



### January 2010: VOLUME 2, NUMBER 3

### *C. difficile* Infection (CDI): 2010 Update

#### In this Issue...

*Clostridium difficile* was originally reported as the cause of antibiotic-associated diarrhea in 1978. Methods to diagnose and treat the infection evolved rapidly, so that virtually all physicians had easy access to diagnostic tests to detect toxin and to antibiotics (metronidazole and vancomycin) that were usually effective in treatment. Since 2000, there has been a substantial increase in the number of cases and an escalating rate of serious disease with a four-fold increase in mortality. This appears to be largely explained by the emergence of the NAP-1 strain, which is now implicated in causing more frequent disease (including most epidemics), more serious disease, and infection that is more likely to relapse. These challenges in management have resulted in new methods for testing, new emphasis on antibiotic and infection control, and substantial refinements in the approach to serious disease and relapsing disease.

In this issue we review the escalating rates of *Clostridium difficile* infection (CDI), new diagnostic methods, and contemporary approaches to management.



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At the conclusion of this activity, participants should be able to:

- Describe the contemporary importance of *C. difficile* infection (CDI) in medicine in terms of escalating rates of infection and mortality.
- Evaluate the relative merits of numerous testing methods.
- Explain how to treat CDI with respect to the usual infection, the seriously ill patient, and the patient with recurrent disease.

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*Clostridium difficile* infection (CDI) is topical because of rapid changes in three clinically important areas: 1) escalating rates of disease and of serious disease; 2) recognition of the insensitivity of the EIA test for diagnosis and the introduction of multiple new test strategies, and 3) evolving methods for management.

The escalating rate of cases in the 2000-2005 period was initially thought to be regional and/or due to improved recognition or reporting. It now appears to be generalized throughout most of the US, Canada and Europe, and much of it seems to reflect the emergence of the NAP-1 strain. The supporting data are nicely reviewed by Rupnik et al, which provides extensive information on the *C. difficile* toxins and pathophysiologic mechanisms, as well as the epidemiology and pathogenesis discussed herein.<sup>1</sup> Suffice it to say that CDI is by far the most common enteric bacterial pathogen in the US and Europe, it is the most common lethal enteric pathogen in these areas, it is usually iatrogenic, and >95% of patients respond to therapy. A few additional points:

- The association with age, hospitalization, and antibiotics is emphasized; however, there have been increasing reports of community-acquired cases without recent antibiotic exposure, severe disease in pregnancy, pediatric cases, and CDI associated with PPI use.
- The role of NAP-1 is emphasized, but in practice the physician will rarely know if a case is NAP-1 or not, as identification would require culturing stool and sending it to a reference lab for typing. However, this information is not important for patient management, since severe disease can be caused by any strain of *C. difficile*, and the clinical features should determine management decisions.
- The role of fluoroquinolones in these infections has changed. While not an issue before 2000, it is important now, with at least one hospital unable to control a CDI epidemic until the use of these agents was totally restricted.<sup>2</sup>

With regard to diagnostic testing, the big concern is the lack of sensitivity of the EIA assay to detect toxin A or A/B, since this is the test used in 95% of labs. The review by Peterson and Rovicsek<sup>3</sup> is state-of-the-art, but there are a few points to emphasize:

- While the cost comparisons listed in the Table (see *Testing for CDI* herein) are taken from the authors' manuscript, the figures are quite deceptive because they account for only the cost of the reagents and not the technician's time—and those tests which are more technically complicated (e.g. cytotoxin and culture-toxin) will be substantially more expensive. Further, the sensitivity of EIA testing is stated as 70-80%, but this is quite generous; in our lab it was only 43% sensitive when compared to cytotoxin testing.<sup>4</sup> Also, it must be remembered that both culture-toxin and PCR will only detect the presence of toxigenic *C. difficile* which could be caused by carriers without CDI, which may cause false positive tests. As about two-thirds of *C. difficile* strains produce toxin, and about 15-30% of hospitalized patients without CDI are colonized, this makes clinical correlations critical.
- The practical application of the cost comparison table is that, while most physicians will not be able to dictate the test that their lab will employ for CDI, it is important for them to know which test used since this will determine interpretation. At present most labs use EIA—the problem is false negatives and this concern is not usually corrected by getting multiple EIA tests. The new test that is attracting great attention is PCR assay for detecting toxigenic *C. difficile*, but here the problem could be false positives due to relatively high carriage rates in hospitalized patients. With this test, it is the clinical correlations that are particularly important.
- It is also important to emphasize that all of these tests are used for diagnosis, but they are not good as a test-of-cure. Response to treatment is based on clinical observations and not the toxin test, although the reason the test is not of value here is an enigma.

The treatment strategies for CDI are being refined due to increased concerns about 2 completely different challenges: the patient who has severe life-threatening CDI and the patient with multiple relapses.

The European guidelines summarized in this issue do a good job of providing guidance for care of the patient with newly detected CDI, but in my view they fall short in their recommendations for managing relapsing disease.<sup>5</sup> Relapse is a complication in about 20% of patients who are treated with either metronidazole or oral vancomycin, and are characterized by recurrence of the same symptoms, including a distinctive stool odor that many patients recognize. The relapse may involve the same *C. difficile* strain or a new one. Among those who relapse, the probability of a second relapse is about 40% and increases further with each subsequent relapse, so that some patients will have months or even years of relapsing disease.<sup>6</sup> Physicians who care for many CDI patients are all aware of this.

In terms of management, the recommendations noted in the article for “taper/pulse” are spelled out in more detail in a review article from the Netherlands.<sup>7</sup> The recommendation is for dosing vancomycin at 125 mg 4 x daily for 14 days, then twice daily for 7 days, then once daily for 7 days, then on alternative days for 8 days and then every third day for 15 days. With further relapses there is the option of adding IVIG (400 mg/kg) every 3 weeks for 2-3 doses. My preference for this setting is oral vancomycin in a dose of 125 mg every other day for 6 weeks. Other strategies include pulse dose of vancomycin followed by a one week course of rifaximin.<sup>8</sup> The problem here is concern with rifaximin resistance which, like rifampin, can be sudden and profound in an individual patient or in an epidemic.<sup>9</sup> Probiotics are often used by patients because of advocacy on the web and availability in health food stores. Supporting data are slim, but they usually do no harm.<sup>10</sup>

Finally there is the fecal transplant.<sup>7</sup> These had been done for CDI before *C. difficile* was known to cause CDI, and have been the subject of intrigue by both patients and physicians ever since. A recent review of 16 published reports from 1958-2008 showed 159 cases with 144 (91%) cures, an outstanding record considering that this is usually a last ditch intervention for the most refractory patients. In the US, availability of the procedure is sharply limited due to several concerns: 1) esthetics, 2) concern for liability, 3) lack of clarity in methods, and 4) lack of an ICD-9 code for billing. Nevertheless, it usually works if you can find someone to do it.

#### Commentary References

1. Rupnik M, Wilcox MH, Gerding DN. [Clostridium difficile infection: new developments in epidemiology and pathogenesis](#). *Nat Rev Microbiol*. 2009;7(7):526-536.
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4. Ticehurst JR, Aird DZ, Dam LM, Borek AP, Hargrove JT, Carroll KC. [Effective detection of toxigenic Clostridium difficile by a two-step algorithm including tests for antigen and cytotoxin](#). *J Clin Microbiol*. 2006;44(3):1145-1149.
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Rupnik M, Wilcox MH, Gerding DN. **Clostridium difficile infection: new developments in epidemiology and pathogenesis.** *Nat Rev Microbiol.* 2009;7(7):526-536.

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With regard to epidemiology, the authors noted that the number of cases (as determined by discharged diagnosis) for the US in the year 2000 was less than 150,000, and increased to more than 300,000 cases/year in the US in 2006. They also report a substantial increase in mortality, from about 0.5/100,000 population in 2000 to more than 2.0/100,000 in 2006 (a four-fold increase). Several countries in Europe also experienced this type of epidemic pattern, which is now largely attributed to the emergence of a new strain of *C. difficile* that is often referred to as the NAP-1 strain, but is also called ribotype 027 or toxinotype III (these names simply reflect different methods of classification of the same strain). Much of the early work identifying this rather alarming increase in the number of cases was reported in Canada,<sup>1</sup> but was subsequently identified in most states of the US and in Europe.<sup>2,3</sup>

There are 2 important features of this organism that possibly account for both the increase in cases and the increase in virulence. First, this strain of *C. difficile* is highly resistant to fluoroquinolones, and many of the cases are now associated with the use of that class of drugs. It should be noted that extensive studies of *C. difficile* done before the year 2000 showed that this NAP-1 strain was rare and that *C. difficile* resistance to the fluoroquinolone class was also rare. The second important feature of this organism is the fact that it produces large amounts of toxin *in vitro*, which presumably correlates with greater toxin production *in vivo*.<sup>4</sup>

With regard to risks, there are 3 that are particularly important for CDI. The first is advanced age. While it has been noted from very early studies in the 1980's that elderly patients are more prone to CDI and the mechanism remains unclear, nevertheless, the association with advanced age has been consistent and impressive. The second risk is antibiotic exposure. The classic drug to cause this condition was clindamycin, an association so frequent that when this organism was first identified as a cause of antibiotic-associated colitis, the condition was frequently referred to as "clindamycin colitis." Subsequently, cephalosporins with a broad spectrum of activity (e.g. ceftriaxone or cefotaxime) became the most common causes—not because of high incidence per use, but because of the extensive use of these agents. The more recent dramatic increase in cases that are fluoroquinolone-associated now make clindamycin, broad spectrum cephalosporins, and fluoroquinolones the "big three" for CDI. However, as noted by the authors, nearly all antibiotics may cause this complication. The third risk is hospitalization or residence in a chronic care facility, attributed to the fact that hospitals and chronic care facilities harbor large numbers of elderly patients with a high frequency of antibiotic exposure, and that they reside in facilities that are heavily contaminated by *C. difficile*. These risk factors are well confirmed, but the review points out that there are some notable exceptions that appear to reflect a changing epidemiology possibly attributed to the emergence of the NAP-1 strain. For example, some areas have found large numbers of cases acquired in the community without antibiotic exposure.<sup>5,6</sup>

These observations collectively indicate that rates of CDI are increasing. This is a serious iatrogenic complication, and early detection with appropriate testing is important, since treatment is usually highly effective.

## References

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2. McDonald LC, Killgore GE, Thompson A, et al. [An epidemic, toxin gene-variant strain of Clostridium difficile.](#) *NEJM.* 2005;353(23):2433-2441.

3. Kuijper EJ, Coignard B, Tull P; ESCMID Study Group for Clostridium difficile; EU Member States; European Centre for Disease Prevention and Control. [Emergence of Clostridium difficile-associated disease in North America and Europe](#). *Clin Microbiol Infect*. 2006;12 [Suppl 6]:2-18.
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## TESTING FOR CDI

Peterson LR, Rovicsek A. **Does my patient have Clostridium difficile infection?** *Ann Intern Med*. 2009;151(3):176-179.

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This state-of-the-art document makes several important points. First, the testing should be confined to patients who have diarrhea, defined as 3 or more loose stools per day for at least 1-2 days. A concern is that the rate of *C. difficile* colonization in outpatients is low, but increases with hospitalization to reach nearly 50% at 4 weeks. Thus, tests that detect the organism may be sensitive but not specific. The emphasis needs to be on toxin or toxigenic *C. difficile* in the context of an appropriate clinical presentation. With regard to available assays, the authors review 5 different tests that are done in various laboratories. It should be noted that about 95% of laboratories in the US use the EIA test because it is cheap and fast, but this test is losing favor and is unlikely to survive as the major test method in the US.

The review makes the following points, which are summarized below and in the Table that follows:

- **EIA** : Reagents are commercially available to test toxin A or both toxin A and B. It is important to test both A and B since there are some strains that produce only B toxin; most labs know this and use only the A/B test. The advantages of this test are that it is cheap, fast, necessary reagents are commercially available, and it is relatively specific. The key problem is that it lacks sensitivity, so that a negative test does not exclude CDI diagnosis. Some researchers have attempted to improve the diagnostic sensitivity by getting multiple tests on the same patient, but the authors show this approach does not increase the diagnostic yield.
- **Cytotoxin**: This test detects toxin B and was the first test available (in 1978). Many view it as the “gold standard”, but it takes 2-3 days, is technically complex, and has not proven as sensitive as culture-toxin or PCR (discussed below).
- **Glutamine dehydrogenase (GDH)**: This detects the designated protein that is a marker for *C. difficile* and detected by a latex test or EIA. It is cheap and fast, but lacks specificity since it only detects the presence of *C. difficile*. Its main contemporary use is for screening, followed by a more definitive test in those samples that are positive.
- **Culture-toxin**: This is a favored method in Europe because it has great sensitivity. The stool is heat shocked to eliminate all bacteria except *Clostridial* spores, and then a broth culture is grown for detection of toxin. Key disadvantages are the long time required and the complexity of the test.
- **PCR**: This detects the gene to produce toxin B, which is present in all toxigenic strains. This is the new test and is now being used by more and more laboratories. The FDA has cleared 3 assays that are now commercially available.

This information is summarized in the following Table:



**Table 1. Relative Merits of Tests for CDI**

Test	Purpose	Time	Cost	Sensitivity	Specificity
EIA	Detect toxin A or A/B	Hours	\$5–17	70–80%	>97%
Cytotoxin	Detect toxin B (and A)	2–3 days	\$7–13	70–80%	>97%
GDH	Detect <i>C. difficile</i>	Hours	\$17	70–80%	>90%
Culture-toxin	Detect toxigenic <i>C. difficile</i>	2–5 days	\$10–22	>90%	95–97%
PCR	Detect toxigenic <i>C. difficile</i>	Hours	\$7–50	>90%	>97%

The authors conclude that: 1) “a prudent approach” is “the most sensitive rapid test”, 2) the test used should not be repeated for 7-14 days, and 3) if another test is deemed necessary it should use a different testing method.

## TREATMENT

Bauer MP, Kuijper EJ, van Dissel JT. **European Society of Clinical Microbiology and Infectious Diseases (ESCMID): treatment guidance document for Clostridium difficile infection (CDI).** *Microbiol Infect.* 2009;15(12):1067-1079.

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The treatment of CDI consists of oral antibiotics, either metronidazole or vancomycin, usually given for 10 days. Most patients respond rapidly within an average of 4 days to resolution of diarrhea. These treatments were well established in the late 1970's and have never been seriously challenged. What has happened is refinement of the specific regimens and sharp distinction between use of these drugs in patients who are not seriously ill and those who have serious or complicated CDI. Perhaps most important has been the emergence of oral vancomycin as the preferred drug for patients with more serious disease. This could have been anticipated on the basis of pharmacology, since oral vancomycin goes right to the site of infection in the colon, whereas metronidazole given by mouth is nearly completely absorbed and very little gets to the colonic lumen. Resistance is not the problem; the issue is getting the medication to the site of the infection. Nevertheless, there continues to be enthusiasm for metronidazole for patients who are not seriously ill, since it seems to perform reasonably well in patients who are not too sick, and it has a great price advantage with the pill formulations.<sup>1</sup>

A multitude of recent studies have converged to provide the basis for the recently published management guidelines from the ESCMID, summarized in the following Table:

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**Table 2. Recommendations for Treatment of CDI**

**Uncomplicated Cases**

- Not severe cases: metronidazole 500 mg po tid x 10 days
- Severe cases: vancomycin 125 mg po qid x 10 days

**Oral treatment not possible**

- Not severe: metronidazole 500 mg IV tid x 10 days
- Severe: metronidazole 500 mg tid IV x 10 days plus vancomycin intracolonic 500 mg in 100 mL NS q 4–12 hours and/or vancomycin by NG tube

**Colectomy**

Recommended if the patient has systemic signs of inflammation and is unresponsive to antibiotics including those with severe ileus. This should be done before the serum lactate is 5 mmol/L

**Relapses**

Oral vancomycin 125 mg qid po for 10 days and "consider a taper/pulse strategy"

As noted above, an important distinction is made for patients who have uncomplicated cases and those who are considered to have "severe colitis". The definition of severe is considered for the patient with CDI plus any of the following: fever >38.5°C, rigors, signs of peritonitis, WBC >15,000/mm<sup>3</sup>, marked left shift with bands exceeding 20% of PMNs, serum creatinine exceeding 50% of baseline, elevated lactate, pseudomembranous colitis (PMC) by endoscopy, intestinal distention, thick colonic wall by imaging, or pericolonic fat stranding by CT scan.

**References**

1. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. [A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity.](#) *Clin Infect Dis.* 2007 Aug 1;45(3):302-7.

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