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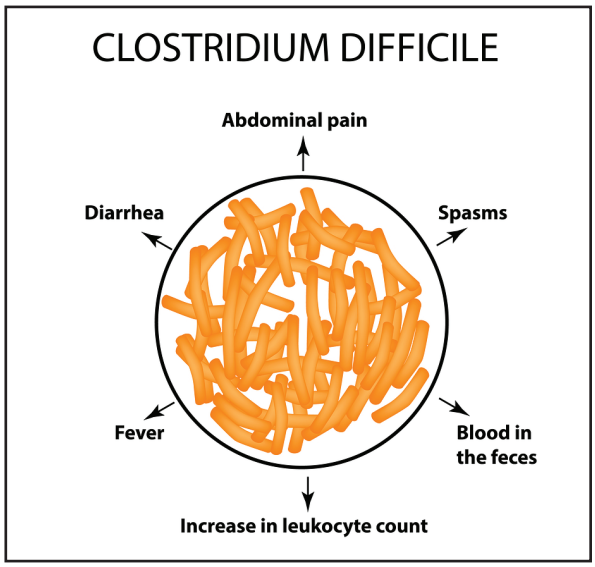
PHARMACY CONTINUING EDUCATION FROM WF PROFESSIONAL ASSOCIATES

"Update: *C. diff.*"

June 2017

Clostridium difficile infection (CDI) remains a leading source of morbidity and mortality among hospitalized patients, since its original description as the cause of pseudomembranous colitis[1, 2] This lesson reviews the epidemiology, diagnosis and treatment of *C. difficile* infections.



This lesson provides 1.25 (0.125 CEUs) contact hours of credit, and is intended for pharmacists & technicians in all practice settings. **The program ID # for this lesson is 707-000-17-006-H01-P for pharmacists & 707-000-17-006-H01-T for technicians.**

Participants completing this lesson by May 31, 2020 may receive full credit. Release date for this lesson is June 1, 2017.

To obtain continuing education credit for this lesson, you must answer the questions on the quiz (70% correct required), and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.

If you have any comments, suggestions or questions, contact us at the above address, or call 1-847-945-8050. **Please write your name, NABP eProfile (CPE Monitor®) ID Number & birthdate (MM/DD) in the indicated space on the quiz page.**

The objectives of this lesson are such that upon completion participants will be able to:

For Pharmacists:

1. Describe the epidemiology of CDI in the U.S.
2. Define CDI.
3. Discuss prevention of onset of CDI.
4. Discuss prevention of transmission of CDI.
5. Comment upon diagnostic tests for CDI.
6. List the options for treating CDI.

For Technicians:

1. Define CDI.
2. Discuss prevention of onset of CDI.
3. Discuss prevention of transmission of CDI.
4. List the options for treating CDI.

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INTRODUCTION

Clostridium difficile infection (CDI) remains a leading source of morbidity and mortality among hospitalized patients, since its original description as the cause of pseudomembranous colitis[1, 2] This lesson reviews the epidemiology, diagnosis and treatment of *C. difficile* infections.

EPIDEMIOLOGY

The reported incidence of *C. difficile* infection has risen dramatically since the 1990s.[3] In the mid 1990s, the reported incidence of CDI in acute care hospitals in the United States was 30 to 40 cases per 100,000 population and rose to almost 50 cases per 100,000 in 2001 and up to 84 cases per 100,000 in 2005. In 2011, it was estimated that *C.difficile* caused half a million infections with only 24% of the cases occurring in the acute care setting. Also, an estimated 83,000 patients had at least one recurrence and 29,000 died within 30 days of the diagnosis.[4] In addition to the rise of endemic CDI, there have been multiple outbreaks in many medical centers, both nationally and internationally. Not only is the increase in the number of outbreaks concerning, but the disease severity and mortality are alarming as well.

WHAT IS *CLOSTRIDIUM DIFFICILE*?

Clostridium difficile (C. difficile) is a spore-forming, obligate-anaerobic, gram-positive rod bacterium. It earned the name "difficile" because of the difficulty with which microbiologists originally cultivated this species.[5] This organism is usually a harmless one that lives with the GI flora. In fact, it has been reported in 7% of asymptomatic patients upon admission. *C.difficile* causes no symptoms whatsoever—unless we provoke trouble by treating patients with antibiotics.[6]

DOES EVERYONE WHO CARRIES *C. DIFFICILE* IN THE GUT DEVELOP CDI?

No. In fact, patients who are colonized with *C. difficile* at the time of admission seem to have a lower risk of developing CDI during hospitalization than do their counterparts who acquire *C. difficile* for the first time in the hospital.[7] Furthermore, not all *C. difficile* can make a person sick. Some strains of *C. difficile* harbor genes for two toxins, conveniently named toxin A and toxin B. Non-toxigenic strains of *C. difficile* never cause clinical disease. It is the presence of one or both of these toxins that places patients at risk for CDI. However, most patients who harbor toxigenic strains of *C. difficile* still will not develop CDI, even when exposed to antibiotics. Thus, testing for *C. difficile* should only be performed in patients who have a clinical syndrome compatible with CDI.

WHAT IS *C. DIFFICILE* INFECTION (CDI)?

Some patients who harbor toxigenic strains of *C. difficile* in their GI tract will develop clinical illness, usually when they are treated with antimicrobials for other conditions.*8* This illness may occur anywhere on a spectrum that spans from mild-moderate disease (watery diarrhea with or without abdominal pain or cramping) to severe disease (significant leukocytosis, hypovolemia, or fever), to severe disease with complications (toxic megacolon-induced ileus, intestinal perforation, bacteremia, or sepsis). Colonoscopy may reveal findings that range from shallow ulcers to frank pseudomembranes and gross colitis. Classic microscopic findings on pathological specimens include "volcano-like" eruptions of pseudomembranous exudates from the inflamed colon wall. The term "CDI" is intended to embrace the gamut of clinical presentations and severity.

HOW DO YOU PREVENT THE ONSET OF CDI?

Use antimicrobials wisely. Antimicrobial therapy plays an integral role in the pathogenesis of CDI by altering the normal flora of the colon and allowing toxigenic *C. difficile* to flourish.[8] Almost all antimicrobials have been associated with CDI, but the drugs most commonly implicated include fluoroquinolones, clindamycin, third-generation cephalosporins, penicillins, and sulfonamide antibiotics. As little as one dose of an antibiotic can increase the risk of CDI, and this increased risk may continue for up to eight weeks after discontinuing the drug. Thus, for this reason among many others, it is recommended using antimicrobials only when necessary, and then using the narrowest spectrum of activity and the shortest duration appropriate for any given indication. Evidence suggests that antimicrobial stewardship programs that alter prescribing patterns of antimicrobials in a hospital setting can reduce the incidence of CDI.[9]

Unfortunately, there are no other easy ways to cut the risk of CDI. Because stomach acidity serves as an important defense against the acquisition of enteric pathogens, it has been hypothesized that acid blockade with Proton Pump Inhibitors (PPIs) might increase risk of CDI acquisition. The accumulation of observational data associating the risk of PPI use and CDI lead to an FDA warning in August 2012. The FDA warning states that there may be an association between CDI and a diagnosis of CDI should be considered for patients taking PPIs who develop diarrhea that does not improve.[10] In addition to PPIs increasing the risk of the first episode of CDI, a recently published meta-analysis suggests that patients taking acid suppressants (PPIs, histamine-2-receptor antagonists or both) were at higher risk of recurrent CDI.[11]

"Probiotic" products have not been definitively shown to prevent CDI. In a large, multicenter,

randomized, placebo-controlled trial, a multistrain lactobacilli and bifidobacteria was ineffective in the prevention of CDI.[12] In fact there is evidence to suggest that there may be an increased risk of harm when they are used among certain patient populations.[13]

HOW DO YOU PREVENT THE TRANSMISSION OF CDI IN THE HOSPITAL?

As soon as CDI is suspected, (before definitive testing confirms the diagnosis), there are several actions to consider while the patient is hospitalized[14]:

1. Consider discontinuing or narrowing current antimicrobial therapy if possible.
2. Administer supportive care without the use of anti-motility agents.
3. Initiate proper "special contact precautions," including wearing gown and gloves when in the patient's room, diligent hand washing with soap and water, and careful environmental disinfection.

- Gowns are necessary. Spores can hitch a ride on clothing. Use of the gown as a barrier can help to prevent nosocomial outbreaks of CDI.
- Washing hands is imperative. Alcohol-based hand gels are not sporicidal and are not efficient in removing *C. difficile* from your hands. Proper hand washing with soap and water for at least 30 seconds is required to remove the skin oil that harbors the *Clostridium* spores. Even though you have worn gloves for direct patient contact, careful hand washing is mandatory before leaving the patient's room.
- *C. difficile* can fly through the room! This happens, in particular, when bed linens are changed, and microscopic stool particles are flung in to the air, later settling on any surface below.[15, 16] However, that does not mean that you can catch it by breathing it in.
- When the patient leaves the room, he or she must also cleanse his or her hands and wear a gown and gloves.
- To minimize the spread of CDI, it is essential that these measures be promptly implemented when the diagnosis is suspected, rather than waiting for its confirmation.

WHY DON'T WE TEST ALL ASYMPTOMATIC PATIENTS FOR THE PRESENCE OF *C. DIFFICILE* TOXINS UPON ADMISSION, AND PREEMPTIVELY TREAT THOSE WHO ARE POSITIVE?

This approach yielded no sustained benefits when tested in a randomized, placebo-controlled trial.[17] Furthermore, an unacceptably high number of patients would be exposed to anti-C. *difficile* antibiotics, placing them at risk for adverse drug reactions and accelerating the selection of drug-resistant fecal flora.

WHEN SHOULD THE DIAGNOSIS OF CDI BE CONSIDERED?

CDI should be ruled out when the patient develops diarrhea (not just soft stools, but truly watery or liquid stools), particularly if he or she is currently being treated with antibiotics, or has recently been treated with antibiotics. Approximately 5-25% of patients receiving antibiotics will develop antibiotic-associated diarrhea (AAD) during or following their course, but only 10-20% of AAD cases are caused by *C. difficile*.[18, 19] Outbreaks of severe *C. difficile* colitis have been described among patients admitted from skilled nursing facilities (SNFs), and thus CDI

should be ruled out in all patients admitted for diarrhea from SNFs, regardless of their antibiotic history.[20] There have also been alarming case reports of community-acquired, fulminant CDI among patients who had no discernible antibiotic exposure, and thus it is worth considering this diagnosis in anyone admitted for major diarrhea and colitis.[21] Making a definitive diagnosis of CDI is essential not only for treatment of the individual patient, but also for preventing the spread of *C. difficile* to other patients and healthcare workers.

WHICH DIAGNOSTIC TESTS SHOULD BE USED TO MAKE A DIAGNOSIS OF CDI?

Diagnosing CDI in a timely fashion is necessary for the overall management of nosocomial CDI. Empiric treatment without diagnostic testing is inappropriate if diagnostic tests are available, because only 10-20% of hospitalized patients with antibiotic associated diarrhea will have CDI.

The laboratory tests for *C. difficile* either evaluate the presence of the toxin or the presence of the organism. The optimal strategy to provide the most timely, cost-effective and accurate diagnosis is still controversial.

The cytotoxicity assay (or tissue culture assay) is the gold standard for diagnosis of CDI, but due to its high cost and long turnaround time few clinical laboratories still use it. This test is performed by adding a prepared stool sample on to a monolayer of cells. If the *C. difficile* toxin is present, it will exert a cytopathic effect in the tissue culture. Only a few toxin molecules are required for the test to become positive, thus making it a highly sensitive test (94-100%).[22]

Commercial Enzyme Immunoassays (EIA) that detect either toxin A or detect both toxins A and B are a rapid alternative to the culture based testing. Most diagnostic tests that have been developed detect the toxins A and B produced by *C. difficile*. In animal models, toxin B was demonstrated to be the primary toxin responsible for CDI. Unfortunately, the EIAs are not as sensitive or specific as the cytotoxicity assays. When compared to culture and cytotoxicity assays, the sensitivity is 63% to 94%, with a specificity of 75% to 100%.[22]

Molecular diagnostics are also an option for laboratories. There are commercially available real-time PCR assays (Cepheid Gene Xpert, BD-GeneOhn Cdiff assay and IVD RT-PCR) that detect for the gene encoding for toxin B. When the Cepheid Xpert assay was compared to the cell cytoxicity neutralization for the diagnosis of CDI, the sensitivity and specificity of the Cepheid assay was 97% and 93% percent, respectively.[23] Due to the high sensitivity of the molecular methods and lack of ability to distinguish between true CDI disease and asymptomatic carriage, some medical centers use a combination of the EIAs with the PCR testing.[24]

Lastly, microbiology laboratory tests can culture *C. difficile* for the diagnosis of CDI. Because these assays detect the organism rather than the toxin, patients colonized with *C. difficile* strains without the toxin may be thought to have CDI. In one study, up to 10-20% of hospitalized patients were colonized without symptoms of CDI.[25] The common antigen detects an essential enzyme produced by all *C. difficile* isolates, GDH.[22] Some medical centers may use these methods along with toxin assays for positive samples to determine which patients have CDI.

Stool culture is the most sensitive test, but is not used in clinical practice, rather for epidemiological studies. Costs and convenience issues have moved many medical centers to replace cultures with less expensive and more rapid immunoassays.

WHAT IS THE "HYPERVIRULENT" STRAIN OF *C. DIFFICILE*? WILL TESTING SCHEMES DETECT IT?

Yes, the current testing methods will detect all strains of *C. difficile*, including that which has been described as the source of outbreaks in North America (often called "toxinotype III / ribotype 027" or "NAP1/BI"). Hospital outbreaks of a severe and recurrent CDI were noted throughout Quebec, Canada. This strain accounted for 67-82% of the isolates in Quebec and was associated with the use of fluoroquinolones. Patients infected with the NAP1/BI/027 strain during this outbreak were shown to have more severe disease than patients with other strains.[26] The NAP1/BI/027 strain has spread to at least 40 U.S. states.[22] However, medical centers do not routinely type isolates because treatment is the same, regardless of strain.

DOES EVERYONE WITH CDI NEED TO BE TREATED?

Yes. Patients with a clinical diagnosis of diarrhea, and whose fecal analysis confirms the presence of toxigenic *C. difficile*, meet criteria for CDI. These patients are at risk for serious sequelae including hypovolemia, bacteremia, sepsis, ileus, and toxic megacolon. Thus, they deserve rapid initiation of anti-CDI treatment combined with stopping or focusing the offending antibiotic when possible. On the other hand, patients with asymptomatic carriage of *C. difficile*—whether toxigenic or not—do not need treatment, and thus looking for *C. difficile* in patients without diarrhea or other symptoms of colitis is not necessary.

SHOULD CDI BE TREATED EMPIRICALLY, OR IS IT BETTER TO WAIT FOR LAB CONFIRMATION BEFORE STARTING THERAPY?

Consider empiric therapy right away in patients whom the suspicion of CDI is strong. Time is of the essence in patients because getting anti-*C.difficile* treatment on board immediately may prevent progression to more serious forms of the disease. In decades past, some experts advocated stopping antibiotics at the first sign of CDI and waiting to see whether clinical improvement would follow without initiation of anti-*C. difficile* therapy; although this succeeded in 20-25% of cases, therefore this approach is no longer advocated because of the increasing severity of clinical illness.[22] If symptoms are relatively mild, and the patient is hemodynamically stable, it may be fine to wait for test results which should come back within 24 hours. But, if the patient has severe diarrhea, treatment should be started immediately.

On the other hand, treatment should be stopped right away if CDI is ruled out by fecal analysis. This empiric approach will expose some patients to antibiotics unnecessarily; however, the practice is justified based on the high incidence of CDI, its potential for significant patient harm, the rapid turnaround time for CDI testing, and the relatively benign toxicity profile of first-line therapies.

WHAT ARE THE TREATMENT OPTIONS FOR CDI?

Until recently, the answer to this question was straightforward: oral metronidazole was recommended as first-line therapy for virtually all patients able to take medicine by mouth, and oral or rectal vancomycin was reserved for those who failed to improve on first-line therapy. However, recent publications suggest that the patient's clinical status should influence the choice of antibiotic for initial treatment of CDI.

Oral metronidazole is well absorbed in the small intestine, with small amounts excreted in the feces via enterohepatic circulation. Fecal concentrations of both the intravenous and oral

forms of metronidazole are small but sufficient to be bactericidal against *C.difficile*. Overall, metronidazole is well tolerated, although side effects can include a metallic taste, nausea, vomiting, diarrhea, peripheral neuropathy, pruritus, rash, headache, confusion and dizziness. Alcohol consumption should be avoided with metronidazole because it may result in a disulfiram reaction.[22] It is not FDA-approved for the treatment of CDI.

Oral vancomycin is FDA-approved for the treatment of CDI. Because it is poorly absorbed from the GI lumen, high fecal concentrations are easily achieved while systemic toxicities are rare.[22,27] The dose of oral vancomycin reported in the literature ranges from 125 mg PO q6h to 500 mg PO q6h. Patients randomized to either the low or high end of this range demonstrated no significant differences in clinical response or failure rates.[28] Therefore, for all patients except the most severely ill, we recommend the lower dose of vancomycin due to its lower cost. Intravenous vancomycin does not achieve appreciable concentrations within the bowel and should not be used for the treatment of CDI.[22]

Both metronidazole and vancomycin inhibit the growth and toxin production of *C.difficile*. But which drug is better for CDI? Three prospective randomized trials have compared the efficacy of metronidazole with that of vancomycin. In the first trial, a total of 101 patients with CDI were randomized to receive either metronidazole (250 mg PO q6h) or vancomycin (500 mg PO q6h) for 10 days.[29] The mean time to resolution of diarrhea was 2.8 days and 2.4 days in the vancomycin and metronidazole groups, respectively. There were two treatment failures in the metronidazole group versus none in the vancomycin group, but this was not statistically significant (p=0.20). Among patients who achieved clinical cure, two treated with metronidazole relapsed after completing therapy versus six relapses in the vancomycin group (p=0.17). In the second trial, a total of 119 patients were randomized in an open-label design to receive either metronidazole (500 mg PO TID) or fusidic acid (500 mg PO TID) or vancomycin (500 mg PO TID) or teicoplanin (400 mg PO BID) for 10 days.[30] The clinical cure rates ranged from 93% to 96% between groups and were not significantly different. The relapse rates were not different between the metronidazole and vancomycin groups (p>0.8). Based on these studies, metronidazole has been favored over vancomycin because of its similar efficacy, lower cost, and, theoretically, lower risk of creating vancomycin-resistant Enterococcus.[22]

Nevertheless, clinicians who have seen patients with severe CDI who fail initial treatment with metronidazole continued to wonder whether the sickest patients might benefit from up-front vancomycin therapy.[31, 32] In an attempt to address this question, a randomized, prospective, double-blind, placebo-controlled trial was conducted to compare the efficacy of vancomycin versus metronidazole in patients with CDI, stratified by disease severity.[33] Disease was considered severe among patients who had any two or more of the following: age >60 years, temperature >38.3°C, albumin <2.5 mg/dL, or peripheral WBC count >15,000 cells/mm3 within 48 hours of enrollment. Patients with endoscopic evidence of pseudomembranous colitis, or disease requiring treatment in the intensive care unit, were also considered to have severe disease. Study participants were randomized to receive either metronidazole 250 mg PO QID with placebo liquid or vancomycin liquid 125 mg PO QID with placebo tablets for ten days. Among patients with mild disease, the cure rates were similar between the metronidazole and vancomycin groups (90% vs. 98%, respectively, p =0.36). However, patients with severe disease had a significantly higher cure rate with vancomycin compared to metronidazole (97% vs. 76%, respectively, p= 0.02). Relapse occurred after initial cure in 7% of the patients in the vancomycin group versus 14% of the patients in the metronidazole group, but this was not

statistically significant (p=0.27).

This study can be criticized for its inclusion criteria for "severe" disease. Specifically, a great proportion of patients with CDI are over age 60, febrile, and have WBC counts >15,000 cells/mm3, and thus some of the cases classified as "severe" in this study would have been classified as "moderately ill" by many physicians. Confirmation of the superiority of vancomycin over metronidazole among the severely ill will require future studies with larger patient cohorts and more rigorously defined criteria for disease severity. However, many specialists in infectious diseases and gastroenterology believe that these results validate a clinical phenomenon they have personally witnessed: sicker patients are slightly more likely to fail treatment with metronidazole than with vancomycin.

Formal guidelines for the treatment of CDI have been published and endorsed by the Infectious Diseases Society of America (IDSA) and the Society of Healthcare Epidemiology of America (SHEA).[22] They emphasize a risk-stratification scheme similar to that described above. Table 1 summarizes treatment recommendations based on severity of illness. Patients started on metronidazole for mild-moderate disease should be reassessed daily for response to therapy, and their regimen may be escalated from metronidazole to vancomycin at any time if their disease score elevates to "severe" or if they fail to make measurable improvement after 3-5 days of metronidazole treatment, then it may be prudent to replace oral metronidazole therapy with oral vancomycin.

I HAVE READ ABOUT NEWER TREATMENTS FOR CDI. IF METRONIDAZOLE OR VANCOMYCIN JUST ISN'T WORKING, SHOULD I CONSIDER USING NEWER DRUGS?

Fidaxomicin, a non-absorbable macrocyclic antibiotic, was FDA approved for the treatment of *C. difficile* diarrhea in 2011. Fidaxomicin (previously referred to as OPT-80) has activity against the clostridia species, including *C. difficile*, with limited activity against normal gut flora. Fidaxomicin is bactericidal against *C. difficile* and works by inhibiting RNA synthesis. It has minimal systemic absorption; the detectable concentrations remain confined to the gastrointestinal tract. Louie et al, evaluated the efficacy of fidaxomicin by comparing it to vancomycin in a randomized, controlled trial.[34] Patients with life-threatening or fulminant CDI, toxic megacolon, previous exposure to fidaxomicin, a history of ulcerative colitis or Crohn's disease or more than one occurrence of CDI within 3 months were excluded from the trial. A total of 629 patients were randomized to either fidaxomicin (200mg twice daily) or vancomycin (125mg four times daily) for 10 days. The clinical cure rate for fidaxomicin was non-inferior to vancomycin (88.2% vs. 85.5%, p = NS) in the modified intent-to-treat analysis. Fewer patients had a recurrent infection with fidaxomicin compared to vancomycin (15.4% vs 25.3%, P =0.005) in patients with non-NAP1/BI/027 strain in the modified intent-to-treat analysis. Among patients who had the more "severe" NAP1/BI/027 strain, there was no difference in risk of recurrence. Adverse events were similar for fidaxomicin and vancomycin. The estimated retail cost of a 10-day course of fidaxomicin is approximately $3400. Although the data looks promising for fidaxomicin, the cost of the agent may prohibit widespread use at this time.

Rifaximin has been used in combination with vancomycin in an effort to reduce recurrent CDI, but its role remains unclear. Rifaximin should certainly never be used alone for the treatment of initial CDI.[22]

WHAT ABOUT TREATMENT OF SEVERE, COMPLICATED CDI?

CDI infections can result in hypotension, shock, ileus or megacolon. In general, the oral route of administration is the preferred treatment method for CDI, because higher drug levels are delivered to the GI lumen. But, ileus may impair the delivery of orally-administrated vancomycin to the colon. Therefore, it is appropriate to treat these patients with IV metronidazole in combination with oral vancomycin. Intravenous vancomycin should not be used for CDI because it does not achieve significant concentrations in the colonic lumen. In severe cases, high doses of oral vancomycin (up to 500mg) may be given by mouth or by nasogastric tube (NGT) to maximize detectable concentrations into the colon.[22]

Reported failures with intravenous metronidazole have led to the addition of intracolonic vancomycin for patients with severe CDI although only observational data support its use. [35, 36] These case reports describe oral vancomycin administered by NGT in addition to intravenous metronidazole and intracolonic vancomycin, thus obscuring the potential benefit of any single component of therapy. Patients with severe CDI complicated by ileus or megacolon may be candidates for vancomycin retention enemas. These patients should first be considered for vancomycin delivery by nasogastric tube (NGT); however, if consultants from general surgery feel that the ileus is too severe to warrant delivery of any fluid from above, then the use of rectal vancomycin is rational (although not rigorously studied). One protocol published in the literature involves placing an 18-inch Foley catheter rectally, inflating the balloon, instilling 500 mg of vancomycin mixed in 1-2 L of normal saline, clamping the catheter for one hour, and unclamping and removing the catheter; this process is repeated every 4-12 hours.[36, 37] There is no guarantee that this solution will reach the entirety of the involved colon, of course, and controversy will likely continue to surround the question of rectal therapy.

Severely ill patients may require surgical intervention. Colectomy can be a life-saving intervention for patients with megacolon, colonic perforation, an acute abdomen, or septic shock.[22] Loop ileostomy and colonic lavage with post-operative antegrade instillation of vancomycin may be an alternative to colectomy and preservation of the colon.[38]

IF MY PATIENT IS ALREADY ON ANTIBIOTICS FOR ANOTHER REASON, SHOULD THEY BE STOPPED? WHAT IF MY PATIENT'S PRIMARY INFECTION IS STILL NOT CURED?

Stopping antibiotics can be a crucial step towards curing your patient because it alleviates the selective pressure on the colonic flora which allowed *C. difficile* to flourish. Virtually any antibiotic can trigger the disease; ß-lactams and fluoroquinolones are commonly implicated.

IF THE PATIENT IS ON EMPIRIC BROAD-SPECTRUM ANTIBIOTICS, ARE THEY STILL INDICATED? IF SOME FORM OF ANTIBIOTIC COVERAGE IS NECESSARY, CAN YOU REDUCE THE SPECTRUM OR PLAN FOR A SHORTER COURSE?

Antibiotics should be discontinued unless they are absolutely necessary. Most antibiotic courses last less than two weeks, but for some diseases it is simply not appropriate to cut the primary antibiotic course short; osteomyelitis and infective endocarditis are examples. Continuing antimicrobials while patients are being treated for CDI leads to lower cure rates, an extended time to resolution of diarrhea, and is associated with more recurrences.[39]

Among the minority of patients who remain on their original offending antibiotic regimen beyond 14 days, it may be advisable to continue low-dose vancomycin until one week

beyond cessation of the primary regimen, in order to minimize the risk of recurrent CDI. In an observational retrospective cohort study, the use of oral vancomycin (either 125m g BID or 250mg BID) in patients with the diagnosis of CDI and systemic antimicrobials, the use of oral vancomycin prophylaxis leads to lower CDI recurrence compared to those not given prophylaxis (4.2% vs 26.6%, p<0.001)[22,40]

WHAT IS THE EVIDENCE FOR USING IVIG (IMMUNOGLOBIN THERAPY) FOR CDI?

Intravenous immune globulin (IVIG) has been reported to assist with the treatment of refractory, severe CDI.[41] Because the disease is mediated by exo- and enterotoxins, the use of IVIG is rational. Antibodies present in the pooled blood product may neutralize either or both of these toxins, thus slowing the progression of colonic injury while allowing antibiotics to kill the pathogen. However, convincing data in the form of a randomized trial are lacking. The largest study to date found no benefit of IVIG for treating CDI although it suffered from methodological problems. Significant obstacles and concerns, including the lack of standardized dosing, risks of potentially serious side effects, and extraordinary cost prevent recommending this approach in all but the most difficult-to-treat cases.

Of note, the FDA recently approved monoclonal antibodies against *C. difficile* toxins B (CDB1), Bezlotoxumab (Zinplava®).[42] The antibodies were administered as a single infusion in patients with symptomatic *C. difficile* infection who were receiving either metronidazole or vancomycin or fidaxomicin. The rate of recurrence (during 84 days after the administration of the monoclonal antibodies) was lower among patients who received bezlotoxumab (17% vs. 28%, P <0.001), but the use of bezlotoxumab did not improve initial clinical cure. Overall, bezlotoxumab was tolerated, but patients with history of congestive heart failure may be predisposed to CHF exacerbation after receiving this drug.[43] The cost is estimated to be around $3900 for one dose (www.drugs.com, accessed April 15 2007).

WHAT IS THE EVIDENCE FOR PROBIOTIC USE IN PATIENTS WITH CDI?

Because CDI is caused by an imbalance in the normal colon flora, the concept of replacing that normal flora is very seductive. The colon, a profoundly complex environment, is home to a staggering array of microbes. Significant differences between individual hosts make this environment even more challenging to study and manipulate.[44] Deciding which member(s) of the flora should be replenished, and in what proportion to establish them, is a daunting task—especially considering the lack of standardization or FDA approval for any of these products. Nonetheless, investigators have undertaken studies using a variety of microbes felt to be beneficial, or at least harmless. Some investigators have demonstrated that the yeast *Saccharomyces boulardii* , in combination with anti-*C. difficile* antibiotics, may help to prevent recurrent episodes of CDI.[45-47] However, a handful of reports of therapeutic strains causing disease among immunosuppressed hospitalized patients have given pause, and neither FDA approval nor widespread international adoption of this approach has occurred.[48-50] There are similar concerns regarding the use of *Lactobacillus* species for the supplemental treatment of CDI, although they have not been studied as rigorously as *Saccharomyces*.[13] The IDSA/SHEA guidelines do not endorse the routine use of probiotics for prevention or treatment of CDI.[18]

"Fecal biotherapy" is the ultimate probiotic experience. Stool from an asymptomatic donor is homogenized and instilled in the patient's colon via retention enema or colonoscope.[51, 52] A randomized controlled trial evaluated oral vancomycin plus fecal biotherapy, oral vancomycin

alone, or oral vancomycin with bowel lavage in patients with recurrent CDI disease. The study was terminated early due to a success rate of curing recurrent disease in the fecal biotherapy group (93% vs 27%).[53]

Challenges including donor selection, co-pathogen screening, and safety prevent this technique from being used in all but the most difficult-to-treat cases, although it is likely that this technique will be used more and more often.

IS THERE A ROLE FOR ORAL OR RECTAL CHOLESTYRAMINE IN ORDER TO BIND THE TOXINS THAT ARE CAUSING DISEASE?

The use of a binding resin is intriguing, and in the future it may become part of the standard of care, but for now it is not recommended. The principal concern is that the resin will bind not only the *C. difficile* toxins but also the antibiotics being used to treat the infection.[54] A placebo controlled trial using a different resin, colestipol, demonstrated no benefit.[55] Among patients with ileus, the use of this substance may in theory lead to impaction and mechanical complications. Nevertheless, industry has taken note of this concept, and at least one company is in the process of seeking FDA approval of a toxin-binding resin for this indication.

PASSING SO MUCH LIQUID STOOL MAKES THE PATIENT MISERABLE AND THE NURSES UNHAPPY. CAN WE PRESCRIBE AN ANTIMOTILITY MEDICATION?

This is not suggested. Using antimotility agents is strongly discouraged, as it may increase the time that toxins spend in contact with the colon, leading to more severe disease.[8, 56]

HOW SHOULD I STOP THERAPY? IS IT BETTER TO TAPER OFF CDI THERAPY, OR JUST STOP?

For initial episodes of CDI, it is probably best to stop therapy once the patient has received 10-14 days of therapy and is diarrhea-free (or dramatically improved). 75-90% of patients treated in this fashion will achieve a full and durable cure.

WHAT ABOUT THE PATIENTS WHO GET CDI AGAIN? HOW SHOULD I TREAT RECURRENCES?

Regardless of the initial regimen chosen, approximately 10-25% of patients who achieve full symptomatic cure of CDI will experience recurrent symptoms after completing antibiotic therapy, frequently within two weeks of finishing their initial course. This may happen because of altered gut flora following antibiotic therapy, persistence of the original toxigenic strain, or infection with a new strain of *C. difficile*.[57]

Recently, a systematic review was published combining 39 studies (7005 patients) evaluating the treatment failure and recurrence rate of patients treated with metronidazole or vancomycin for CDI. Majority of the studies included were retrospective in nature, so the conclusions should be evaluated cautiously. The reported treatment failure was 22.4% with metronidazole from 16 studies and 14.2% with vancomycin from 8 studies (p=0.002). Recurrence of CDI was found to be 27.1% following treatment with metronidazole from 18 studies and 24% following vancomycin treatment from 8 studies (p=0.26). Although the differences between study design, patient populations, and geography lead to a large variation in the outcomes, this systematic review

confirmed that treatment failure (22.3%) and recurrence rates (22.1%) of CDI are high.

Diarrhea that returns after treating CDI is probably, but not always, caused by *C. difficile* again, and thus it is reasonable to repeat fecal analysis for the pathogen when symptoms return. On the other hand, a positive test may indicate carriage of *C. difficile* rather than true infection. Thus, clinicians should consider alternate causes of diarrhea even when testing is positive for toxigenic *C. difficile*. As before, stop or narrow primary antibiotics if possible, administer supportive care, and reinitiate empiric therapy per the criteria in Table 1. Although described in the literature, drug resistance rarely causes clinical recurrences[44] and therefore patients with mild-moderate disease should receive metronidazole for their recurrence regardless of their prior regimen.[22, 44]

Treatment for recurrent CDI should again last for approximately 10-14 days or until symptoms are dramatically improved.

Approximately half of patients will experience a flare of symptoms after their first or even their second recurrence of CDI.[22] These patients usually require a switch from metronidazole to vancomycin and a longer course of therapy, perhaps featuring pulses or tapering doses of vancomycin, in order to minimize toxicity while improving therapeutic outcome. Numerous strategies for tapering anti-*C. difficile* therapy have been described in the literature, but they are based on observational studies, and no strategy has demonstrated clear superiority.[22] A reasonable tapering regimen in the usual dosage of vancomycin 125mg four times daily for 10-14 days, then reducing the frequency to twice daily for a week, then reducing the frequency to once daily for a week, then continuing 125mg every 2 or 3 days for 2-8 weeks until the normal flora is restored.

Fidaxomicin was compared to vancomycin for treatment of the first recurrence of CDI. Recurrence occurred in 36% of patients treated with vancomycin and 20% of patients treated with fidaxomicin, p =0.045). Patients treated with vancomycin developed recurrence earlier than those treated with fidaxomin p=0.003).[58] This study affirms the previously published data that patients treated fidaxomicin may have lower recurrence rates. The next round of CDI guidelines will likely include fidaxomicin as recommended agent for patients at high risk for recurrence (i.e. age > 65, immunosuppressed, etc.).

CONCLUSION

CDI remains a challenge for clinicians to diagnose, prevent and treat. *C.difficile* has become a nuisance in hospitalized patients and some outpatient settings. Avoiding unnecessary antibiotic therapy is a key to preventing CDI. Strict infection control policies (including environmental decontamination, hand hygiene, patient isolation) are the mainstay for preventing transmission of CDI among hospitalized patients. Timely diagnosis and treatment of CDI also aids in preventing its spread.

Table 1. Guidelines for classification and initial treatment of first or second episode of CDI [18]

Disease severity	Clinical Data	Treatment	Duration	Comments
Initial episode, Mild-moderate	• WBC <15,000/mm3 AND • Serum creatinine less than 1.5 times the premorbid level	Metronidazole 500 mg PO q8h	10-14 days	Consider changing to oral vancomycin in 3-5 days if lack of clinical response noted
Severe	• WBC count ≥15,000/mm3 OR • Serum creatinine ≥ 1.5 times the premorbid level	Vancomycin 125 mg PO q6h	10-14 days	
Severe, with complications	Any: Hypotension • Shock • Toxic megacolon • Perforation • Severe colitis on CT scan	Ileus or unable to take PO: metronidazole 500 mg IV q8h + vancomycin by NGT and/or retention enema	10 days minimum	
First recurrence		Same as for initial episode or fidaxomicin	10 days minimum	

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LESSON EVALUATION

Please fill out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

1. Does the program meet the learning objectives?

Describe the epidemiology of CDI in the U.S.	YES NO
Define CDI	YES NO
Discuss prevention of onset of CDI	YES NO
Discuss prevention of transmission of CDI	YES NO
Comment upon diagnostic tests for CDI	YES NO
List the options for treating CDI	YES NO

2. Was the program independent & non-commercial? YES NO

	Low Relevance						Very Relevant
3. Relevance of topic	1	2	3	4	5	6	7

4. What did you like most about this lesson?_____

5. What did you like least about this lesson?_____

Please Mark the Correct Answer(s)

1. **Appropriate handwashing practices for a *C.diff* patient include:**
   A. Alcohol-based hand gel.
   B. Alcohol-based hand gel for nurses.
   C. Gowns & gloves unnecessary.
   D. None of these.

2. **A 64 y/o male with an ileus is found to have CDI. An appropriate option is IV metronidazole & rectal vancomycin.**
   A. True B. False

3. **What is *C.diff*?**
   A. Spore-forming obligate anaerobe.
   B. Aerobic gram-negative rod guidelines.
   C. Gram-positive rod.
   D. Intestinal parasite.

4. **A 53 y/o male is admitted for CHF exacerbation. On day 2, patient has diarrhea & *C.diff.* testing. Toxin B PCR is positive. Patient has had 2 episodes of *C.diff.* within last year. Which treatment shows promise for recurrent *C.diff.*?**
   A. Vancomycin. B. Fidaxomicin.
   C. Metronidazole po. D. None of these.

5. **A 67 y/o female is admitted for Urinary Tract Infection & is prescribed levofloxacin. Patient has a history of kidney transplant & is on Tacrolimus. Would a probiotic prevent *C.diff.* in this patient?**
   A. No, the data doesn't not support this.
   B. No, the patient is at risk for fungemia.
   C. Yes, probiotics will definitely decrease risk.
   D. A and B.

6. **Preventive strategies for *C.diff.* are:**
   A. Use antimicrobials wisely.
   B. Appropriate hand hygiene.
   C. Environmental cleaning.
   D. All of these.

7. **A 65 y/o male with end-stage liver disease is admitted to the ICU for gram-negative bacteremia. He improves with ceftazidime. On the 7th day, he has elevated WBC count (>25 cells/mm3), fever & a rising Serum creatinine. You send the stool for *C.diff.* testing. Which risk factor(s) does the patient have for CDI?**
   A. Hospital stay. B. Age.
   C. Exposure to antibiotics. D. All of these.
   E. A and B only.

8. **Use case scenario in question 7. According to IDSA guidelines, how would you classify the severity of the CDI episode?**
   A. Mild. B. Mild to moderate.
   C. Severe. D. Severe with complications.

9. **Use case scenario in question 7. According to IDSA guidelines, how would you treat this patient?**
   A. PO vancomycin 500mg q6h.
   B. IV metronidazole 500mg q6h.
   C. IV vancomycin 125 mg q6h.
   D. PO vancomycin 125mg q6h.

10. **Use case scenario in question 7. The administration of Bezlotoxumab will help cure C.diff.**
    A. True B. False