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Antibiotic Commonsense

"An investment in knowledge always pays the best interest." Benjamin Franklin

Clostridium difficile: An Update

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Clostridium difficile, a toxin-producing, spore-forming, anaerobic gram positive bacillus, is a significant cause of infectious diarrhea. Disease can range from mild gastrointestinal symptoms to life-threatening toxic megacolon and death. In the United States, *C. difficile*-associated mortality increased from 5.7 per million population to 23.7 per million from 1999 to 2004.[1] Since 2002, we have also witnessed an increase in the severity of *C. difficile* infections (CDI). An aging patient population with numerous comorbidities, excessive antibiotic use, and the emergence of the hypervirulent North American pulsed-field gel electrophoresis type 1 (NAP1) strain all contribute to the increase in severity.

Risk Factors

C. difficile is not part of the normal fecal flora (< 3% in healthy adults) and is usually acquired in the hospital or long-term care environment, anywhere from 20–40% depending on duration of stay.[2] Age ≥ 65 years and multiple medical comorbidities are well-defined risk factors. Specific conditions, including inflammatory bowel disease and Crohn's often have a higher rate of CDI when compared to controls.[2] This may be due to a combination of colonic disruption and use of immunosuppressive medications to control the conditions. Proton pump inhibitors (PPIs) have been associated with a threefold increase in the risk of CDI, presumably due to inhibition of gastric acid, the body's natural defense against *c. difficile* spores.[3] While it remains unclear whether PPIs truly increase incidence of CDI, this serves as an important reminder that PPIs are not without risk and should be prescribed appropriately. There are also cases of community acquired CDI, often in younger patients, where common risk factors are absent. In one study, half of all patients had no antibiotics in the previous month and one third had no health care exposure of any kind.[4]

Antibiotic Exposure

Systemic antibiotic exposure is the most important modifiable risk for acquisition of CDI. Antibiotics disrupt the normal intestinal flora, which normally prevent *C. difficile* by conferring "colonization resistance."[1] The risk varies depending on the agent's ability to disrupt normal fecal flora, especially anaerobes, enabling *C. difficile* to establish in the bowel. There is a well-defined dose-dependent increase in the risk of CDI with increasing cumulative dose, number, and days of antibiotic exposure.[5] In a recent study, Patients who received two antibiotics compared to those receiving only one agent were at a 2.5-fold increased risk of CDI.[5]

Table 1 highlights common antibiotic classes and their potential for contributing to CDI. The ability of clindamycin and cephalosporins to induce CDI is 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.[6] Now quinolone use is associated with a 3-fold increase in the risk of developing CDI in hospitalized patients.[7] While testing for NAP1 is not widely available, experts feel the virulent strain is becoming increasingly prevalent in Pierce County, making judicious use of quinolones and all antimicrobial agents essential.

Table 1. Classification of Antibiotics According to Risk of Contributing to CDI[8]

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

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Pathogenesis and Clinical Presentation

Most cases of CDI present during or after antibiotic use. It is important to note that presentation can occur weeks, even months after exposure to an antibiotic and can be triggered by as little as one dose of surgical prophylaxis.[6] Clinically significant diarrhea (≥ 3 watery stools/day) following recent antibiotic exposure and/or hospitalization should prompt evaluation. Additional events that impair the normal colonic mucosa may also precipitate CDI, including GI surgery, colitis, chemotherapy, and treatment with stool softeners and laxatives. Therefore fever, leukocytosis, and abdominal pain combined with any of the above should raise suspicion for CDI.[4]

Diagnosis

Only watery, unformed stool samples should be sent for analysis.[4] Formed stool should generally not be tested as it can detect asymptomatic carriage, which may be present in over 20% depending on age and location.[2]

Table 2 summarizes common diagnostic tests for CDI. Enzyme immunoassay (EIA) to detect toxins A and B is the most frequently encountered test. It is quick, easy to perform and inexpensive. The sensitivity of the test is relatively low, however, and false negatives are common. High clinical suspicion of CDI should override a negative EIA.[4]

The MultiCare health system utilizes polymerase chain reaction (PCR), 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 positives and detection of asymptomatic colonization are common.

Treatment

Asymptomatic Colonization

The PCR test can easily detect asymptomatic *C. difficile* colonization, which should not be treated. Treating a colonized patient offers no benefit and actually *increases* the risk of developing active CDI. Therefore, only symptomatic patients, with diarrhea significantly different from baseline should be treated.[4]

Cessation of Precipitating Antibiotic

Cessation of antibiotic therapy should occur in all patients with CDI when feasible. If antibiotic therapy must be continued, is should be narrowed when possible to antimicrobials less likely to exacerbate CDI.[6]

Mild and Moderate Disease

For younger patients with no fever, leukocytosis and mild to moderate diarrhea, simply discontinuing the offending antibiotic will result in resolution of symptoms in roughly 25% of patients and reduce the likelihood of recurrence.[6] For those whose inciting antibiotic therapy cannot be stopped or have symptomatic mild-moderate disease requiring treatment, metronidazole 500 mg PO every 8 hours for 10-14 days is the treatment of choice due to its low cost and equal efficacy compared to vancomycin for mild CDI.[9]

Table 2. Available Diagnostic Studies to Identify *C. difficile* [1, 2, 4, 6]

	Sensitivity (%)	Specificity (%)	Cost	Time
PCR (detects toxin A & B genes)	> 90	> 97	$$	24 hr
Enzyme Immunoassay (detects toxin A & B)	**70-85**	~ 95	$	24 hr
Cytotoxin assay w/ tissue culture (detects toxin B)	75-85	> 97	$$$	48-72 hr
Anaerobic stool culture (detection of toxigenic CD)	> 90	> 95	$$$	> 72 hr
Glutamate dehydrogenase assay (GDH)	60-85	85-95	$	24 hr

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Severe Disease
Vancomycin has been proven more effective than metronidazole in severe CDI and is the agent of choice. Table 3 summarizes the criteria for distinguishing mild-moderate from severe CDI. Any patient scoring two or more points on the following scale should receive vancomycin 125 mg PO QID as initial therapy.[2, 9]

Table 3. Criteria for Severe *C. difficile* Infection[1, 2]

Two Points Each
• ICU Admission • Pseudomembranous colitis
One Point Each
• Age > 60 years • WBC > 15,000 cells/mm^3 • Fever ≥ 38.4°C • Hypoalbuminemia (<2.5 mg/dL)

Test for Cure
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.[4]

Recurrent Disease
Despite optimal first-line therapy, 20% of patients will have recurrence of CDI, usually developing 1-2 weeks after completing initial therapy, but can be delayed by up to 2 months.[6] First recurrence should be treated with the same regimen as for the initial episode, but should be stratified based on severity of disease.[9] Subsequent recurrences are treated with longer tapers of oral vancomycin.

Probiotics
While there is some weak evidence for probiotic supplements containing *S. boulardii* or *L. rhamnosus* for prevention of CDI and its recurrence, the IDSA recommends against use of these agents due to limited data. Furthermore, these agents are relatively contraindicated in immunocompromised patients and those with central venous catheters due to rare reports of fungemia.[10]

Fidaxomicin
Fidaxomicin (Difficid®) is a macrocyclic antibiotic recently approved for CDI treatment. Fidaxomicin was shown to be noninferior to oral vancomycin for the initial treatment of CDI.[11] Although this study was not designed to look at relapse rates, fidaxomicin appeared to be superior to vancomycin in reducing CDI relapse, possibly because fidaxomicin has less collateral effect on normal bowel flora than oral vancomycin.[11] Importantly, fidaxomicin was not superior to vancomycin when used to treat disease caused by the NAP1 strain. At a cost of nearly $3,000 for a 10-day course compared to approximately $50 for compounded vancomycin, it cannot be recommended for routine use until further evidence demonstrates substantial superiority and the ability to truly reduce recurrences and hospitalizations.[2, 11]

Take Home Message
C. difficile is a significant health-care associated pathogen. Early identification, appropriate interpretation of diagnostic studies, and adequate therapy are all essential to improve care for those affected by CDI. Moving forward, measures must be implemented to reduce stop *C. difficile* disease before it starts. In addition to isolation procedures and hand hygiene, numerous studies demonstrate that reductions in overall broad spectrum antibiotic use in result in significant CDI reductions.[12, 13] Prudent antibiotic use is essential. Minimizing the frequency, duration, and number of antibiotic agents prescribed can reduce CDI.[9]

Clostridium difficile: An Update (continued)

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