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Diagnosis and Management of Clostridium difficile Infections

In this Issue...

Clostridium difficile (*C. difficile*) is clearly the most important and most common bacterial infection of the GI tract in the U.S. Although this pathogen has been known and studied for nearly 30 years, there now appears to be an epidemic of a new and problematic strain, designated North American pulsed-field gel electrophoresis type 1 (NAP1).

In this issue, we discuss the history of *C. difficile*-associated diarrhea, and review the current literature describing antibiotic treatment strategies, diagnostic testing options, the challenges posed by recurrent infection, and the impact of emergency colectomy on the survival of patients infected by the hypervirulent NAP1 strain.

Program Information

[CME Info](#)
[Accreditation](#)
[Credit Designations](#)
[Target Audience](#)
[Learning Objectives](#)
[Internet CME Policy](#)
[Faculty Disclosures](#)
[Disclaimer Statement](#)

Length of Activity

1.0 hours Physicians

Expiration Date

October 31, 2009

Next Issue

November 30, 2007

THIS ISSUE

- [COMMENTARY from our Guest Author](#)
- [COMPARISON OF TREATMENT AGENTS](#)
- [COMPARISON OF DIAGNOSTIC TESTING ASSAYS](#)
- [THE CDC REPORT ON NAP1](#)
- [IMPACT OF EMERGENCY COLECTOMY](#)

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GUEST AUTHOR OF THE MONTH



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Guest Faculty Disclosures

John G. Bartlett, MD has disclosed that he serves on the HIV Advisory Board for GlaxoSmithKline, Abbott, Bristol-Myers Squibb, Pfizer, and Tibotec. He is also on the Policy Board for Johnson & Johnson.

Unlabeled/Unapproved Uses

The author has indicated that his discussion includes reference to unlabeled / unapproved uses of metronidazole.

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LEARNING OBJECTIVES

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

- Describe the contemporary standards for diagnosing and managing *C. difficile*-associated diarrhea
- Explain the important changes in disease management that accompany the epidemic of the *C. difficile* NAP1 strain
- Discuss the role of oral vancomycin and oral metronidazole in *C. difficile*-associated diarrhea

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COMMENTARY

The history of antibiotic-associated colitis goes back to the beginning of the antibiotic era, with the accounts of *Staphylococcus aureus* enterocolitis reported primarily by surgeons in the 1950s through 1970. In 1974, Tedesco et al¹ reported on 200 consecutive patients who received clindamycin at Barnes Hospital in St. Louis; of these, 42 developed diarrhea and 20 had pseudomembranous colitis (PMC) detected with endoscopy. However, unlike the reports of enterocolitis attributed to *S. aureus*, this organism could not be recovered in stool, leading to a search for alternative pathogens that eventuated in the detection of *C. difficile*. Over the next several years this new disease, "clindamycin colitis", was extensively studied. Among the key findings:



- The disease was caused by a toxin or toxins designated Toxin A and Toxin B, produced by *C. difficile*.
- The diagnostic test of choice was a cytotoxin assay, which proved to be extremely sensitive and specific for this diagnosis. However, studies in the 1980s showed an enzyme immunoassay (EIA) to be faster, easier, and cheaper, and it was adopted as the standard test by at least 95% of laboratories in the U.S.
- Despite the original appellation of "clindamycin colitis", it was learned that all antibiotics with an antibacterial spectrum of activity could cause this complication. However, there was a hierarchical order, with the dominant agents found to be clindamycin and broad-spectrum betalactams, especially third generation cephalosporins.
- The pathophysiology of the disease appeared to be a reflection of suppression of normal flora by the antibiotics in patients who were colonized by or who acquired *C. difficile*. In the colon this organism usually remained dormant as a spore, but in the presence of suppressed competing flora, it reverted to the vegetative form with toxin production. These toxins, A and B, were noted to be highly potent in causing a severe inflammation in experimental animals.
- The risk factors for *C. difficile* were identified as antibiotic exposure, elderly age, and hospitalization or residence in a chronic care facility. The latter risk presumably reflects clustering of patients who are vulnerable due to advanced age and high rates of antibiotic exposure, in an environment where *C. difficile* is commonly found on the walls, beds, and other surfaces, as well as on the hands of the healthcare workers who care for these patients.
- The clinical features of *C. difficile* were diarrhea in almost all cases, and evidence of inflammation with colitis in most. The signs of inflammation included cramps, fecal leukocytes, fever, leukocytosis, and colitis demonstrated by computerized tomography or endoscopy.
- Oral vancomycin was the first agent used to treat *C. difficile*; its use had substantial precedent in the treatment of *S. aureus* enterocolitis. This drug also made theoretical sense: all strains were sensitive and continued to be highly sensitive *in vitro*, and the drug is not absorbed when taken orally, so that levels in the colon (where the putative agent colonizes) reach levels that are commonly 100-1000 times the minimum inhibitory concentration (MIC). However, metronidazole was also uniformly active against *C. difficile*. Although the pharmacology of this drug was not particularly good for reaching the colon lumen, therapeutic trials supported its use, and it became a favored drug because of low price and concerns about oral vancomycin promoting colonization with vancomycin-resistant Enterococcus (VRE).
- While most of the studies showed that the great majority of patients responded to either of these drugs, there were two important problems. First, some patients had ileus, making it very difficult to get vancomycin by mouth to the colonic lumen. The second problem was relapse: about 20% of patients who were treated with either agent did well, but then had recurrent disease when the treatment was discontinued. Some of these patients had multiple relapses.

This summary represents the state-of-the-art for *C. difficile* knowledge until about five years ago. Since then, there has been a substantial increase in interest and concern about *C. difficile*. Issues include morbidity and mortality attributed to this organism, the adequacy of the current diagnostic testing, the problems associated with standard management, and the impression that there is more frequent disease occurrence, more severe disease, and more disease that is refractory to the standard treatment. Some or most of this may now be attributed to a newly recognized "hypervirulent strain" of *C. difficile*.

The NAP1 Strain

The increasing problem of *C. difficile* was first recognized by Jacques Pepin et al, who reported that the rates of this complication in Sherbrooke, Quebec had increased more than ten fold in persons who were over the age of 65 years.² This increase, initially noted in 2002, showed that the disease was not only more

frequent, but also was more severe, with an attributable mortality of 6-17%; further, it was more refractory to therapy and more prone to relapse. There was initial skepticism that these findings were, in fact, real. However, the observations of Pepin et al were also observed at McGill University (also in Quebec), in at least 24 states in the U.S., and in several countries in Europe. The presumed explanation was the appearance of the NAP1 strain, as summarized by Blossom and McDonald from the CDC (reviewed herein). This "hypervirulent strain" appears now to be an important cause of this disease in most states of the U.S., and has also been reported from several countries in Europe. This strain is relatively new, and as noted in the review from the CDC, may cause more disease as a result of extensive use of fluoroquinolones, with more serious disease possibly the result of an increase in toxin production. With regard to the U.S., the number of reported cases is noted to have increased more than two-fold during the past decade, and the anecdotal experience is that many of these cases are now apparently more serious than those seen previously.

The diagnostic testing for *C. difficile* in the U.S. is done by the EIA test, which has become the standard for more than 95% of laboratories. There have been extensive studies showing reduced sensitivity of this assay, which was reported in the CDC review as 60-95%. However, at Johns Hopkins Hospital, the sensitivity was only 40%, necessitating a shift to an alternative diagnostic testing strategy.³ Nevertheless, there appear to be substantial differences in this experience. Musher et al (reviewed herein) have reviewed a series from Houston that appears to show that the EIA from multiple suppliers provides an excellent correlation with the "gold standard" cytotoxin assay. The explanation for the difference between this and prior reports remains unclear. The current recommendation is for physicians to simply use caution when depending on the EIA, until there are better data on the relative sensitivity of this test.

With regard to treatment, there has always been the problem of the occasional case that is treated late in the course when there is ileus or toxic megacolon, which preclude getting an orally administered drug to the site of the infection (the colonic lumen). This concern is now elevated because of the more severe consequences of the NAP1 strain. The review by Lamontagne et al (summarized herein) provides important information about the risks for severe disease, which include a leukemoid reaction and advanced age. The leukemoid reaction is of particular interest, since it is a property of *C. difficile* that is shared with *C. sordellii*, another Clostridia species that produces toxin antigenically related to *C. difficile*. Both have the property of causing a leukemoid reaction despite very different clinical expression. Colectomy is also discussed in the Lamontagne article: although this is rarely required with *C. difficile* infection, the authors report the procedure seems to show substantial benefits in patients who have very advanced disease. Some caution is advised here, since there may be substantial selection bias, as surgeons may simply have refused to operate on patients with the most advanced disease. Nevertheless, it may be important to get surgery consultations in patients who are critically ill, and to use Lamontagne's paper to get surgeons to more seriously consider this intervention if other therapeutic modalities fail.

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3. Ticehurst J R, Aird DZ, Dam LM et al. [Effective Detection of Toxigenic *Clostridium difficile* by a Two-Step Algorithm Including Tests for Antigen and Cytotoxin.](#) *J Clin Microbiol.* 2006;44:1145-1149.

COMPARISON OF TREATMENT AGENTS

Zar FA, Bakkanagari K, 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;45:302-7.

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The authors performed a prospective, randomized, double blind trial to determine the relative merits of metronidazole versus vancomycin. The eligibility criteria included antibiotic-associated diarrhea with a positive toxin assay for toxin A or endoscopic evidence of PMC. One hundred fifty participants were stratified by severity of disease. Severe disease was classified as having endoscopic evidence of PMC, admission to the intensive care unit, or two of the following: age >60 years, temperature >38.3°C, albumin <2.5 mg/dL, or WBC >15,000/mm³ (n=69). Mild disease was defined simply as lacking the criteria for severe disease (n=81). Participants were randomized to metronidazole 250 mg qid (n=79) or oral vancomycin 125 mg qid (n=71) for 10 days.

The outcome was classified as cured if there was resolution of diarrhea by day 6 and a negative stool for toxin A at days 6 and 10. Failure was defined as the inability to achieve the criteria for cure, or death after at least 5 days of treatment, or the requirement for a colectomy or relapse by day 21 post-treatment.

The results of the study showed those classified with severe disease had a higher cure rate with vancomycin (97% vs. 76%, respectively; p=0.02). For the 81 patients classified as mild disease, the response rates were 98% vs. 90% for vancomycin and metronidazole, respectively a difference that is not statistically significant (Table 1). The frequency of relapse was 14/137 (10%); while somewhat more frequent with severe disease, there was no difference for relapse rates based on randomization to vancomycin or metronidazole. These results are summarized in the following table:

Table 1: Vancomycin vs. Metronidazole for *C. difficile* Infection

	Vancomycin n=71	Metronidazole N=79	P
No. Cured			
Mild disease	39/40 (98%)	37/41 (90%)	0.36
Severe disease	30/31 (97%)	29/38 (76%)	0.02
Relapse			
Mild disease	2/39 (5%)	3/37 (8%)	0.67
Severe disease	3/30 (10%)	6/29 (21%)	0.30

Although it is unconventional to use the toxin assay as a test-of-cure, only two patients were deemed failures only because of a positive toxin assay without persistent diarrhea or other evidence of clinical failure. The authors conclude that metronidazole and vancomycin are therapeutically equivalent for patients with *C. difficile* infection that is considered mild, but that vancomycin is superior in those with severe disease as described by this protocol.



COMPARISON OF DIAGNOSTIC TESTING ASSAYS

Musher DM, Manhas A, Jain P, et al. **Detection of *Clostridium difficile* toxin: comparison of enzyme immunoassay results with results obtained by cytotoxicity assay.** *J Clin Microbiol.* 2007;45:2737-9.

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Musher et al performed a two-stage test to investigate the relative merits of the enzyme immunoassay for *C. difficile* toxin A and toxin B versus the "gold standard" cytotoxin assay.

The first stage compared outcomes using the cytotoxin assay versus one commercially available EIA test for toxin A/B (EIAPREM™, Meridian Bioscience, Cincinnati OH). The results were based on 446 consecutive stool samples submitted to the clinical microbiology laboratory. Seventy-six showed positive results by cytotoxin assay, while the EIA test showed 75 positives; of the 370 samples that were negative by cytotoxin assay, 10 showed positive in the EIA test. Thus, the EIA test showed a sensitivity of 98.7% and a specificity of 97.3%, with a positive predictive value of 75/85 (88.2%) and a negative predictive value of 360/361 (99.7%). The conclusion of this first stage was that the correlation between these two tests was really quite good, particularly for the sensitivity of the EIA when compared to the cytotoxin assay.

These initial results led to the second phase of the study, in which 131 fresh fecal samples were tested by the cytotoxin assay versus three EIA tests from different reagent suppliers. The purpose was to determine the relative merits of the different commercially available immunoassays. Of the 131 samples selected, the cytotoxin assay was positive in 54 and negative in 77.

The following table summarizes the results with the different EIA kits from the three suppliers. While all three showed some minor variations, each of the EIA tests performed well compared to the cytotoxin assay in terms of sensitivity.

Table 2: Comparison of the Cytotoxin Assay with 3 Commercially Available EIA Tests

	Cytotoxin	EIA1	EIA2	EIA3
Positive	54	57	62	51
Negative	77	74	69	80
Discordant				
CT + EIA-	—	2	2	5
CT - EIA+	—	5	10	2

EIA1 = Premier Toxin A & B (Meridan Bioscience)

EIA2 = *C. DIFFICILE* TOX A/BII (EIA Tech; Tech Lab)

EIA3 = EIAPRO (Remel)

The authors conclude that the commercially available EIA tests showed good sensitivity and specificity compared to the cytotoxin assay - which, while considered the "gold standard", is more labor intensive and costly, and delays reported results.



THE CDC REPORT ON NAP1

Blossom DB, McDonald LC. **The challenges posed by reemerging *Clostridium difficile* infection.** *Clin Infect Dis.* 2007;45:222-7.

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The report from the CDC emphasizes the changing epidemiology of *C. difficile* and discusses the appearance of a new "hypervirulent strain" in North America and Europe. The following is a bulleted summary of this contemporary problem with *C. difficile* as viewed by experts from the CDC:

- **Increased Rates of *C. difficile* Infection:** The diagnosis of *C. difficile* by IDC-9 listings from short stay hospitals in the U.S. have shown relatively stable rates for the age category 15-64 years (<50/100,000 population), but a significant increase in persons >64 years, from approximately 170/100,000 population in the year 2000 to about 340/100,000 population in 2003.¹
- **The NAP1 Strain:** Much of this increase is attributed to a unique strain that was uncommon in prior reports of *C. difficile*, but then emerged with multiple near-simultaneous outbreaks in hospitals in the U.S., Quebec and several countries in Europe.^{2,3} This strain was identified by pulsed field electrophoresis as the NAP1 strain, by restriction enzyme analysis as the BI strain, by PCR as ribotype O27, and by toxin analysis of regulatory genes as toxinotype III. Although oversimplifying, the appellation of this new strain is referred by the method used to identify it: therefore, this is the "NAP1/BI/O27/toxinotype III" strain. While all of these terms are used interchangeably, many refer to it simply as the "NAP1" strain.
- **Virulence:** The virulence of this new epidemic strain is largely attributed to the production of substantial amounts of toxin according to *in vitro* assays, and this may reflect the deletion of *tcdC* which is a negative regulator of toxins A and B.^{2,4,5} This strain of *C. difficile* also produces a "binary toxin" which is related to the iota-toxin of *C. perfringens*. While this "binary toxin" seems to be a relatively good marker of the NAP1 strain, it is unclear if it represents any contribution to pathology, since it does not produce disease when inoculated into intestinal loops of experimental animals.
- **New Risk Factors:** The most important new observation is the high frequency of fluoroquinolones as inducing agents. The presumed explanation is the fact that the majority of NAP1 strains are highly resistant to this antibiotic, whereas the historic strains were almost uniformly sensitive. Another relatively new risk factor is agents that suppress gastric acid, especially proton pump inhibitors (PPIs), although the data on these are inconsistent.⁶
- **Diagnostic Challenges:** The majority of laboratories in the U.S. use EIAs, which are relatively easy to perform and give rapid results; however, EIAs show sensitivity rates of only 6-95% compared to cytotoxin assays. The authors note that many European laboratories offer culture followed by a test for toxigenic potential by the recovered strain, which may be the most sensitive test available.⁷
- **Treatment Concerns:** Failure rates with metronidazole in more recent reports have generally been 16-38%,^{8,9} and vancomycin is preferred for the more seriously ill patients. A second treatment problem is relapse. The previously reported rate was relatively consistent at 20%; now, with the emergence of the NAP1 strain, it is now reported as high as 50-65%.¹⁰ There are no clear guidelines for management, although human stool transplants "have shown some promise" and "few data support the use of probiotics".¹¹
- **Prevention Challenges:** Contact precautions are standard: patients should be in a single room with exclusive use of a bathroom (or patient cohorting), hand washing should be done with soap and water rather than alcohol-based

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sanitizers, and environmental cleaning should be done with a sporicidal such as a 1:10 dilution of household bleach. Antibiotic control is also important, especially in epidemics, where restricted use of clindamycin has proven successful.¹² Under current conditions, prevention may also require control of fluoroquinolones; the authors conclude that the restriction or reduced use should apply to all fluoroquinolones rather than specifically selected agents within the class.

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IMPACT OF EMERGENCY COLECTOMY

Lamontagne F, Labbe AC, Haeck O, Lesur O, Lalancette M, et al. **Impact of emergency colectomy on survival of patients with fulminant Clostridium difficile colitis during an epidemic caused by a hypervirulent strain**. *Ann Surg*. 2007;245:267-72.

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Lamontagne's group performed a retrospective analysis of patients who were seriously ill with *C. difficile*-associated diarrhea to determine factors that correlated with a lethal outcome. The only criterion for inclusion was transfer or direct admission to the ICU due to the severity of this complication. The study was done at the University of Sherbrooke in Quebec, Canada, which has been the source of much of the information about the NAP1 strain.

The study included 165 patients with diarrhea or colitis who had confirmed infections with *C. difficile* that were sufficiently severe to require hospitalization in the intensive care unit. Of these, 87 (53%) had an ultimately lethal outcome. Factors that correlated with the lethal outcome included the leukemoid reaction, elderly age,



lactic acidosis and immunosuppression. Of particular note was the fact that patients who underwent a colectomy had a risk ratio of 0.2, indicating an 80% reduction in mortality. These observations are summarized in Table 3.

Table 3: Correlates with Mortality in 87 of 165 (53%) patients who died after transfer to the ICU for severe *C. difficile* infection

Factor	Relative Risk of Death
WBC > 50,000/mm ³	18
Age > 75 years	7
Immunosuppression	9
Lactate > 5 mg/dh	12
Colectomy	0.2

The authors conclude that emergency colectomy substantially reduces the mortality associated with fulminant *C. difficile* infection.

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- Describe the contemporary standards for diagnosing and managing *C. difficile*-associated diarrhea

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- Explain the important changes in disease management that accompany the epidemic of the *C. difficile* NAP1 strain
- Discuss the role of oral vancomycin and oral metronidazole in *C. difficile*-associated diarrhea

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- **Paul G. Auwaerter, MD** has disclosed that he has served as a consultant for Novartis, Pfizer, Ortho-McNeil, Schering-Plough, and Genzyme. He is on the Speakers' Bureau for Schering-Plough and has also disclosed that he is a Stock Shareholder for Johnson & Johnson.
- **Sara E. Cosgrove, MD, MS** has disclosed that she has received grants or research support from Merck and served on the Advisory Boards for Ortho-McNeil, Cadence Pharmaceuticals, and Theravance/Astellas.

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