Clostridium difficile

What is Clostridium difficile?

Clostridium difficile, a toxin-producing, spore-forming, anaerobic gram-positive bacillus, is a significant cause of infectious diarrhea, called *C. difficile* infection (CDI).

Who gets CDI?

Persons 65 years of age and older, as well as those with multiple medical co-morbidities, are at increased risk for CDI. People with some conditions, including inflammatory bowel disease and Crohn's Disease, often have a higher rate of CDI. This may be due to a combination of colonic disruption and use of immunosuppressive medications to control those conditions. It is suspected that proton pump inhibitors (PPIs) are also associated with an increase in the risk of CDI, presumably due to inhibition of gastric acid, the body's natural defense against *C. difficile* spores. Other events that impair the normal colonic mucosa may also precipitate CDI, including gastrointestinal surgery, colitis, chemotherapy, and treatment with stool softeners and laxatives. There are also cases of community acquired CDI, often in younger patients, where common risk factors are absent.

Antibiotic exposure is the most important modifiable risk for acquisition of CDI. The risk varies depending on the antibiotic's ability to disrupt normal intestinal flora, enabling *C. difficile* to establish in the bowel. There is a well-defined dose-dependent increase in the risk of CDI with increasing doses and days of antibiotic exposure. In a recent study, patients who received two antibiotics compared to those receiving only one had a 2.5-fold increased risk of CDI.

Table 1 highlights common antibiotic classes and their potential for contributing to CDI. The abilities of clindamycin and cephalosporin to induce CDI are well known. Recently, fluoroquinolones have emerged as a significant risk factor. Widespread use of these broad agents over the last decade directly influenced the development of the highly fluoroquinolone resistant (NAP1) strain of *C. difficile*.

Table 1. Classification of Antibiotics Relative to Risk of Contribution to CDI

High Risk
Fluoroquinolones Carbapenem Cephalosporins (2nd, 3rd, and 4th generation) Clindamycin
Medium Risk
Penicillins: Penicillin + β-lactamase inhibitors (i.e., amoxicillin/clavulanate, piperacillin/tazobactam) 1st generation cephalosporin Macrolides (i.e., azithromycin, clarithromycin
Low Risk
Tetracyclines Sulfamethoxazole/Trimethoprim Aminoglycosides Fosfomycin Rifampin Linezolid Nitrofurantoin

How is *C. difficile* spread?

C. difficile is not part of the normal fecal flora in most people. Infection is most often acquired in a medical setting, such as a long-term care environment, hospital, or clinic, from a contaminated surface or a healthcare provider's hands.

What are the symptoms of CDI?

Clinically significant diarrhea (≥ 3 watery stools/day) following recent antibiotic exposure and/or hospitalization should prompt evaluation. Fever, leukocytosis, and abdominal pain combined with any of the above should raise suspicion for CDI. It is important to note that presentation can occur weeks or even months after exposure to an antibiotic and can be triggered by as little as one dose of medication.

What is the appropriate testing for CDI?

NOTE: Only watery, unformed stool samples should be sent for analysis; *C. difficile* detected in formed stool likely indicates asymptomatic carriage and should **not** be treated.

The most frequently used diagnostic test for CDI is enzyme immunoassay (EIA) to detect toxins A and B. It is an easy, inexpensive test to perform. The sensitivity of the test is relatively low, however, false negative results are common. **High clinical suspicion of CDI should override a negative EIA.**

PCR (polymerase chain reaction) is a more expensive but far more sensitive test than EIA, virtually eliminating false negative results. By detecting the organism, however, and not the active disease, false positive results and detection of asymptomatic carriage are common.

Diagnostic tests, such as PCR and EIA, should **not** be repeated after a course of therapy to assess for clearance of *C. difficile*. The spores continue to persist for weeks, even months, after an effective course of antibiotic therapy and do not represent true disease in the absence of symptoms.

Does having CDI once make a person immune to later infection with *C. difficile*?

No. People can contract CDI repeatedly.

What are the complications associated with CDI?

Illness can range from mild gastrointestinal symptoms to life threatening toxic megacolon and death. Since 2002, an increase in the severity of CDI has been seen, and in the United States CDI-associated deaths increased 400% between 2000 and 2007. CDI is now linked to 14,000 deaths per year, mostly in people 65 and over. *C. difficile* infections result in at least $1 billion in extra healthcare costs annually.

What are the recommended treatments/interventions for CDI?

Cessation of Precipitating Antibiotic:

Cessation of antibiotic therapy should occur in all patients with CDI when feasible. If antibiotic therapy must be continued, it should be narrowed when possible to antimicrobials less likely to exacerbate CDI.

For Asymptomatic Colonization:

Only symptomatic patients with diarrhea significantly different from baseline should be tested and treated. PCR can too easily detect asymptomatic *C. difficile* colonization, a condition which should not be treated. Treating a colonized patient offers no benefit and actually increases the risk of developing active CDI.

Table 2. Recommendations for the Treatment of Clostridium difficile Infection in Adults

Clinical Definition	Supportive Clinical Data	Recommended Treatment	Strength of Recommendation / Quality of Evidence
Initial episode, non-severe	Leukocytosis with a white blood cell count of ≤15000 cells/mL and a serum creatinine level <1.5 mg/dL	Vancomycin 125 mg given 4 times daily for 10 days, or	Strong / High
		Fidaxomicin 200 mg given twice daily for 10 days	Strong / High
		Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days	Weak / High
Initial episode, severe	Leukocytosis with a white blood cell count of ≥15000 cells/mL or a serum creatinine level >1.5 mg/dL	Vancomycin 125 mg 4 times per day by mouth for 10 days, or	Strong / High
		Fidaxomicin 200 mg given twice daily for 10 days	Strong / High

Initial episode, fulminant	Hypotension or shock, ileus, megacolon	Vancomycin, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of vancomycin. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal vancomycin, particularly if ileus is present.	Strong / Moderate (oral vancomycin) Weak / Low (rectal vancomycin) Strong / Moderate (intravenous metronidazole)
First recurrence	…	Vancomycin 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode; or Use a prolonged tapered and pulsed vancomycin regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10-14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2-8 weeks); or Fidaxomycin 200 mg given twice daily for 10 days if vancomycin was used for the initial episode	Weak / Low Weak / Low Weak / Moderate
Second or subsequent recurrence	…	Vancomycin in a tapered and pulsed regimen, or Vancomycin 125 mg 4 times a day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, or Fidaxomicin 200 mg given twice daily for 10 days, or Fecal microbiota transplantation	Weak / Low Weak / Low Weak / Low Strong / Moderate

What are the best treatments of fulminant CDI?

For fulminant CDI*, vancomycin administered orally is the regimen of choice (strong recommendation, moderate quality of evidence). If ileus is present,vancomycin can also be administered per rectum (weak recommendation, low quality of evidence). The vancomycin dosage is 500 mg orally 4 times per day, and 500 mg in approximately 100 mL of normal saline per rectum every 6 hours as a retention enema. Intravenously administered metronidazole should be administered together with oral or rectal vancomycin, particularly if ileus is present (strong recommendation, moderate quality of evidence). The metronidazole dosage is 500 mg intravenously every 8 hours.*

* Fulminant CDI, previously referred to as severe, complicated CDI, may be characterized by hypotension r shock, ileus or megacolon.

If surgical management is necessary for severely ill patients, perform subtotal colectomy with preservation of the rectum (strong recommendation, moderate quality of evidence). Diveting loop ileostomy with colonic lavage followed by antegrade vancomycin flushes is an alternative approach that may lead to improved outcomes (weak recommendation, law quality of evidence).

What can be done to prevent the spread of CDI?

In addition to early identification, accurate interpretation of diagnostic tests, and appropriate therapy for CDI, it is essential that measures be implemented to reduce *C. difficile* transmission.

Core Prevention Measures:

- Evaluate and optimize testing for CDI
- Institute a laboratory-based alert system for immediate notification of positive test results
- Use Contact Precautions for duration of diarrhea –wear gloves and gowns whenever working with patients with CDI, even during short visits
- Clean and disinfect equipment and the environment with bleach* or another EPA-approved, spore-killing disinfectant
- Perform hand hygiene in compliance with the Society for Healthcare Epidemiology of America (SHEA) /Infectious Disease Society of America (IDSA) guidelines**
- Educate other healthcare providers, housekeeping, administration, patients, and families about CDI
- When a patient transfers, notify the receiving facility if the patient has CDI
- Cohort patients being treated for CDI whenever possible, and provide a dedicated commode for each patient

Supplemental Prevention Strategies:

- Extend use of Contact Precautions beyond duration of diarrhea (e.g., 48 hours)
- Presumptively isolate symptomatic patients pending confirmation of CDI
- Implement use of soap and water for hand hygiene before exiting the room of a patient with CDI
- Implement universal glove use on units with high CDI rates
- Ensure that environmental cleaning is adequate and that high-touch surfaces are not being overlooked
- Identify and remove environmental sources of *C. difficile*, including replacement of electronic rectal thermometers with disposables
- Assign patients with CDI to private rooms when possible
- During an outbreak of CDI, instruct visitors to wash their hands with soap and water after caring for or contact with patients with CDI

Bleach can kill spores, but other standard disinfectants cannot. Limited data suggest cleaning with bleach (1:10 dilution prepared fresh daily) reduces *C. difficile* transmission; bleach may be most effective in reducing burden where CDI is highly endemic.

Alcohol-based hand sanitizers are not effective in eradicating *C. difficile* spores, and spores may be difficult to eradicate even with hand washing. For these reasons, adherence to glove use and Contact Precautions should be emphasized for preventing *C. difficile* transmission via the hands of healthcare personnel.

[The primary reason hand hygiene with soap and water is not recommended for CDI prevention in non-outbreak settings is that there are no studies which have found an increase in CDI with the use of alcohol-based hand hygiene products or a decrease in CDI with the use of soap and water. Conversely, several studies did identify decreases in methicillin-resistant Staphylococcus aureus (MRSA) or vancomycin resistant enterococcus (VRE) associated with the use of alcohol-based hand hygiene products. However, because of the theoretical increase in risk of *C. difficile* transmission the authors of the SHEA/IDSA Clinical Practice Guidelines for CDI felt it was prudent to recommend preferential use of soap and water when caring for a patient with CDI in an outbreak setting.]