Perspectives on C. difficile Infections
Risk, Recurrence, and Refining Management Strategies

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Defining the Impact of C. difficile Infection

Clostridium difficile (C. difficile) is a gram positive, spore-forming rod. It causes disease through the production of the cytotoxic toxins A and B. Most patients who acquire C. difficile never develop symptoms but when it causes disease this can range from mild, self-limiting diarrhea to a fulminant, life-threatening colitis. It is primarily a healthcare-associated pathogen, and recent antibiotic exposure is the most important risk factor for infection. In the last decade a new predominant strain of C. difficile has been identified, commonly referred to as the BI, NAP1, and/or O27 strain, depending on the typing mechanism used. This strain is thought to have several important virulence factors, including increased production of toxins A and B, a third toxin (binary toxin), and fluoroquinolone resistance, and has been associated with dramatic increases in the incidence and severity of C. difficile infection (CDI). 1-3

Cases of CDI in US hospitals have continued to increase. According to the Agency for Healthcare Research and Quality Nationwide Inpatient Sample, there were approximately 139,000 patients discharged from acute care facilities who were diagnosed with CDI in 2000; this increased to 336,000 patients in 2008. This increase was observed in all types of hospitals in locations across the US. 6 The severity of CDI has also increased. In a 2002–2003 outbreak in Quebec, the attributable mortality was 17% 6 and an analysis of CDI-attributable outcomes in nonsurgical patients in St. Louis in 2003 reported attributable mortality of 6%. 6 The morbidity and healthcare costs associated with CDI are also substantial. In an analysis of an outbreak in St. Louis, CDI patients were 2.2-times more likely to be readmitted for acute care and 1.6 times more likely to be discharged to a long-term care facility (LTCF). 6 Although estimates of the increase in hospital costs attributable to CDI vary between $6,000 and $15,000 (2008 US dollars), 7-10 the attributable increase in length of stay has been consistent, with CDI patients spending approximately an additional 3 days in the hospital due to CDI. 8 This is important because the observed increase in cost is driven primarily by this increased duration of hospital stay. In addition, current estimates of costs attributable to CDI are probably underestimated; for example, indirect hospital costs include those associated with isolation of patients with CDI in semi-private rooms, thus preventing potential additional admissions. In addition, the current estimates do not include costs associated with outpatient treatment of CDI, or the costs associated with the increase in discharges to LTCFs. 8-11 An analysis of Medicare payments estimated that, of the costs of CDI including outpatient and LTCF costs, nearly three-quarters of the total ($10,268 of $16,593) were due to inpatient costs. 11 There is little information on the costs associated with CDI outside the hospital setting. 8-10

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Risk: Identifying the At-Risk Population

The most important traditional risk factor for CDI is exposure to antimicrobials, notably cephalosporins, clindamycin, and, more recently, ﬂuoroquinolones (Figure 1).13,14 Increasing age and severity of comorbid illness are also recognized risk factors for CDI. While CDI incidence has increased in all age groups, the incidence and rate of increase are greatest among patients aged over 65 years.

Figure 1. Risk Factors for CDI13-23

Traditional Risk Factors

- Antimicrobial exposure
  - High risk: cephalosporins, clindamycin, ﬂuoroquinolones (risk elevated <90 days after discontinuation – potentially <150 days)
  - Increasing age
  - Increasing severity of illness
  - Healthcare exposure
    - C. difﬁcile exposure, antimicrobial exposures, elderly, severity of illness (risk elevated <90 days after discharge)

Other Risk Factors

- Gastrointestinal surgery
- Inflammatory bowel disease
- Gastric acid suppression
- Proton pump inhibitors
- Immunosuppression

Community Associated CDIs

- Recent antimicrobial exposure in <70% (potentially as low as 40%)
- Still the major risk factor
- Younger and healthier than hospital acquired CDI
- Median age <85 years
- But, older and sicker than community controls
- ?Exposure to infants
- Wilcox (2006): 14% vs 2% exposure in controls (P=0.02)
- Pregnancy: Risk factor for severe CDI? – 38% with complication

Nontraditional risk factors have also been identiﬁed (Figure 1), and CDI is increasingly recognized within the community setting.14,17,21,23 Although recent antimicrobial exposure remains important, it is less frequently identiﬁed in community-associated than hospital-associated CDI (Figure 1).14,17,20,21,23 Data on the effect of gastric acid suppressants are conﬂicting and inconsistent.15,17 In a systematic review of the effects of proton pump inhibitor (PPI) therapy on the risk of enteric infection, the pooled adjusted relative risk (RR) range of CDI was 1.2 to 5.0 (17 of 27 studies).24 Although the absolute risk for an individual patient is small.25 Within the gastroenterology patient population, those with inﬂammatory bowel disease (IBD) are also at increased risk of CDI. These patients appear to have worse outcomes, with higher rates of hospitalization, surgery, and mortality compared to CDI patients who do not have IBD, or IBD patients who do not have CDI.26,27

Recurrence: Reviewing the Consequences of the Clinical Challenge

The objectives of therapy for CDI are to resolve symptoms and clear the infection.13 However, after initial clinical cure, a substantial proportion of patients will suffer recurrence; this proportion has increased with the emergence of the BI/NAP1/027 strain.28,29 The rate of recurrence is currently estimated to be 20 to 40% after the ﬁrst episode30,31 increasing to 45 to 65% with subsequent recurrences.32,33 Resistance to the two traditionally used antimicrobial agents, metronidazole and vancomycin, is rare and not sufﬁcient to explain initial treatment failures or recurrence.34

Currently accepted models of the pathogenesis of CDI suggest that patients colonized with C. difﬁcile who receive antimicrobial therapy have disrupted gut microﬂora, which allows C. difﬁcile to grow, if the infection is with a toxigenic strain, the patient is at risk of developing symptomatic CDI. Factors which make symptomatic disease more likely include low antibody response to C. difﬁcile toxins and underlying disease.34 After CDI therapy, the gut flora slowly recover, however, during this period the patient is at risk of recurrence as remaining spores or newly acquired spores germinate, grow, and release toxins. Later, the ﬂora may still be recovering, although there is increasing resistance to growth of C. difﬁcile and reacquisition of spores or the reintroduction of antimicrobials can lead to recurrent disease. One shortfall of established therapy for CDI is the effect that therapy has on gut microﬂora prolonging disruption and thus the time the gut is “permissive” of C. difﬁcile. Newer agents, including ﬁdadoxomicin, have more limited effects on bowel microﬁora, which would be anticipated to assist recovery of the gut after CDI.35,37

In a pooled analysis of two phase III trials of therapy for CDI conducted in North America and Europe, the risk of recurrence of CDI was increased with older age (>60 years old), concurrent cardiovascular disease, and renal impairment.38 Recurrence was also more likely in patients receiving concomitant antimicrobial therapy compared with those in whom antimicrobial therapy was discontinued (33% vs 15%). In these patients, it was further reported that initial response to CDI therapy was also reduced by continued antimicrobial therapy.39

Further analysis of recurrences in these studies, examined according to the time since CDI therapy was completed, indicated that “early” recurrence (within 2 weeks) was only inﬂuenced by treatment arm (ﬁdadoxomicin vs vancomycin). However, patient factors became more important predictors of late recurrence (Table 1 on page 3).38 The factors associated with late recurrence suggest that a substantial proportion of these cases may represent reinfection in individuals in whom the gut flora and mucosal integrity are still recovering, although this requires further study.
Refining Management Strategies: Options for Treating *C. difficile* Infection

In patients with CDI, the inciting antimicrobial agent should be discontinued as soon as practicable. For over 25 years, vancomycin and metronidazole have been the main treatment options for CDI. Although comparative studies are limited, and there is a notable lack of data from patients infected with the BI/NAP1/027 strain, it is generally accepted that metronidazole is inferior to vancomycin in patients with severe CDI in terms of initial clinical response. Patients treated with metronidazole may also have a longer time until resolution of symptoms.

Current Society for Healthcare Epidemiology of America/Infectious Diseases Society of America (SHEA/IDSA) recommendations for first episodes of CDI are that patients with “mild” or “moderate” CDI should receive oral metronidazole (which is not FDA-approved for this indication), while those with “severe” disease should be treated with oral vancomycin (Table 2). However, the definition of disease severity is largely subjective, based on consensus, and for example, differs from that used in the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Guidelines. A number of scoring tools to predict severity (in terms of outcomes and/or treatment response/nonresponse) have utilized clinical, laboratory, and/or imaging parameters. However, all have shortcomings or are only capable of identifying specific subpopulations (for example those with nonresponse to metronidazole) and remain unvalidated.

Using a composite score derived from age, temperature, white cell count, albumin, and simultaneous use of antibiotics, Miller and colleagues showed a correlation of this score with successful cure of CDI at the end of therapy. Chopra and colleagues demonstrated a correlation with this score and mortality in a cohort of older adults with CDI.

The most recent compound to become available for the treatment of CDI is fidaxomicin, a novel macrocyclic antibiotic with activity against *C. difficile* and limited activity against other gut flora. Systemic absorption of fidaxomicin is minimal.

Two identical phase III trials compared fidaxomicin 200 mg bid with vancomycin 125 mg qid. Initial clinical cure rates with fidaxomicin were consistent in both studies and were noninferior to vancomycin (Figure 2). Importantly, however, rates of recurrence were significantly lower with fidaxomicin in both studies (Figure 2).

In a multivariate, combined analysis of the two studies, the only factor associated with early (within 2 weeks) recurrence was treatment type (ie, fidaxomicin or vancomycin); the pooled odds ratio (OR) for recurrence was 0.34 in favor of fidaxomicin (95% confidence interval [CI] 0.22–0.53; *P*<0.001) (Figure 3 on page 4). Fidaxomicin was also associated with fewer recurrences in those individuals who continued to receive antibiotic therapy (16.9% vs 29.2%; *P*=0.048).

Novel agents currently in development for CDI include antibodies to toxins and other poorly absorbable antibiotics. There is also ongoing research into fecal microbiota transplantation (FMT) as a therapeutic approach. Although data are currently limited to small case series, some impressive responses have been reported for individuals with multiple recurrences. Concerns with FMT include the potential for transmission of pathogens, the nonstandardization of donor stool, and the obvious esthetic issues.

Probiotics—either alone or as adjuvant therapy—may appear an attractive option to aid reconstitution of the bowel microflora in patients with CDI. A meta-analysis found most studies to be of insufficient quality, although there was a significant reduction of

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**Table 1. Predictors of Early vs Late Recurrence of CDIs**

<table>
<thead>
<tr>
<th></th>
<th>No Recurrence (n=772)</th>
<th>Early Recurrence (n=129)</th>
<th>Late Recurrence (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Age &gt;60 years</td>
<td>55.1</td>
<td>62.0</td>
<td>ns</td>
</tr>
<tr>
<td>Concurrent cardiovascular disease</td>
<td>34.8</td>
<td>43.4</td>
<td>ns</td>
</tr>
<tr>
<td>At enrollment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin level &lt;2.5 g/L</td>
<td>19.5</td>
<td>24.4</td>
<td>ns</td>
</tr>
<tr>
<td>Creatinine clearance rate &lt;60 mL/min</td>
<td>25.0</td>
<td>33.1</td>
<td>ns</td>
</tr>
<tr>
<td>WBC count &gt;12,000/μL</td>
<td>25.0</td>
<td>29.3</td>
<td>ns</td>
</tr>
<tr>
<td>At the end of CDI therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin level &lt;2.5 g/L</td>
<td>11.6</td>
<td>17.0</td>
<td>ns</td>
</tr>
<tr>
<td>Creatinine clearance rate &lt;60 mL/min</td>
<td>27.9</td>
<td>29.6</td>
<td>ns</td>
</tr>
<tr>
<td>WBC count &gt;12,000/μL</td>
<td>9.6</td>
<td>11.0</td>
<td>ns</td>
</tr>
<tr>
<td>Time to diarrhea resolution &gt;60 hours</td>
<td>33.2</td>
<td>41.1</td>
<td>ns</td>
</tr>
<tr>
<td>Any antibiotic exposure during CDI therapy</td>
<td>17.8</td>
<td>20.9</td>
<td>ns</td>
</tr>
<tr>
<td>Any antibiotic exposure after completion of CDI therapy</td>
<td>19.3</td>
<td>17.8</td>
<td>ns</td>
</tr>
</tbody>
</table>

*Defined as the recurrence of CDI during follow-up days 1–14. *Defined as the recurrence of CDI during follow-up days 15–30.

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**Table 2. Current (2010) SHEA/IDSA Guidelines for CDI**

<table>
<thead>
<tr>
<th>Clinical Definition</th>
<th>Criteria</th>
<th>Recommended Treatment (first episode)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate</td>
<td>WBC &lt;15,000 and creatinine &lt;1.5 × patient’s baseline</td>
<td>Metronidazole 500 mg 3 times per day by mouth for 10–14 days</td>
</tr>
<tr>
<td>Severe</td>
<td>WBC &gt;15,000 or creatinine &gt;1.5 × patient’s baseline</td>
<td>Vancomycin 125 mg 4 times per day by mouth for 10–14 days</td>
</tr>
<tr>
<td>Severe, complicated</td>
<td>hypotension, shock, ileus, or megacolon due to CDI</td>
<td>Vancomycin 500 mg by mouth/NG tube 4 times per day + Metronidazole 500 mg 3 times per day (IV)</td>
</tr>
</tbody>
</table>

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**Figure 2. Fidaxomicin for CDI: Comparison With Vancomycin**

![Figure 2. Fidaxomicin for CDI: Comparison With Vancomycin](https://www.surveymonkey.com/s/1396E)

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recurrence in a subgroup of patients (RR 0.59, 95% CI 0.35–0.98) in one study. In the other study, recurrence in a subgroup of patients (RR 0.59, 95% CI 0.35–0.98) in one study. In the other

Recurrence

The authors concluded that there was insufficient evidence to recommend probiotics for CDI.

References


Figure 3. Fidaxomicin for CDI: Time to Recurrence

![Figure 3. Fidaxomicin for CDI: Time to Recurrence](https://www.surveymonkey.com/s/1396E)

Days From Treatment Completion

Proportion of Patients With No CDI Recurrence

<table>
<thead>
<tr>
<th>Fidaxomicin</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td>0.1</td>
<td>0.95</td>
</tr>
<tr>
<td>0.2</td>
<td>0.9</td>
</tr>
<tr>
<td>0.3</td>
<td>0.85</td>
</tr>
<tr>
<td>0.4</td>
<td>0.8</td>
</tr>
<tr>
<td>0.5</td>
<td>0.75</td>
</tr>
<tr>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>0.7</td>
<td>0.65</td>
</tr>
<tr>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>0.9</td>
<td>0.55</td>
</tr>
<tr>
<td>1.0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Log rank: P=0.001; Wilcoxon: P=0.001

Conclusion

With three antimicrobials now available for the treatment of CDI, treatment strategies require refinement. For example, an update to the SHEA/IDSA Guidelines, fidaxomicin might be considered instead of vancomycin for individuals at high risk of recurrence. Such therapy would be expected to be associated with reduced recurrence and, therefore, reduced healthcare utilization. However, it is not clear whether initial treatment with a more potent agent for all cases of CDI would further improve clinical outcomes or be cost-effective. Moreover, even although current guidelines suggest a stratified approach to management, there is presently no widely accepted clinical assessment tool to accurately and rapidly assess CDI in terms of severity, outcomes, risk of treatment failure, or recurrence.

The authors concluded that there was insufficient evidence to recommend probiotics for CDI.
**Perspectives on *C. difficile* Infections**

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**POST ACTIVITY QUESTIONS**

Instructions: For each question circle the most appropriate response.

1) **The highly virulent strain of *C. difficile* is termed:**

- A. BI
- B. NAP1
- C. 027
- D. All of the above

2) **Approximately, what is the attributable increase in hospital stay in patients with *C. difficile* infection?**

- A. None
- B. 1 day
- C. 3 days
- D. 7 days

3) **The most important traditional risk factor for *C. difficile* infection is recent antimicrobial exposure; true or false?**

- A. True
- B. False

4) **Recurrence of symptoms after resolution of *C. difficile* infection is due to resistance to metronidazole; true or false?**

- A. True
- B. False

5) **In Phase III clinical trials, which of the following best describes the outcomes of fidaxomicin therapy as compared with vancomycin therapy?**

- A. Cure and recurrence rates were similar
- B. Cure rates were equivalent, but recurrence was reduced with fidaxomicin
- C. Cure rates were improved with fidaxomicin
- D. Time to symptom resolution was longer with fidaxomicin

6) **In the clinical trials of fidaxomicin compared with vancomycin, patient factors become more important in determining the risk of late (>2 weeks) recurrence; true or false?**

- A. True
- B. False

7) A patient is admitted with suspected *C. difficile* infection following antibiotic therapy for sinusitis. Would you suspend therapy with the inciting antimicrobial?

- A. Yes
- B. No

- Would you await the results of toxin testing before initiating specific therapy for *C. difficile*?

- C. Yes
- D. No
We greatly value your opinion. Please complete this evaluation and submit it to the registration desk at the conclusion of this activity. Your responses will be used in future planning of activities and materials.

I am a(n): [ ] MD  [ ] DO  [ ] PharmD  [ ] RN  [ ] NP  [ ] PA  [ ] Other: ____________________________________________

Upon completion of this activity, participants will be able to:

<table>
<thead>
<tr>
<th>Description</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Describe the risk factors for, and consequences of, infection with C. difficile</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Explain the current clinical unmet needs and the impact of nonsustained response in terms of further treatment options</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Review the outcomes of therapy for C. difficile with FDA-approved and non-approved antibiotic therapy</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>Identify best practice prevention and management strategies for C. difficile infection</td>
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<td>3</td>
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Please indicate the extent of your agreement with the following statements:

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<thead>
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<th>Statement</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Agree</th>
<th>Strongly Agree</th>
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<tr>
<td>The faculty for this activity were effective</td>
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<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>The teaching and learning methods were effective</td>
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<tr>
<td>The learning assessment used for this activity was appropriate</td>
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<td>2</td>
<td>3</td>
<td>4</td>
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</table>

Overall, was this activity free from bias?
[ ] Yes  [ ] No

Of the patients you will see in the next week, about how many will benefit from the information you learned today?
[ ] More than 50 patients  
[ ] 26 to 50 patients  
[ ] 11 to 25 patients  
[ ] 1 to 10 patients  
[ ] Not applicable

Based on what I learned today, I will improve my practice by incorporating the following [check all that apply]:
[ ] Improved diagnosis/patient assessment  
[ ] Useful therapies and appropriate uses  
[ ] Cutting-edge science in this therapeutic area  
[ ] Best practices of my colleagues and leaders  
[ ] Other (explain): __________________________

Please rank each CME delivery method/format within C. difficile that is most effective for learning (1=least effective to 6=most effective):

<table>
<thead>
<tr>
<th>Method/format</th>
<th>Rank</th>
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<tr>
<td>Live symposia at national/regional conferences</td>
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<td>Live local meetings</td>
<td>2</td>
</tr>
<tr>
<td>Live grand rounds</td>
<td>3</td>
</tr>
<tr>
<td>Internet webcasts</td>
<td>4</td>
</tr>
<tr>
<td>Internet/print monographs</td>
<td>5</td>
</tr>
<tr>
<td>Other (explain)</td>
<td>6</td>
</tr>
</tbody>
</table>

Please rank the professional practice value of today’s educational event against each of the following forms of information/education in terms of improving your practice (1=least valuable to 5=most valuable):

<table>
<thead>
<tr>
<th>Form of Information/education</th>
<th>Rank</th>
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<tr>
<td>Sales representative visits</td>
<td>3</td>
</tr>
<tr>
<td>Non-certified education</td>
<td>4</td>
</tr>
<tr>
<td>Other (explain)</td>
<td>5</td>
</tr>
</tbody>
</table>

Based on your experience, which of the following are the primary barriers to implementing changes in practice [check all that apply]:
[ ] Lack of knowledge regarding evidence-based strategies  
[ ] Lack of convincing evidence to warrant change  
[ ] Lack of time/resources to consider change  
[ ] Insurance, reimbursement, or legal issues  
[ ] Other (explain): __________________________

What motivated you to participate in this activity?
[ ] CME credits  
[ ] Faculty  
[ ] Topic or therapeutic area  
[ ] Format type