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April 2018 ~ Resource #340405

Clostridium difficile in Adults

Clostridium difficile (*C. difficile*) is spore-forming, gram-positive, anaerobic bacteria that can lead to infections of the gastrointestinal tract. Many cases of *C. difficile* infection are healthcare-associated, though cases in the community are increasing in number.[7] The effects of *C. difficile* on a patient can range from asymptomatic carrier status to causing a potentially fatal infection.[7] Symptoms of infection commonly include watery diarrhea (at least three bowel movements per day for two or more days), abdominal pain or tenderness, decreased appetite, fever, and nausea.[7] The chart below addresses common questions about *C. difficile* including risk factors, prevention, and treatment.

Abbreviations: *C. difficile* = *Clostridium difficile*; CDI = *Clostridium difficile* infection (previously referred to as *Clostridium difficile*-associated diarrhea or CDAD); FMT = fecal microbiota transplantation; IV = intravenous; PPI = proton pump inhibitor.

Topic/Question	Clinical Pearls/Pertinent Information
How is *C. difficile* classified?	• *C. difficile* is the most common cause of: o Healthcare-associated infection in adults (United States).[1] o Infectious diarrhea in hospitals and long-term care facilities (Canada).[6] • CDI includes symptoms (usually diarrhea) and either a stool test positive for *C. difficile* toxins or detection of toxigenic *C. difficile,* or pseudomembranous colitis. Severity is defined as:[1] o Non-severe: elevated white blood cell count, but still ≤15,000 cells/mL **and** serum creatinine <1.5 mg/dL. o Severe: elevated white blood cell count of at least 15,000 cells/mL **or** serum creatinine >1.5 mg/dL. o Fulminant: hypotension or shock, ileus, or megacolon. • About 25% of patients will have a recurrent CDI.[1] o Recurrence is defined as new symptom and laboratory confirmation AFTER a previous episode in the past two to eight weeks.[1] ▪ Risk of recurrence, severity, and mortality increase with subsequent infections.[1]
What are risk factors for *C. difficile*? *Continued…*	• Antibiotics suppress bacteria that normally live in the bowel.[1,7,14] o Antibiotic use is the **most important modifiable risk factor** for CDI.[1,38] o Consider restricting antibiotic use to help control infection rates, especially high-risk antibiotics (e.g., clindamycin, fluoroquinolones).[1,34] • Chronic kidney disease (CKD) and end-stage renal disease (ESRD).[1] • Gastrointestinal conditions (e.g., inflammatory bowel disease) or surgery.[7,14] • Increased age (e.g., ≥65 years old).[7,14,34]

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Risk factors, continued	• Immunosuppression (e.g., chemotherapy, human immunodeficiency virus [HIV]).[7,14,34] • Long length of stay in a healthcare setting (e.g., hospital, nursing home).[7,14,34] • Previous CDI.[14,34] • Proton pump inhibitor use has been associated with *C. difficile*.[1,7,14,34] o For every 533 hospitalized patients taking a daily PPI, at least one will develop *C. difficile*.[39] o Evaluate appropriateness and discontinue inappropriate PPIs.
What laboratory tests are used to identify *C. difficile*?	• Use a stool toxin test as part of a multistep algorithm (e.g., glutamate dehydrogenase [GDH] plus toxin, nucleic acid amplification test [NAAT] plus toxin).[1] • Hundreds of *C. difficile* isolates have been identified and many are associated with resistance.[22] • The ribotype 027 strain appears to be one of the most virulent and is associated with increased incidence, severity, and mortality since the mid-2000s.[1] o This strain is also known as the North American pulsed field type 1 [NAP1] or restriction endonuclease analysis pattern "BI."[1] **Antigen detection** (e.g., glutamate dehydrogenase [GDH]):[7] • Rapid turn-around time (e.g., <1 hour) • Often used in combination with polymerase chain reaction (PCR) or toxigenic culture because non-specific (e.g., will be positive for carriers of non-toxigenic strains of *C. difficile*). **Molecular assays** (PCR assays, includes nucleic acid amplification test [NAAT]):[7] • Sensitive and specific for toxin-producing *C. difficile* (tests for gene coding for *C. difficile* toxin). **Stool culture**:[7] • Most sensitive of the *C. difficile* tests, but has a slow turn-around time (e.g., 48 to 96 hours). • Non-toxigenic cultures are associated with false positive results due to colonization with non-toxigenic strains. o Check to see if your lab has a **toxigenic culture** to minimize false positive results. • Labor intensive because it requires an appropriate environment for growth of an anaerobic organism. **Toxin testing**:[7] • Tissue culture cytotoxicity o Detects toxin B only. o Results typically available in 24 to 48 hours. o Less sensitive than PCR or toxigenic culture. • Enzyme immunoassay o Can detect both toxin A and toxin B. Some labs may offer a toxin B-only assay. o Not as sensitive as culture cytotoxicity, PCR, or toxigenic cultures.

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How does colonization differ from infection?	• Colonization:[7] **no** clinical symptoms, test positive for *C. difficile* and/or associated toxins. • Infection:[7] **symptoms present**, tests positive for *C. difficile* and/or associated toxins. • Colonization with *C. difficile* is more common than infection.[7] • Many patients remain colonized even after successful treatment of CDI.[7] o Therefore, testing to confirm eradication of *C. difficile* after treatment is not recommended.[7,37]
What strategies should be used to prevent the spread of *C. difficile*?	• Antimicrobial stewardship programs are critical to limit inappropriate prescribing of antibiotics.[1,37] o Routinely reassess antibiotic use and de-escalate, if possible, especially for those who develop *C. difficile*.[18] • Routinely use proper hand hygiene.[1] o **Soap and water preferred** as alcohol-based hand sanitizer does not kill *C. difficile* spores, especially:[1,21,33] ▪ During an outbreak. ▪ After direct contact with contaminated stool or an area that has likely been contaminated. • Use contact precautions until 48 hours after diarrhea has resolved.[1,18,33] o Use private rooms for hospitalized patients infected with *C. difficile*, when possible.[1,18,33,37] o Follow policies for personal protective equipment with infected patients (e.g., gloves, gown, mask).[1,18,33] o Use disposable or patient-dedicated equipment when possible to limit exposure (e.g., blood pressure cuff).[1] o Clean reusable equipment with a sporicidal disinfectant before using with other patients (e.g., bleach solutions [1:10 bleach solution], 7.5% hydrogen peroxide solutions, alkalinized glutaraldehyde).[1,13,16,18,34] • There are insufficient data to recommend empiric contact precautions when patients with a history of CDI are admitted to the hospital.[36] • Notify staff members of CDI when patients are transferred to a new room or facility.[18]
What are the treatment options for a FIRST EPISODE of nonsevere or severe *C. difficile*? *Continued*	• Consider one of the following options to treat nonsevere (mild) or severe cases of *C. difficile*: o **Vancomycin** 125 mg orally four times a day for ten days (price varies based on formulation).[1] ▪ The oral solution (e.g., *Firvanq* [U.S. only]) or compounding an oral solution from the intravenous product may cost less than the oral capsules. ▪ Pooled data including all severity levels show that ten days of treatment with oral vancomycin may be more effective compared to metronidazole, number needed to treat ~10 [Evidence Level B-2].[1] • This may be due to success rates in more severe cases. Though the data are inconsistent, some studies show oral vancomycin may be up to 20% more effective than metronidazole.[15] o **Metronidazole** 500 mg orally three times a day for ten days **for nonsevere or mild cases** (~$15 [U.S.], ~$25 [Canada]).[1,34,37,a] ▪ Repeated or prolonged exposure to metronidazole has been associated with neurotoxicities (e.g., confusion, headache).[1,8]

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Treatment for first episode, continued	o **Fidaxomicin** (*Dificid*) 200 mg orally twice daily for ten days (~$3,700 [U.S.], ~$2,000 [Canada])[1,a] ▪ Though recommended as a first-line therapy, use may be limited due to cost. ▪ If cost is not an issue, may consider due to potential for reduced recurrence compared to vancomycin:[24,27,28] • Fidaxomicin and vancomycin have similar recurrence rates with the severe BI/NAP1/027 strain. • There is less recurrence with fidaxomicin compared to vancomycin with non-BI/NAP1/027 strains. • Though standard practice based on clinical trials is to use ten days of therapy, up to 14 days can be used for patients with a delayed response or more severe cases.[1,34] Extended durations are more commonly needed with metronidazole.[1]
What are the treatment options for patients with FULMINANT *C. difficile* infections?	• Higher doses of vancomycin are recommended for **fulminant cases** of *C. difficile*:[1] o Vancomycin 500 mg four times a day orally or via nasogastric tube.[1] ▪ Consider rectal administration every six hours in patients unable to take things orally or with an ileus.[1] • For rectal administration mix vancomycin in 100 mL to 500 mL of sterile 0.9% sodium chloride injection and administer as a retention enema for about one hour.[1,8-10,37] ▪ Monitoring of serum vancomycin concentrations can be considered to rule out drug accumulation.[1] • Despite lack of good oral absorption, serum vancomycin levels may be seen with higher doses, especially in patients with long durations of therapy, impaired kidney function, or impaired intestinal wall integrity.[1] o Add metronidazole 500 mg every 8 hours IV to vancomycin, especially if ileus present.[1,37] • For patients that don't respond to the combination of vancomycin and metronidazole: o Consider IV tigecycline (*Tygacil*) with a loading dose of 100 mg, followed by 50 mg twice daily.[1] o Surgery may be necessary, especially for severely ill patients (e.g., white blood cell count ≥25,000, lactate level ≥5 mmol/L).[1] Options include:[1] ▪ Subtotal colectomy has been used for patients with megacolon, perforation of the colon, an acute abdomen, or septic shock and organ failure. ▪ Though more studies are needed, emerging data indicate that a diverting loop ileostomy with colonic lavage and antegrade vancomycin flushes may be a less invasive alternative with improved outcomes (e.g., preserves colon, reduced mortality).[1,23]

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Topic/Question	Clinical Pearls/Pertinent Information
How does use of other antibiotics affect the treatment of *C. difficile*?	• Concomitant antibiotic use DURING treatment of *C. difficile* does not appear to impact treatment success or required duration of antibiotic therapy.[15] • Antibiotic use AFTER treatment of CDI may increase the risk of recurrence.[15] • There are not enough data to recommend changes to *C. difficile* antibiotic regimens for patients requiring concomitant antibiotic therapy or additional antibiotics after completing treatment for *C. difficile*.[1] • There are limited data on prophylaxis against *C. difficile* in patients requiring antibiotics to reduce recurrence.[1] • Prophylactic vancomycin or fidaxomicin can be considered in patients receiving systemic antibiotic therapy.[1] • Specific **prophylaxis doses** have not be well established but may include:[1,29] o Vancomycin 125 mg orally once or twice daily. o Fidaxomicin 200 mg orally once daily. • Considerations when determining whether or not to provide prophylaxis might include:[1] o Time since most recent CDI treatment. o Number and severity of previous *C. difficile* infections. o Overall health status/frailty of the patient.
What are the available options for oral vancomycin?	• Oral options and approximate cost for vancomycin 125 mg four times daily for ten days: o Capsules:[a] ~$500 to $600 (U.S.) or ~$220 (Canada) o Commercially available oral solution (e.g., *Firvanq* is replacing *FIRST-Vancomycin* [U.S. only]):[a] $125 o Compounded oral solution using powder for injection:[a] ~$60 (U.S.) or ~$550 (Canada) • In the U.S., pharmacies sometimes compound the oral solution as a less expensive alternative compared to using the vancomycin capsules.[19,20] o The compounded oral solution is known to be poorly tolerated due to the bitter and unpleasant taste.[19,20] o The commercially available vancomycin solution offers a potentially more palatable alternative to the high-priced capsules and poorly-tolerated compounded oral solution. • Example protocol to compound oral vancomycin solution from the powder for injection:[11] o Grind 5 gm of vancomycin powder for injection into a fine powder using a mortar and pestle. o Add a small amount of an oral suspension vehicle to moisten the powder (e.g., *Ora-plus*). o Transfer the vancomycin mixture into a graduated cylinder able to hold >100 mL. o Use oral suspension vehicle two or three times to "wash" the mortar and pestle to ensure all active vancomycin is transferred to the graduated cylinder. o Add additional oral suspension vehicle to the graduated cylinder to achieve a final volume of 100 mL. o Pour entire contents into appropriate bottle for dispensing. o Label with concentration of 50 mg/mL, and auxiliary labels to refrigerate, protect from light. o Assign a use by date of 90 days.

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What are the treatment options for a FIRST RECURRENT EPISODE of *C. difficile*?	• Treatment is the same whether caused by a new strain or the same strain as the initial *C. difficile* infection.[1] • Choice of therapy for **first recurrent episode** of *C. difficile* will be based on previous treatment.[1] o First episode treated with metronidazole, use:[1] ▪ Vancomycin 125 mg orally four times daily for ten days. o First episode treated with vancomycin, use one of the following:[1] ▪ Tapered and pulsed vancomycin. For example: • 125 mg orally four times per day for ten to 14 days, **followed by** • 125 mg orally two times per day for a week, **followed by** • 125 mg once per day for a week, and then once every two or three days for up to eight weeks. o The every two- to three-day doses at the end of the taper are considered "pulses" with a goal of preventing *C. difficile* spores from forming while restoring the normal flora.[40] • Alternative 42-day taper may include:[34] o Vancomycin 125 mg orally four times per day for seven days, twice a day for seven days, once a day for seven days, every other day for seven days, and every three days for 14 days. ▪ Fidaxomicin 200 mg orally twice daily for ten days.
What are the treatment options for ADDITIONAL RECURRENT EPISODES of *C. difficile*?	Options for treatment of **subsequent recurrent episodes** of CDI include one of the following:[1] • Vancomycin using a tapered and pulsed regimen (see treatment for a first recurrent episode of *C. difficile* for regimen). • Vancomycin 125 mg orally four times per day by mouth for ten days **followed by** rifaximin (*Xifaxan* [U.S.]) 400 mg three times daily for 20 days (rifaximin cost:[a] ~$1,600 [U.S.], only available as 550 mg strength in Canada as *Zaxine*). • Fidaxomicin 200 mg orally twice daily for ten days. • Fecal microbiota transplantation (FMT) o Often reserved for patients that experience more than two recurrences (e.g., three or more episodes of CDI) [Evidence Level C].[1,35,37]
What is the role of probiotics and *C. difficile*?	• It is too soon to recommend widespread use of probiotics to prevent CDI.[1,34] • Preliminary data show probiotics may reduce the risk of a first-episode of *C. difficile*, but studies are needed to confirm optimal dose and duration of therapy (*Lactobacillus* [e.g., *Culturelle*], *Saccharomyces boulardii* [e.g., *Florastor*]).[4,5,25] • Some data support the use of probiotics to prevent recurrence in **patients at high-risk or those with a history of *C. difficile*** (e.g., *Saccharomyces boulardii*).[2-5,26] For patients who wish to try a probiotic: o Recommend *Saccharomyces boulardii* (e.g., *Florastor*) 10 billion colony-forming units twice daily for four weeks starting within two days of initiating antibiotics for *C. difficile*.[2,3] • See our chart, *Comparison of Common Probiotic Products*, for more about their efficacy for *C. difficile*.

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What is the role of fecal transplantation in *C. difficile*?	• Fecal microbiota transplantation (FMT) is also known as bacteriotherapy.[12] • FMT involves the transfer of stool from a healthy donor into the gastrointestinal tract of another individual.[12,35] • Most commonly used to treat recurrent *C. difficile* (e.g., three or more episodes of CDI).[12,35]
What is the role of bezlotoxumab* in *C. difficile*? *Approved for use after completion of the 2018 Infectious Diseases Society of America *C. difficile* guidelines, therefore not included in their recommendations.[1]	• Bezlotoxumab ([*Zinplava*] U.S. only) is a monoclonal antibody that specifically binds to *C. difficile* toxin B. It is for use with antimicrobial therapy to reduce recurrence (cost: ~$3,800/dose).[30,31,a] • Given as a 10 mg/kg one-time intravenous infusion over one hour with antibiotic treatment for *C. difficile*.[30] o Use in combination **with the standard antibiotics** to treat *C. difficile* including fidaxomicin, metronidazole, and vancomycin.[30,31] o Requires a 0.2 to 5 micron in-line or add-on filter for administration.[30] o Common adverse effects include abdominal pain, diarrhea, headache, fever, and nausea.[30,31] • Data are not available to assess safety and efficacy when combined with fecal transplantation.[31] • Bezlotoxumab may reduce the risk of recurrent CDI in adults at high-risk of recurrence compared to standard antibiotic therapy [Evidence Level A-1].[31] • A monoclonal antibody targeting *C. difficile* toxin A, actoxumab, is also in development.[32]
How should patients be educated to prevent the spread of *C. difficile* at home?	• Wash hands with soap and water, especially:[16,17] o After using the toilet o After touching dirty surfaces o Before eating or handling/preparing food • Avoid sharing personal care items (e.g., bath towels, razors, toothbrushes).[16,17] • Advise family members and visitors to wash their hands before and after personal contact.[16,17] • Clean commonly touched surfaces, including in the bathroom and kitchen, with an appropriate solution or wipes (e.g., 1:10 bleach solution, 1 part bleach mixed with 9 parts water, *Clorox Healthcare Bleach Germicidal Wipes*).[16,17] • Try to designate one bathroom that only the person infected with *C. difficile* uses.[17]

a. Pricing is wholesale acquisition cost (WAC). U.S. medication pricing by Elsevier, accessed March 2018.

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In accordance with our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

Level	Definition	Study Quality
A	Good-quality patient-oriented evidence.*	1. High-quality RCT 2. SR/Meta-analysis of RCTs with consistent findings 3. All-or-none study
B	Inconsistent or limited-quality patient-oriented evidence.*	1. Lower-quality RCT 2. SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings 3. Cohort study 4. Case control study
C	Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening.	

***Outcomes that matter to patients** (e.g., morbidity, mortality, symptom improvement, quality of life).
RCT = randomized controlled trial; **SR** = systematic review
[Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *Am Fam Physician* 2004;69:548-56. http://www.aafp.org/afp/2004/0201/p548.pdf.]

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