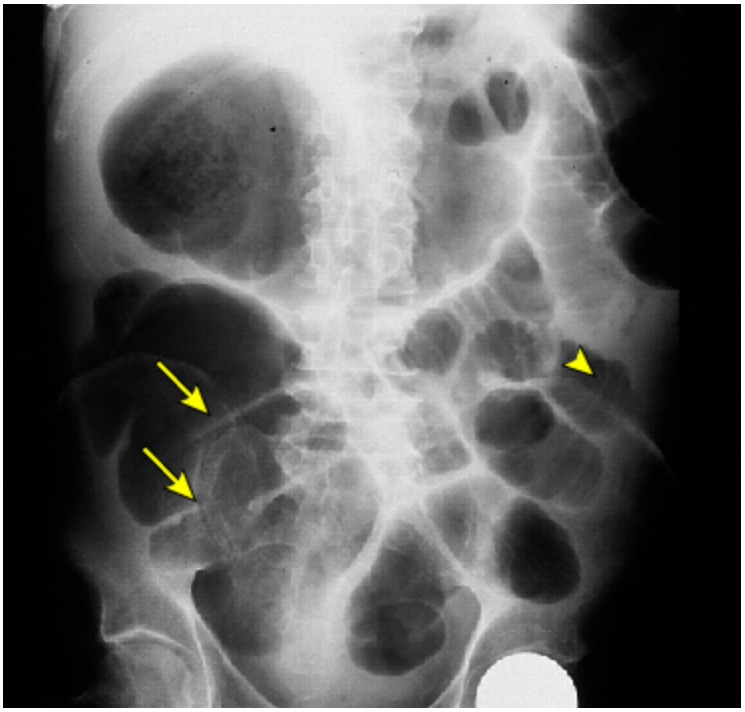
toxin production and also detects asymptomatic carriers of toxigenic *C. difficile*.

- If both tests are done and are discordant (an indeterminate result), there are several possible explanations:
  - The patient has active toxigenic *C. difficile* infection (one or the other of the tests was a false negative).
  - The patient has nontoxigenic *C. difficile* colonization (the GDH test was positive, but the toxin test was a true negative).
  - The patient is an asymptomatic carrier of toxigenic *C. difficile* but does not have active disease (again, one or the other of tests was a false negative, perhaps related to the density of the organism in stool). Patients should only be tested if they are symptomatic to avoid detection of asymptomatic carriage.

IBD: inflammatory bowel disease; GDH: glutamate dehydrogenase; EIA: enzyme immunoassay; NAAT: nucleic acid amplification testing.

Graphic 100540 Version 10.0

Toxic megacolon in *Clostridioides difficile*

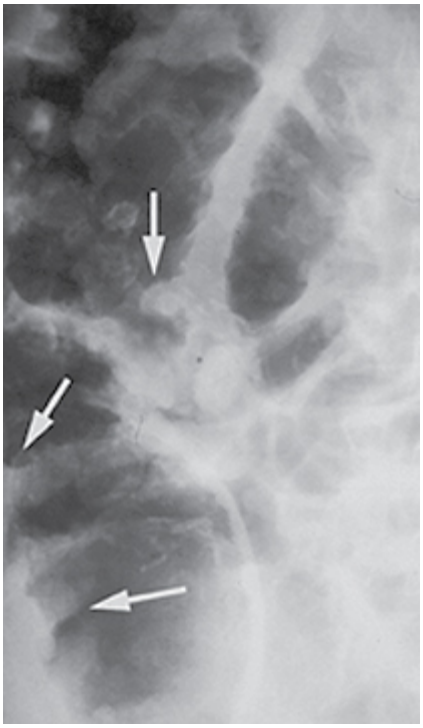


Plain film of the abdomen from a patient with toxic megacolon associated with *Clostridioides* (formerly *Clostridium*) *difficile* infection. The large and small intestines are grossly dilated. Dilatation of the small bowel, which has the thin transverse folds of the valvulae conniventes (arrowhead), is seen best in the left lower quadrant. Large bowel dilatation occupies most of the right lower quadrant and has characteristic thick haustral markings that do not extend across the entire lumen (arrows).

Courtesy of J Thomas Lamont, MD.

Graphic 59217 Version 8.0

Thumbprinting in pseudomembranous colitis

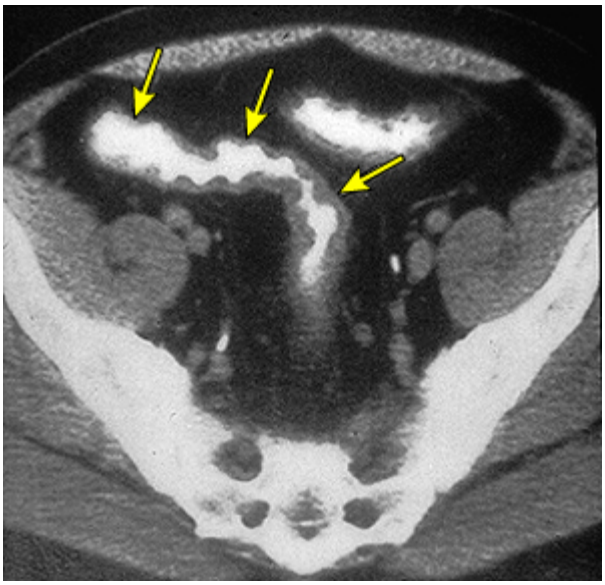


Plain film of the abdomen demonstrates marked thickening of the wall of the ascending colon (arrows), producing a thumbprinting pattern. This appearance is seen in all forms of colitis.

Courtesy of Jonathan Kruskal, MD, PhD.

Graphic 52929 Version 4.0

Clostridioides difficile colitis – computed tomography

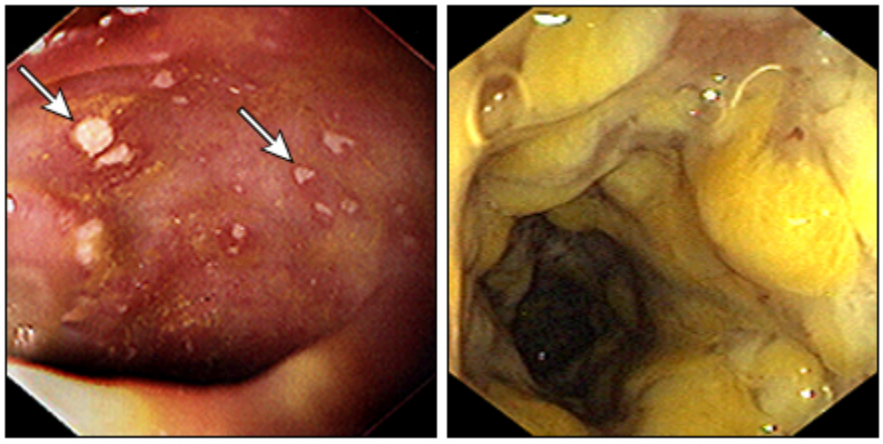


Computed tomography (CT) scan shows marked thickening of the wall of the sigmoid colon (arrows). This appearance is not specific for pseudomembranous colitis and may be seen with any form of colitis.

Courtesy of Jonathan Kruskal, MD, PhD.

Graphic 57812 Version 9.0

Pseudomembranous colitis



Endoscopic appearance of *Clostridioides* (formerly *Clostridium*) *difficile*-induced pseudomembranous colitis.

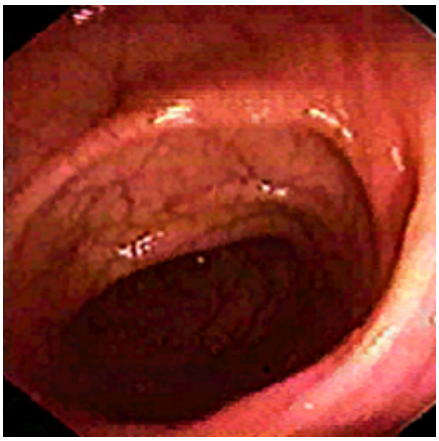
(Left panel) Scattered pseudomembranes are visible on top of the mucosa, being separated by areas of relatively normal mucosa. Some of the lesions have a red halo (arrows).

(Right panel) Yellow pseudomembrane circumferentially covering the entire colonic mucosa.

Courtesy of James B McGee, MD.

Graphic 53774 Version 5.0

Normal sigmoid colon

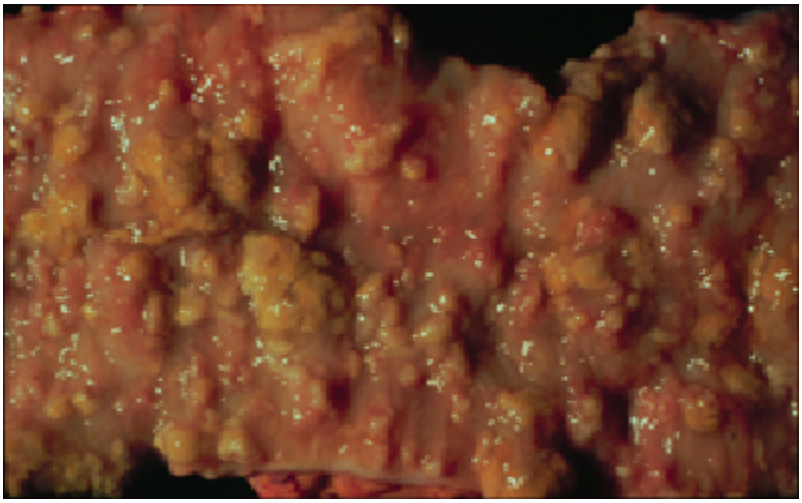


Endoscopic appearance of the normal sigmoid colonic mucosa. The fine vasculature is easily visible, and the surface is shiny and smooth. The folds are of normal thickness.

Courtesy of James B McGee, MD.

Graphic 55563 Version 1.0

Pseudomembranous colitis

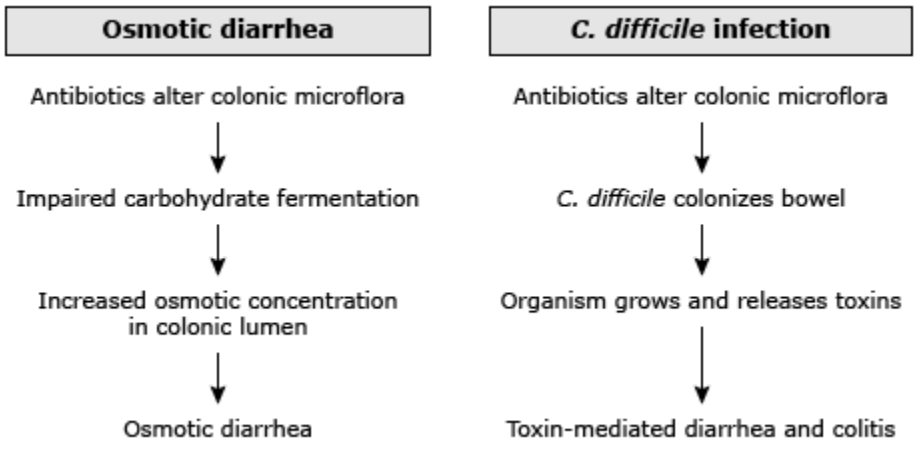


Gross appearance of the colon from a patient with pseudomembranous colitis. The pseudomembranes are yellow or off-white raised plaques 0.2 to 2.0 cm in diameter, which are scattered over fairly normal-appearing intervening mucosa.

Courtesy of J Thomas Lamont, MD.

Graphic 62422 Version 2.0

Antibiotic-associated osmotic versus *Clostridioides* (formerly *Clostridium*) *difficile* diarrhea



Graphic 69745 Version 6.0

Rome III diagnostic criteria* for irritable bowel syndrome

Recurrent abdominal pain or discomfort¶ at least three days per month in the last three months associated with two or more of the following:
(1) Improvement with defecation
(2) Onset associated with a change in frequency of stool
(3) Onset associated with a change in form (appearance) of stool

* Criteria fulfilled for the last three months with symptom onset at least six months prior to diagnosis.

¶ Discomfort means an uncomfortable sensation not described as pain. In pathophysiology research and clinical trials, a pain/discomfort frequency of at least two days a week during screening evaluation for subject eligibility.

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Graphic 54997 Version 6.0

Contributor Disclosures

J Thomas Lamont, MD Equity Ownership/Stock Options: Allurion [Weight loss]. Consultant/Advisory Boards: Teledoc [Gastrointestinal diseases]. All of the relevant financial relationships listed have been mitigated. **Ciarán P Kelly, MD** Equity Ownership/Stock Options: Cour Pharmaceuticals [Celiac disease]. Grant/Research/Clinical Trial Support: Merck [C difficile infection]; Milky Way Life Sciences [C difficile infection, Celiac disease]; Pfizer [C. difficile infection]; Takeda [Celiac disease]. Consultant/Advisory Boards: Cour Pharmaceuticals [Celiac disease]; Facile Therapeutics [C difficile infection]; Ferring [C difficile infection]; Finch [C difficile infection]; J&J Jannsen [Celiac disease]; Kanyos/Anokion [Celiac disease]; Merck [C difficile infection, celiac disease]; Milky Way Life Sciences [C difficile infection, Celiac disease]; Pfizer [C difficile infection, Celiac disease]; RVAC Medicines [C difficile infection]; Seres Therapeutics [C difficile infection]; Summit [C difficile infection]; Takeda [Celiac disease]; Teravance [Celiac disease]. All of the relevant financial relationships listed have been mitigated. **Johan S Bakken, MD, PhD** No relevant financial relationship(s) with ineligible companies to disclose. **Stephen B Calderwood, MD** Consultant/Advisory Boards: Day Zero Diagnostics [Whole genome sequencing for microbial identification and determination of antimicrobial susceptibility]. All of the relevant financial relationships listed have been mitigated. **Milana Bogorodskaya, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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