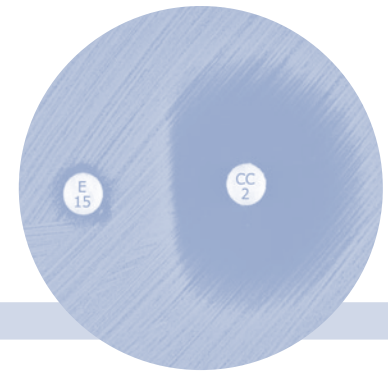


# the d-zone

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## About this Issue

The authors wish to thank Jeannie Chan, Pharm.D., Tim Dellit, M.D., and Chris Surawicz, M.D. for reviewing the manuscript and providing critical insight and expertise.

## Review of the Month

A timely review of another organism that has been giving us grief recently.

Munoz-Price LS, Weinstein RA. Acinetobacter infection. *N Engl J Med* 358 (12): 1271-81, 2008.

## Quote of the Month

The future of microbes and mankind will probably unfold as episodes of a suspense thriller that could be entitled "Our Wits Versus Their Genes."

—Joshua Lederberg

## the d-zone

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Pottinger P., Jain R. Treatment of *Clostridium difficile*-Associated Disease. *The D-Zone* 2008; Vol. 37 (Supp 3): S9-S14.

## Treatment of *Clostridium difficile*-Associated Disease

By Paul Pottinger, M.D. and Rupali Jain, Pharm.D., UWMC Antimicrobial Stewardship Program

### What is CDAD, and how should I prevent and diagnose it?

Please see the previous issue of *The D-Zone*, which addresses the definition, prevention, and diagnosis of *Clostridium difficile*-associated disease (CDAD). You can find that issue, and all other D-Zones, at <http://uw.pnrx.org/therapyTopics.asp>.

### The special contact precautions for CDAD patients are a hassle. Do we really need to follow those rules?

Yes, you really do. If you suspect CDAD, please initiate special contact precautions and follow the instructions posted on the door placard: wear gown and gloves when in the patient's room, regardless of whether or not you have touched the patient, and wash your hands with soap and water (not alcohol hand rubs) when you leave the room. If the patient rules out for CDAD, you can stop these precautions.

### Does everyone with CDAD need to be treated?

Yes. As described in our last issue, patients with a clinical diagnosis of diarrhea, and whose fecal analysis confirms the presence of toxigenic *C. difficile*, meet criteria for CDAD. These patients are at risk for serious sequelae including hypovolemia, bacteremia, sepsis, ileus, and toxic megacolon. Thus, they all deserve rapid initiation of anti-CDAD 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 we do not recommend looking for *C. difficile* in patients who have no diarrhea or other symptoms of colitis.

### Should I treat CDAD empirically, or is it better to wait for lab confirmation before starting therapy?

Please consider empiric therapy right away for patients whom you strongly suspect of having CDAD. If your patient does have CDAD, then time may be of the essence, 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 CDAD and waiting to see whether clinical improvement would follow without initiation of anti-*C. difficile* therapy; although this succeeded in 20-25% of cases, we no longer advocate this approach because of the increasing severity of clinical illness observed at UW Medicine and elsewhere.<sup>1</sup> On the other hand, you should stop treatment right away if CDAD is ruled out by fecal analysis. This empiric approach will expose some patients to antibiotics unnecessarily; however, we believe that the practice is justified based on the high incidence of CDAD, its potential for significant patient harm, the rapid turnaround time for CDAD testing, and the relatively benign toxicity profile of first-line therapies.

Treatment of *Clostridium difficile* – Associated Disease (continued)**OK, how should I treat CDAD?**

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, a recent publication suggests that the patient's clinical status should influence our choice of antibiotic for initial treatment of CDAD.<sup>8</sup> We'll cover those recommendations in a moment; first, let's review the drugs themselves and the evidence that led to this new therapeutic approach.

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* under most circumstances. Overall, metronidazole is well tolerated, although side effects can include a metallic taste, nausea, vomiting, diarrhea, pruritis, rash, headache, confusion and dizziness. Alcohol consumption should be avoided with metronidazole because it may result in a disulfiram reaction.<sup>2</sup>

Oral vancomycin is the only drug with an FDA indication for the treatment of CDAD. Because it is poorly absorbed from the GI lumen, high fecal concentrations are easily achieved while systemic toxicities are rare.<sup>2</sup> 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.<sup>3</sup> Therefore, for patients with severe disease, we recommend the lower dose of vancomycin due to its lower cost. Some experts prefer a higher dose for the small number of patients with complicated disease, but this recommendation

is not based on rigorous study, and thus is controversial. Intravenous vancomycin does not achieve appreciable concentrations within the bowel and should not be used for the treatment of CDAD.

Both metronidazole and vancomycin inhibit the growth and toxin production of *C. difficile*. But which drug is better for CDAD? Three prospective randomized trials have compared the efficacy of metronidazole with that of vancomycin. In the first trial,<sup>4</sup> a total of 101 patients with CDAD were randomized to receive either metronidazole (250 mg PO q6h) or vancomycin (500 mg PO q6h) for ten days. 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 patients who relapsed in the vancomycin group ( $p=0.17$ ). In the second trial,<sup>5</sup> 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. The clinical cure rates ranged from 93% to 96% between groups. The relapse rates between the metronidazole and vancomycin groups were the same ( $p>0.8$ ). 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*.<sup>2</sup>

**Table 1.** UW Medicine guidelines for classification and initial treatment of first or second episode of CDAD<sup>1,2,8,35,36</sup>

DISEASE SEVERITY	DEFINITION	TREATMENT	DURATION	COMMENTS
<b>Mild-moderate</b>	<ul style="list-style-type: none"> <li>• WBC &lt;15,000/mm<sup>3</sup></li> <li><b>AND</b></li> <li>• Serum creatinine &lt;50% increase over baseline</li> </ul>	Metronidazole 500 mg PO q8h	10–14 days	Consider changing to oral vancomycin in 3–5 days if lack of clinical response noted
<b>Severe</b>	<ul style="list-style-type: none"> <li>• WBC count ≥15,000/mm<sup>3</sup></li> <li><b>OR</b></li> <li>• Serum creatinine ≥ 50% increase vs. baseline</li> </ul>	Vancomycin 125 mg PO q6h	10–14 days	Vancomycin is recommended as the initial antibiotic for pregnant women
<b>Severe, with complications</b>	<b>ANY:</b> <ul style="list-style-type: none"> <li>• Direct admission to ICU for CDAD</li> <li>• Hypotension</li> <li>• Shock</li> <li>• Toxic megacolon</li> <li>• Perforation</li> <li>• Severe colitis on CT scan</li> </ul>	Ileus or unable to take PO: metronidazole 500 mg IV q8h + vancomycin by NGT and/or retention enema	10 days minimum	Recommend Infectious Diseases consultation for vancomycin dosing and duration of therapy

Treatment of *Clostridium difficile* – Associated Disease (continued)

Nevertheless, clinicians who have seen patients with severe CDAD fail initial treatment with metronidazole continued to wonder whether the sickest patients might benefit from up-front vancomycin therapy.<sup>6,7</sup> In an attempt to address this question, a randomized, prospective, double-blind, placebo-controlled trial was recently published that compared the efficacy of vancomycin versus metronidazole in patients with CDAD who were stratified by disease severity.<sup>8</sup> 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/mm<sup>3</sup> within 48 hours of enrollment. Patients with endoscopic evidence of pseudomembranous colitis, or disease requiring treatment in the intensive care unit (ICU), 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 CDAD are over age 60, febrile, and have WBC counts >15,000 cells/mm<sup>3</sup>, 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 CDAD are forthcoming from the Infectious Diseases Society of America, and we anticipate that they will emphasize a risk-stratification scheme similar to that described above. Therefore, we have developed disease-scoring and treatment recommendations (Table 1). Patients begun on treatment 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.

**What about intravenous (IV) therapy for CDAD?**

In general, the oral route of administration is preferred. It is appropriate to treat patients with IV metronidazole if they are unable to reliably take oral medications or if they have developed ileus that could impede enterohepatic drug circulation. IV vancomycin should not be used for CDAD because it does not achieve significant concentrations in the colonic lumen.

**Are two drugs better than one? Should I combine antibiotics?**

Patients with a first episode of mild–moderate or severe disease but no ileus, no megacolon, and no need for treatment in the intensive care unit should be treated with only *one* anti-*C.difficile* drug at a time. Combination therapy should be used only in patients who are severely ill *and* have complicated disease, as indicated in Table 1. No reliable data have demonstrated a benefit of combination therapy outside of these circumstances; indeed, retrospective data suggest that using metronidazole plus vancomycin simultaneously may increase a patient’s risk of recurrent disease (although this observation may have been due to selection bias).<sup>9,10</sup>

**What about rectal vancomycin therapy for CDAD?**

Patients with severe CDAD 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 per rectum, inflating the balloon, instilling 500 mg of vancomycin mixed in 100 mL of normal saline, clamping the catheter for one hour, and unclamping and removing the catheter; this process is repeated every 4–12 hours.<sup>11</sup> 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. Reported failures with intravenous metronidazole have led to the addition of intracolonic vancomycin for patients with severe CDAD,<sup>12,13</sup> although only observational data support its use. 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. In the absence of stronger published evidence for this practice, we recommend consultation with the Infectious Diseases, Gastroenterology, and General Surgery services if combination oral and rectal vancomycin is considered.

Treatment of *Clostridium difficile* – Associated Disease (continued)**If my patient is already on antibiotics for another reason, do I really need to stop them? 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 that allowed *C. difficile* to flourish. Although clindamycin is strongly associated with CDAD, virtually any antibiotic can trigger the disease;  $\beta$ -lactams and fluoroquinolones are commonly implicated. If your 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 common examples. Among the minority of patients who remain on their original offending antibiotic regimen beyond 14 days, it may be advisable to continue low-dose metronidazole or vancomycin until one week beyond cessation of the primary regimen, in order to minimize the risk of recurrent CDAD.<sup>14</sup> However, the dosing for this practice is controversial, and should be considered in consultation with the Infectious Diseases service.

**I have read about newer treatments for CDAD. If metronidazole or vancomycin just aren't working, should I consider using newer drugs?**

Antimicrobials other than metronidazole and vancomycin have been reported to cure recurrent CDAD. In particular, nitazoxanide and rifaximin appear to have promising anti-CDAD activity.<sup>15,16</sup> In the relatively small series published so far, these drugs have been well tolerated in the treatment of recurrent disease. However, they have not been proven superior to metronidazole or vancomycin for the treatment of primary or recurrent illness in clinical trials, and international experience to date using these agents is limited. Thus, their role for the treatment of CDAD remains investigational. Antibiotics in development for CDAD include ramoplanin (Oscient Pharmaceuticals), difimicin (Optimer Pharmaceuticals), and rifalazil (ActivBiotics), but none are FDA-approved for human use yet. At this time, treatment of CDAD at UW Medicine using agents other than metronidazole and vancomycin should be undertaken only in consultation with Infectious Diseases or Gastroenterology.

**I have heard about using IVIG for CDAD. What's up with that?**

Intravenous immune globulin (IVIG) has been reported to assist with the treatment of refractory, severe CDAD.<sup>17,18</sup> 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 CDAD although it suffered from methodological problems.<sup>19</sup> Significant obstacles and concerns, including the lack of standardized dosing, risks of potentially serious side effects, and extraordinary cost prevent us from recommending this approach in all but the most difficult-to-treat cases. If you are considering using IVIG, an Infectious Diseases consult is warranted for assistance with the decision.

Of note, monoclonal antibodies have shown promise in animal models and are now in Phase II of human development (Medarex, Inc. and Massachusetts Biological Labs). An effort is also underway to develop a *C. difficile* vaccine (Acambis) which has been used experimentally for recurrent CDAD<sup>20</sup> and is now in Phase II of development.

**What about probiotics? I've read that using yogurt or other "live culture" products can prevent or help treat CDAD.**

Because CDAD 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.<sup>21</sup> 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. Investigators at the University of Washington are among the world's leaders in this field, and their work on the yeast *Saccharomyces boulardii* strongly suggests that this organism, in combination with anti-*C. difficile* antibiotics, may help to prevent recurrent episodes of CDAD.<sup>22,23,24</sup> However, a handful of reports of therapeutic strains causing disease among immunosuppressed hospitalized patients have given pause,<sup>25,26,27</sup> and neither FDA approval nor widespread international adoption of this approach has occurred. There are similar concerns regarding the use of *Lactobacillus* species for the supplemental treatment of CDAD, although they have not been studied as rigorously as *Saccharomyces*.<sup>28</sup> We do not believe that evidence is adequate to recommend the use of any species in primary prophylaxis. Hopefully, more data in this field is forthcoming; meanwhile, please consult with Infectious Diseases and Gastroenterology for assistance with the question of probiotic therapy.

Incidentally, "fecal biotherapy" might be thought of as the ultimate probiotic experience: stool from an asymptomatic donor is homogenized and instilled in the patient's colon via retention enema or colonoscopy. There are reports of success using this technique for the treatment of severe, recurrent CDAD.<sup>29</sup> Challenges including donor selection, co-pathogen screening, and safety prevent this technique from being used in all but the most difficult-to-treat cases.

## Treatment of *Clostridium difficile* – Associated Disease (continued)

### **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 we do *not* recommend it. 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.<sup>30</sup> A placebo-controlled trial using a different resin, colestipol, demonstrated no benefit.<sup>31</sup> 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 my patient miserable and the nurses unhappy. Can we prescribe just a little antimotility medication?**

*Please do not.* 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.<sup>32</sup> When treating CDAD, follow the mantra: “Let it flow.”

### **Who needs surgery for CDAD?**

Subtotal or total colectomy may be life-saving interventions for patients with severe CDAD because toxic megacolon may lead to perforation and peritonitis. Determining the indications for surgery is possibly as much an art as a science. Consultants in General Surgery will weigh numerous factors when making this recommendation, including severity of toxic megacolon, risk of imminent perforation, response to therapy, and comorbid conditions. We recommend consulting General Surgery early in cases of severe CDAD or in patients who worsen on medical therapy.

### **How should I stop treatment? Is it better to taper off CDAD therapy, or just stop cold turkey?**

For initial episodes of CDAD, we recommend stopping therapy once your patient has received 10–14 days of therapy and is diarrhea-free (or dramatically improved). Of the patients treated in this fashion, 75–90% will achieve a full and durable cure.

### **What about the patients who get CDAD again? How should I treat recurrences?**

Regardless of the initial regimen chosen, approximately 10–25% of patients who achieve full symptomatic cure of CDAD will experience recurrent symptoms after completing antibiotic therapy, frequently within two weeks of finishing their initial course.<sup>33</sup> 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*.<sup>34</sup>

Diarrhea that returns after treating CDAD 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. As with the initial occurrence, a negative stool assay has 95% negative predictive value against the diagnosis of CDAD. On the other hand, a positive test may indicate carriage of *C. difficile* rather than true infection. Thus, clinicians should carefully 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 reinstitute empiric therapy per the criteria in Table 1. Although described in the literature, drug resistance rarely causes clinical recurrences,<sup>17,18</sup> and therefore patients with mild–moderate disease should receive metronidazole for their recurrence regardless of their prior regimen.<sup>2</sup>

Treatment for recurrent CDAD 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 CDAD.<sup>19</sup> These patients usually require a switch from metronidazole to vancomycin and a longer course of therapy, perhaps featuring pulses or tapering doses of antibiotics, in order to minimize toxicity while improving therapeutic outcome. Numerous strategies for tapering anti-*C. difficile* therapy have been described in the literature,<sup>20,21</sup> but they are based on observational studies, and no strategy has demonstrated clear superiority. We suggest tapering or pulsing therapy only in consultation with Infectious Diseases or Gastroenterology.

### **When should I ask for help, and whom should I call?**

We believe that consultation with the Infectious Diseases and Gastroenterology services is warranted when your patient’s illness is severe or complicated, if he or she fails to improve after 3–5 days of therapy, or when the diagnosis is in doubt. Consultation with General Surgery is also advisable when there is concern for ileus or toxic megacolon.

The authors welcome questions or comments about this article. Our e-mail address is: [abx@u.washington.edu](mailto:abx@u.washington.edu).

Treatment of *Clostridium difficile* – Associated Disease (continued)

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