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Clinical Practice Guidelines for Clostridium difficile Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) •

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## SHEA-IDS A GUIDELINE

# Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA)

Stuart H. Cohen, MD; Dale N. Gerding, MD; Stuart Johnson, MD; Ciaran P. Kelly, MD; Vivian G. Loo, MD; L. Clifford McDonald, MD; Jacques Pepin, MD; Mark H. Wilcox, MD

Since publication of the Society for Healthcare Epidemiology of America position paper on *Clostridium difficile* infection in 1995, significant changes have occurred in the epidemiology and treatment of this infection. *C. difficile* remains the most important cause of healthcare-associated diarrhea and is increasingly important as a community pathogen. A more virulent strain of *C. difficile* has been identified and has been responsible for more-severe cases of disease worldwide. Data reporting the decreased effectiveness of metronidazole in the treatment of severe disease have been published. Despite the increasing quantity of data available, areas of controversy still exist. This guideline updates recommendations regarding epidemiology, diagnosis, treatment, and infection control and environmental management.

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## EXECUTIVE SUMMARY

This guideline is designed to improve the diagnosis and management of *Clostridium difficile* infection (CDI) in adult patients. A case of CDI is defined by the presence of symptoms (usually diarrhea) and either a stool test positive for *C. difficile* toxins or toxigenic *C. difficile*, or colonoscopic or histopathologic findings revealing pseudomembranous colitis. In addition to diagnosis and management, recommended methods of infection control and environmental management of the pathogen are presented. The recommendations are based on the best available evidence and practices, as determined by a joint Expert Panel appointed by SHEA and the Infectious Diseases Society of America (IDSA) (the SHEA-IDS A Expert Panel). The use of these guidelines can be impacted by the size of the institution and the resources, both financial and laboratory, available in the particular clinical setting.

**I. Epidemiology: What are the minimum data that should be collected for surveillance purposes and how should the data be reported?**

1. To increase comparability between clinical settings, use available standardized case definitions for surveillance of (1) healthcare facility (HCF)-onset, HCF-associated CDI; (2) community-onset, HCF-associated CDI; and (3) community-associated CDI (Figure 1) **(B-III)**.

2. At a minimum, conduct surveillance for HCF-onset, HCF-associated CDI in all inpatient healthcare facilities, to detect outbreaks and monitor patient safety **(B-III)**.

3. Express the rate of healthcare-associated CDI as the number of cases per 10,000 patient-days **(B-III)**.

4. If CDI rates are high compared with those at other facilities or if an outbreak is noted, stratify rates by patient location in order to target control measures **(B-III)**.

**II. Diagnosis: What is the best testing strategy to diagnose CDI in the clinical laboratory and what are acceptable options?**

5. Testing for *C. difficile* or its toxins should be performed only on diarrheal (unformed) stool, unless ileus due to *C. difficile* is suspected **(B-II)**.

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6. Testing of stool from asymptomatic patients is not clinically useful, including use as a test of cure. It is not recommended, except for epidemiological studies. **(B-III)**

7. Stool culture is the most sensitive test and is essential for epidemiological studies **(A-II)**.

8. Although stool culture is not clinically practical because of its slow turnaround time, the sensitivity and specificity of stool culture followed by identification of a toxigenic isolate (ie, toxigenic culture), as performed by an experienced laboratory, provides the standard against which other clinical test results should be compared **(B-III)**.

9. Enzyme immunoassay (EIA) testing for *C. difficile* toxin A and B is rapid but is less sensitive than the cell cytotoxin assay, and it is thus a suboptimal alternative approach for diagnosis **(B-II)**.

10. Toxin testing is most important clinically, but is hampered by its lack of sensitivity. One potential strategy to overcome this problem is a 2-step method that uses EIA detection of glutamate dehydrogenase (GDH) as initial screening and then uses the cell cytotoxicity assay or toxigenic culture as the confirmatory test for GDH-positive stool specimens only. Results appear to differ based on the GDH kit used; therefore, until more data are available on the sensitivity of GDH testing, this approach remains an interim recommendation. **(B-II)**

11. Polymerase chain reaction (PCR) testing appears to be rapid, sensitive, and specific and may ultimately address testing concerns. More data on utility are necessary before this methodology can be recommended for routine testing. **(B-II)**

12. Repeat testing during the same episode of diarrhea is of limited value and should be discouraged **(B-II)**.

### III. Infection Control and Prevention: What are the most important infection control measures to implement in the hospital during an outbreak of CDI?

#### A. Measures for Healthcare Workers, Patients, and Visitors

13. Healthcare workers and visitors must use gloves **(A-I)** and gowns **(B-III)** on entry to a room of a patient with CDI.

14. Emphasize compliance with the practice of hand hygiene **(A-II)**.

15. In a setting in which there is an outbreak or an increased CDI rate, instruct visitors and healthcare workers to wash hands with soap (or antimicrobial soap) and water after caring for or contacting patients with CDI **(B-III)**.

16. Accommodate patients with CDI in a private room with contact precautions **(B-III)**. If single rooms are not available, cohort patients, providing a dedicated commode for each patient **(C-III)**.

17. Maintain contact precautions for the duration of diarrhea **(C-III)**.

18. Routine identification of asymptomatic carriers (patients or healthcare workers) for infection control purposes

is not recommended **(A-III)** and treatment of such identified patients is not effective **(B-I)**.

#### B. Environmental Cleaning and Disinfection

19. Identification and removal of environmental sources of *C. difficile*, including replacement of electronic rectal thermometers with disposables, can reduce the incidence of CDI **(B-II)**.

20. Use chlorine-containing cleaning agents or other sporicidal agents to address environmental contamination in areas associated with increased rates of CDI **(B-II)**.

21. Routine environmental screening for *C. difficile* is not recommended **(C-III)**.

#### C. Antimicrobial Use Restrictions

22. Minimize the frequency and duration of antimicrobial therapy and the number of antimicrobial agents prescribed, to reduce CDI risk **(A-II)**.

23. Implement an antimicrobial stewardship program **(A-II)**. Antimicrobials to be targeted should be based on the local epidemiology and the *C. difficile* strains present, but restricting the use of cephalosporin and clindamycin (except for surgical antibiotic prophylaxis) may be particularly useful **(C-III)**.

#### D. Use of Probiotics

24. Administration of currently available probiotics is not recommended to prevent primary CDI, as there are limited data to support this approach and there is a potential risk of bloodstream infection **(C-III)**.

### IV. Treatment: Does the choice of drug for CDI matter and, if so, which patients should be treated and with which agent?

25. Discontinue therapy with the inciting antimicrobial agent(s) as soon as possible, as this may influence the risk of CDI recurrence **(A-II)**.

26. When severe or complicated CDI is suspected, initiate empirical treatment as soon as the diagnosis is suspected **(C-III)**.

27. If the stool toxin assay result is negative, the decision to initiate, stop, or continue treatment must be individualized **(C-III)**.

28. If possible, avoid use of antiperistaltic agents, as they may obscure symptoms and precipitate toxic megacolon **(C-III)**.

29. Metronidazole is the drug of choice for the initial episode of mild-to-moderate CDI. The dosage is 500 mg orally 3 times per day for 10–14 days. **(A-I)**

30. Vancomycin is the drug of choice for an initial episode of severe CDI. The dosage is 125 mg orally 4 times per day for 10–14 days. **(B-I)**

31. Vancomycin administered orally (and per rectum, if ileus is present) with or without intravenously administered metronidazole is the regimen of choice for the treat-

ment of severe, complicated CDI. The vancomycin dosage is 500 mg orally 4 times per day and 500 mg in approximately 100 mL normal saline per rectum every 6 hours as a retention enema, and the metronidazole dosage is 500 mg intravenously every 8 hours. (C-III)

32. Consider colectomy for severely ill patients. Monitoring the serum lactate level and the peripheral blood white blood cell count may be helpful in prompting a decision to operate, because a serum lactate level rising to 5 mmol/L and a white blood cell count rising to 50,000 cells per  $\mu$ L have been associated with greatly increased perioperative mortality. If surgical management is necessary, perform subtotal colectomy with preservation of the rectum. (B-II)

33. Treatment of the first recurrence of CDI is usually with the same regimen as for the initial episode (A-II) but should be stratified by disease severity (mild-to-moderate, severe, or severe complicated), as is recommended for treatment of the initial CDI episode (C-III).

34. Do not use metronidazole beyond the first recurrence of CDI or for long-term chronic therapy because of potential for cumulative neurotoxicity (B-II).

35. Treatment of the second or later recurrence of CDI with vancomycin therapy using a tapered and/or pulse regimen is the preferred next strategy (B-III).

36. No recommendations can be made regarding prevention of recurrent CDI in patients who require continued antimicrobial therapy for the underlying infection (C-III).

## INTRODUCTION

### Summary Definition of CDI

A case definition of CDI should include the presence of symptoms (usually diarrhea) and either a stool test result positive for *C. difficile* toxins or toxigenic *C. difficile*, or colonoscopic findings demonstrating pseudomembranous colitis.

### Definition of CDI

The diagnosis of CDI should be based on a combination of clinical and laboratory findings. A case definition for the usual presentation of CDI includes the following findings: (1) the presence of diarrhea, defined as passage of 3 or more unformed stools in 24 or fewer consecutive hours<sup>1-8</sup>; (2) a stool test result positive for the presence of toxigenic *C. difficile* or its toxins or colonoscopic or histopathologic findings demonstrating pseudomembranous colitis. The same criteria should be used to diagnose recurrent CDI. A history of treatment with antimicrobial or antineoplastic agents within the previous 8 weeks is present for the majority of patients.<sup>9</sup> In clinical practice, antimicrobial use is often considered part of the operative definition of CDI, but it is not included here because of occasional reports of CDI in the absence of antimicrobial use, usually in community-acquired cases.<sup>10</sup> A response to specific therapy for CDI is suggestive of the diagnosis. Rarely (in fewer than 1% of cases), a symptomatic

patient will present with ileus and colonic distension with minimal or no diarrhea.<sup>11</sup> Diagnosis in these patients is difficult; the only specimen available may be a small amount of formed stool or a swab of stool obtained either from the rectum or from within the colon via endoscopy. In such cases, it is important to communicate to the laboratory the necessity to do a toxin assay or culture for *C. difficile* on the nondiarrheal stool specimen.

### Background

The vast majority of anaerobic infections arise from endogenous sources. However, a number of important clostridial infections and intoxications are caused by organisms acquired from exogenous sources. It is the ability of these organisms to produce spores that explains how *C. difficile*, a fastidiously anaerobic organism in its vegetative state, can be acquired from the environment. *C. difficile* is recognized as the primary pathogen responsible for antibiotic-associated colitis and for 15%–25% of cases of nosocomial antibiotic-associated diarrhea.<sup>12-14</sup>

*C. difficile* can be detected in stool specimens of many healthy children under the age of 1 year<sup>15,16</sup> and a few percent of adults.<sup>17,18</sup> Although these data support the potential for endogenous sources of human infection, there was early circumstantial evidence to suggest that this pathogen could be transmissible and acquired from external sources. Cases often appear in clusters and outbreaks within institutions.<sup>19,20</sup> Animal models of disease also provide evidence for transmissibility of *C. difficile*.<sup>21,22</sup> Subsequently, many epidemiologic studies of CDI confirm the importance of *C. difficile* as a transmissible nosocomial pathogen.<sup>1,9,23-25</sup>

### Clinical Manifestations

The clinical manifestations of infection with toxin-producing strains of *C. difficile* range from symptomless carriage, to mild or moderate diarrhea, to fulminant and sometimes fatal pseudomembranous colitis.<sup>13,14,26</sup> Several studies have shown that 50% or more of hospital patients colonized by *C. difficile* are symptomless carriers, possibly reflecting natural immunity.<sup>1,3,5,27</sup> Olson et al<sup>28</sup> reported that 96% of patients with symptomatic *C. difficile* infection had received antimicrobials within the 14 days before the onset of diarrhea and that all had received an antimicrobial within the previous 3 months. Symptoms of CDI usually begin soon after colonization, with a median time to onset of 2–3 days.<sup>1,5,23,27</sup>

*C. difficile* diarrhea may be associated with the passage of mucus or occult blood in the stool, but melena or hematochezia are rare. Fever, cramping, abdominal discomfort, and a peripheral leukocytosis are common but found in fewer than half of patients.<sup>11,13,14,29</sup> Extraintestinal manifestations, such as arthritis or bacteremia, are very rare.<sup>30-33</sup> *C. difficile* ileitis or pouchitis has also been rarely recognized in patients who have previously undergone a total colectomy (for complicated CDI or some other indication).<sup>34</sup> Clinicians should

TABLE 1. Definitions of the Strength of Recommendations and the Quality of the Evidence Supporting Them

Category and grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for <i>or against</i> use
B	Moderate evidence to support a recommendation for <i>or against</i> use
C	Poor evidence to support a recommendation
Quality of evidence	
I	Evidence from at least 1 properly randomized, controlled trial
II	Evidence from at least 1 well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than 1 center), from multiple time-series, or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

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consider the possibility of CDI in hospitalized patients who have unexplained leukocytosis, and they should request stool be sent for diagnostic testing.<sup>35,36</sup> Patients with severe disease may develop a colonic ileus or toxic dilatation and present with abdominal pain and distension but with minimal or no diarrhea.<sup>11,13,14</sup> Complications of severe *C. difficile* colitis include dehydration, electrolyte disturbances, hypoalbuminemia, toxic megacolon, bowel perforation, hypotension, renal failure, systemic inflammatory response syndrome, sepsis, and death.<sup>11,24,25</sup>

### Clinical Questions for the 2010 Update

In 1995, the Society for Healthcare Epidemiology of America (SHEA) published a clinical position paper on *C. difficile*-associated disease and colitis.<sup>37</sup> For the current update, the epidemiology, diagnosis, infection control measures, and indications and agents for treatment from the 1995 position paper were reviewed by a joint Expert Panel appointed by SHEA and the Infectious Diseases Society of America (IDSA). The previous document is a source for a more detailed review of earlier studies.

The SHEA-IDSA Expert Panel addressed the following clinical questions in this update:

- I. What are the minimum data that should be collected for surveillance purposes, and how should the data be reported? Have the risk factors for CDI changed?
- II. What is the best testing strategy to diagnose CDI in the clinical laboratory and what are acceptable options?
- III. What are the most important infection control measures to implement in the hospital during an outbreak of CDI?
- IV. Does the choice of drug for treatment of CDI matter and, if so, which patients should be treated and with which agent?

### PRACTICE GUIDELINES DEFINITION

“Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions

about appropriate health care for specific clinical circumstances.”<sup>38(p8)</sup> Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation.”<sup>38(p8)</sup>

### UPDATE METHODOLOGY

#### Panel Composition

The SHEA Board of Directors and the IDSA Standards and Practice Guidelines Committee convened a panel of experts in the epidemiology, diagnosis, infection control, and clinical management of adult patients with CDI to develop these practice guidelines.

#### Literature Review and Analysis

For the 2010 update, the SHEA-IDSA Expert Panel completed the review and analysis of data published since 1994. Computerized literature searches of PubMed were performed. The searches of the English-language literature from 1994 through April 2009 used the terms “*Clostridium difficile*,” “epidemiology,” “treatment,” and “infection control” and focused on human studies.

#### Process Overview

In evaluating the evidence regarding the management of CDI, the Expert Panel followed a process used in the development of other SHEA-IDSA guidelines. The process included a systematic weighting of the quality of the evidence and the strength of each recommendation (Table 1).<sup>39</sup>

#### Guidelines and Conflict of Interest

All members of the Expert Panel complied with the SHEA and IDSA policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel were provided with the SHEA and IDSA conflict of interest disclosure statement and

were asked to identify ties to companies developing products that might be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory boards or committees. The Expert Panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. No limiting conflicts were identified.

### Revision Dates

At annual intervals, SHEA and IDSA will determine the need for revisions to the guideline on the basis of an examination of the current literature and the likelihood that any new data will have an impact on the recommendations. If necessary, the entire Expert Panel will be reconvened to discuss potential changes. Any revision to the guideline will be submitted for review and approval to the appropriate Committees and Boards of SHEA and IDSA.

## GUIDELINE RECOMMENDATIONS FOR *CLOSTRIDIUM DIFFICILE* INFECTION (CDI)

### I. WHAT ARE THE MINIMUM DATA THAT SHOULD BE COLLECTED FOR SURVEILLANCE PURPOSES, AND HOW SHOULD THE DATA BE REPORTED?

#### Recommendations

1. To increase comparability between clinical settings, use available standardized case definitions for surveillance of (1) healthcare facility (HCF)-onset, HCF-associated CDI; (2) community-onset, HCF-associated CDI; and (3) community-associated CDI (Figure 1) (B-III).
2. At a minimum, conduct surveillance for HCF-onset, HCF-associated CDI in all inpatient healthcare facilities, to detect outbreaks and monitor patient safety (B-III).
3. Express the rate of healthcare-associated CDI as the number of cases per 10,000 patient-days (B-III).
4. If CDI rates are high compared with those at other

facilities or if an outbreak is noted, stratify rates by patient location in order to target control measures (B-III).

#### Evidence Summary

**Prevalence, incidence, morbidity, and mortality.** *C. difficile* accounts for 20%–30% of cases of antibiotic-associated diarrhea<sup>12</sup> and is the most commonly recognized cause of infectious diarrhea in healthcare settings. Because *C. difficile* infection is not a reportable condition in the United States, there are few surveillance data. However, based upon surveys of Canadian hospitals conducted in 1997 and 2005, incidence rates range from 3.8 to 9.5 cases per 10,000 patient-days, or 3.4 to 8.4 cases per 1,000 admissions, in acute care hospitals.<sup>40,41</sup>

Although there are no regional or national CDI surveillance data for long-term care facilities, patients in these settings are often elderly and have been exposed to antimicrobials, both important risk factors for CDI, suggesting that rates of disease and/or colonization<sup>42,43</sup> could potentially be high.<sup>43</sup> A recent analysis of US acute care hospital discharges found that the number of patients transferred to a long-term care facility with a discharge diagnosis of CDI doubled between 2000 and 2003; in 2003, nearly 2% of patients transferred on discharge from an acute care hospital to a long-term care facility carried the diagnosis of CDI. Historically, the attributable mortality of CDI has been low, with death as a direct or indirect result of infection occurring in less than 2% of cases.<sup>28,40,44</sup> However, the attributable excess costs of CDI suggest a substantial burden on the healthcare system. From 1999–2003 in Massachusetts, a total of 55,380 inpatient-days and \$55.2 million were consumed by management of CDI. An estimate of the annual excess hospital costs in the US is \$3.2 billion per year for the years 2000–2002.<sup>45</sup>

**Changing epidemiology.** Recently, the epidemiology of CDI changed dramatically; an increase in overall incidence has been highlighted by outbreaks of more-severe disease than previously observed. An examination of US acute care hospital discharge data revealed that, beginning in 2001, there was an abrupt increase in the number and proportion of patients discharged from the hospital with the diagnosis of “intestinal infection due to *Clostridium difficile*” (*International*



FIGURE 1. Time line for surveillance definitions of *Clostridium difficile*-associated infection (CDI) exposures. A case patient who had symptom onset during the window of hospitalization marked by an asterisk (\*) would be classified as having community-onset, healthcare facility-associated disease (CO-HCFA), if the patient had been discharged from a healthcare facility within the previous 4 weeks; would be classified as having indeterminate disease, if the patient had been discharged from a healthcare facility within the previous 4–12 weeks; or would be classified as having community-associated CDI (CA-CDI), if the patient had not been discharged from a healthcare facility in the previous 12 weeks. HO-HCFA, healthcare facility-onset, healthcare facility-associated CDI.

*Classification of Diseases, Clinical Modification, 9th edition, code 008.45*).<sup>46</sup> Discharge rates increased most dramatically among persons aged 65 years or more and were more than 5-fold higher in this age group than among individuals aged 45–64 years.

Beginning as early as the second half of 2002 and extending through 2006, hospital outbreaks of unusually severe<sup>25</sup> and recurrent<sup>47</sup> CDI were noted in hospitals throughout much of Quebec, Canada. These outbreaks were, like slightly earlier outbreaks in the United States,<sup>48</sup> associated with the use of fluoroquinolones.<sup>25</sup> An assessment found that the 30-day mortality directly attributable to CDI in Montreal hospitals during this period was 6.9%, but CDI was thought to have contributed indirectly to another 7.5% of deaths.<sup>25</sup> The etiological agents of outbreaks both in Quebec and in at least 8 hospitals in 6 US states were nearly identical strains of *C. difficile*.<sup>24,25</sup> This strain has become known variously by its restriction endonuclease analysis pattern, BI<sup>24</sup>; by its pulsed-field gel electrophoresis (PFGE) pattern, NAP1 (for North American PFGE type 1); or by its PCR ribotype designation, 027; it is now commonly designated “NAP1/BI/027.” This strain accounted for 67%–82% of isolates in Quebec,<sup>25</sup> which implies that it might be transmitted more effectively than are other strains. It also possesses, in addition to genes coding for toxins A and B, a gene encoding for the binary toxin. Although the importance of binary toxin as a virulence factor in *C. difficile* has not been established, earlier studies found the toxin was only present in about 6% of isolates.<sup>24</sup> In addition, the epidemic strain has an 18–base pair deletion and an apparently novel single–base pair deletion in *tcdC*,<sup>24,25</sup> a putative negative regulator of expression of toxins A and/or B that is located within the pathogenicity locus downstream from the genes encoding toxins A and B. Consistent with the presence of 1 or more of these molecular markers or other yet undiscovered factors responsible for increased virulence, patients infected with the NAP1/BI/027 epidemic strain in Montreal were shown to have more-severe disease than were patients infected with other strains.<sup>25</sup>

Increased virulence alone may not explain why the NAP1/BI/027 strain has recently become highly prevalent, as it appears this same strain had been an infrequent cause of CDI in North America and Europe dating back to the 1980s.<sup>24</sup> Historic and recent isolates of the NAP1/BI/027 strain differ in their level of resistance to fluoroquinolones; more recent isolates are more highly resistant to these drugs.<sup>24</sup> This, coupled with increasing use of the fluoroquinolones in North American hospitals, likely promoted dissemination of a once-uncommon strain. As of this writing, the NAP1/BI/027 strain has spread to at least 40 US states<sup>24,49</sup> and 7 Canadian provinces,<sup>50</sup> and has caused outbreaks in England,<sup>51,52</sup> parts of continental Europe,<sup>53,54</sup> and Asia.<sup>55</sup>

**CDI in populations previously at low risk.** In the context of the changing epidemiology of CDI in hospitals, disease is occurring among healthy peripartum women, who have been previously at very low risk for CDI.<sup>56,57</sup> The incidence might

also be increasing among persons living in the community, including, but not limited to, healthy persons without recent healthcare contact.<sup>56,58–61</sup> However, there are limited historical data against which to compare the recent incidence.<sup>62–64</sup>

**Routes of transmission and the epidemiology of colonization and infection.** The primary mode of *C. difficile* transmission resulting in disease is person-to-person spread through the fecal-oral route, principally within inpatient healthcare facilities. Studies have found that the prevalence of asymptomatic colonization with *C. difficile* is 7%–26% among adult inpatients in acute care facilities<sup>1,27</sup> and is 5%–7% among elderly patients in long-term care facilities.<sup>42,65</sup> Other studies, however, indicate that the prevalence of asymptomatic colonization may be more on the order of 20%–50% in facilities where CDI is endemic.<sup>9,66,67</sup> The risk of colonization increases at a steady rate during hospitalization, suggesting a cumulative daily risk of exposure to *C. difficile* spores in the healthcare setting.<sup>1</sup> Other data suggest that the prevalence of *C. difficile* in the stool among asymptomatic adults without recent healthcare facility exposure is less than 2%.<sup>16,17</sup> Newborns and children in the first year of life are known to have some of the highest rates of colonization.<sup>68</sup>

The usual incubation period from exposure to onset of CDI symptoms is not known with certainty; however, in contrast to the situation with other multidrug-resistant pathogens that cause healthcare-associated infections, persons who remain asymptotically colonized with *C. difficile* over longer periods of time appear to be at decreased, rather than increased, risk for development of CDI.<sup>1,3,5,69</sup> The protection afforded by more long-standing colonization may be mediated in part by the boosting of serum antibody levels against *C. difficile* toxins A and B<sup>5,69</sup>; however, this protection is also observed, both in humans and in animal models, when colonization occurs with nontoxigenic strains, which suggests competition for nutrients or for access to the mucosal surface.<sup>3,70</sup>

The period between exposure to *C. difficile* and the occurrence of CDI has been estimated in 3 studies to be a median of 2–3 days.<sup>1,22,27</sup> This is to be distinguished from the increased risk of CDI that can persist for many weeks after cessation of antimicrobial therapy and which results from prolonged perturbation of the normal intestinal flora.<sup>71</sup> However, recent evidence suggests that CDI resulting from exposure to *C. difficile* in a healthcare facility can have onset after discharge.<sup>72–74</sup> The hands of healthcare workers, transiently contaminated with *C. difficile* spores, are probably the main means by which the organism is spread during non-outbreak periods.<sup>1,66</sup>

Environmental contamination also has an important role in transmission of *C. difficile* in healthcare settings.<sup>75–78</sup> There have also been outbreaks in which particular high-risk fomites, such as electronic rectal thermometers or inadequately cleaned commodes or bedpans, were shared between patients and were found to contribute to transmission.<sup>79</sup>

**Risk factors for disease.** Advanced age is one of the most

important risk factors for CDI, as evidenced by the several-fold higher age-adjusted rate of CDI among persons more than 64 years of age.<sup>46,80</sup> In addition to advanced age, duration of hospitalization is a risk factor for CDI; the daily increase in the risk of *C. difficile* acquisition during hospitalization suggests that duration of hospitalization is a proxy for the duration, if not the degree, of exposure to the organism from other patients with CDI.<sup>1</sup>

The most important modifiable risk factor for the development of CDI is exposure to antimicrobial agents. Virtually every antimicrobial has been associated with CDI through the years. The relative risk of therapy with a given antimicrobial agent and its association with CDI depends on the local prevalence of strains that are highly resistant to that particular antimicrobial agent.<sup>81</sup>

Receipt of antimicrobials increases the risk of CDI because it suppresses the normal bowel flora, thereby providing a “niche” for *C. difficile* to flourish. Both longer exposure to antimicrobials, as opposed to shorter exposure,<sup>47</sup> and exposure to multiple antimicrobials, as opposed to exposure to a single agent, increase the risk for CDI.<sup>47</sup> Nonetheless, even very limited exposure, such as single-dose surgical antibiotic prophylaxis, increases a patient’s risk of both *C. difficile* colonization<sup>82</sup> and symptomatic disease.<sup>83</sup>

Cancer chemotherapy is another risk factor for CDI that is, at least in part, mediated by the antimicrobial activity of several chemotherapeutic agents<sup>84,85</sup> but could also be related to the immunosuppressive effects of neutropenia.<sup>86,87</sup> Recent evidence suggests that *C. difficile* has become the most important pathogen causing bacterial diarrhea in US patients infected with human immunodeficiency virus (HIV), which suggests that these patients are at specific increased risk because of their underlying immunosuppression, exposure to antimicrobials, exposure to healthcare settings, or some combination of those factors.<sup>88</sup> Other risk factors for CDI include gastrointestinal surgery<sup>89</sup> or manipulation of the gastrointestinal tract, including tube feeding.<sup>90</sup> Another potential and somewhat controversial risk factor is related to breaches in the protective effect of stomach acid that result from the use of acid-suppressing medications, such as histamine-2 blockers and proton pump inhibitors. Although a number of recent studies have suggested an epidemiologic association between use of stomach acid-suppressing medications, primarily proton pump inhibitors, and CDI,<sup>48,61,91-93</sup> results of other well controlled studies have suggested this association is the result of confounding with the underlying severity of illness and duration of hospital stay.<sup>25,47,94</sup>

**Surveillance.** There are few data on which to base a decision about how best to perform surveillance for CDI, either in healthcare or community settings. Nonetheless, interim recommendations have been put forth that, although not evidence-based, could serve to make rates more comparable among different healthcare facilities and systems.<sup>95</sup> There is a current need for all healthcare facilities that provide skilled nursing care to conduct CDI surveillance, and some local or

regional systems may be interested in tracking emerging community-associated disease, particularly in view of the changing epidemiology of CDI. A recommended case definition for surveillance requires (1) the presence of diarrhea or evidence of megacolon and (2) either a positive laboratory diagnostic test result or evidence of pseudomembranes demonstrated by endoscopy or histopathology. If a laboratory only performs *C. difficile* diagnostic testing on stool from patients with diarrhea, this case definition should involve tracking of patients with a new primary positive assay result (ie, those with no positive result within the previous 8 weeks) or a recurrent positive assay result (ie, those with a positive result within the previous 2–8 weeks).

It appears that many, if not most, patients who have the onset of CDI symptoms shortly after discharge from a healthcare facility (ie, within 1 month) acquired *C. difficile* while in the facility and that these case patients may have an important impact on overall rates. Nonetheless, it is not known whether tracking of healthcare-acquired, community-onset CDI (ie, postdischarge cases) is necessary to detect healthcare-facility outbreaks or make meaningful comparisons between facilities.<sup>95</sup> What is clear is that tracking CDI cases with symptom onset at least 48 hours after inpatient admission is the minimum surveillance that should be performed by all healthcare facilities. In addition, if interfacility comparisons are to be performed, they should only be performed using similar case definitions. Because the risk of CDI increases with the length of stay, the most appropriate denominator for healthcare facility CDI rates is the number of patient-days. If a facility notes an increase in the incidence of CDI from the baseline rate, or if the incidence is higher than in comparable institutions, surveillance data should be stratified by hospital location to identify particular wards or units where transmission is occurring more frequently, so that intensified control measures may be targeted. In addition, measures should be considered for tracking severe outcomes, such as colectomy, intensive care unit admission, or death, attributable to CDI. Comparison of incidence rates between hospitals in a given state or region could be more meaningful if rates are age-standardized (because the age distribution of inpatients may vary substantially between facilities) or are limited to specific age groups.

A current surveillance definition for community-associated CDI is as follows: disease in persons with no overnight stay in an inpatient healthcare facility in at least the 12 weeks prior to symptom onset.<sup>10,95</sup> A reasonable denominator for community-associated CDI is the number of person-years for the population at risk.

**Molecular typing.** Molecular typing is an important tool for understanding a variety of aspects of the epidemiology of CDI. The molecular characterization of isolates is essential for understanding the modes of transmission and the settings where transmission occurs. As described above, molecular typing of strains can confirm a shift in the epidemiology of CDI. In addition, tracking certain strains and observing their

clinical behavior has assisted investigators in determining the importance of antimicrobial resistance and virulence factors in outbreaks of epidemic CDI.

Current *C. difficile* typing measures depend on having access to isolates recovered from patient stool specimens. Because of the popularity of using nonculture methods to diagnose *C. difficile* infection, such isolates often are not available, and this may hinder our further understanding of the epidemiology of CDI. It is, therefore, imperative that culture for *C. difficile* be performed for toxin-positive stool samples during outbreaks or in settings where the epidemiology and/or severity of CDI is changing and is unexplained by the results of investigations in similar settings.<sup>96</sup> Outbreaks of CDI in healthcare facilities are most often caused by transmission of a predominant strain; cessation of the outbreak is usually accompanied by a decrease in strain relatedness among *C. difficile* isolates. Because of the clonality of *C. difficile* in outbreaks and in settings with high rates of endemicity, it may be difficult to draw conclusions about some aspects of the epidemiology of *C. difficile*. For example, cases of recurrent disease caused by a strain that is prevalent in a given healthcare facility may just as likely represent reinfection as relapse.

*C. difficile* may be typed by a variety of methods. Current genetic methods for comparing strains include methods that examine polymorphisms after restriction endonuclease digestion of chromosomal DNA, PCR-based methods, and sequence-based methods. DNA polymorphism-based methods include restriction endonuclease analysis,<sup>97</sup> PFGE,<sup>98</sup> and toxinotyping.<sup>99</sup> PCR-based methods include arbitrarily-primed PCR,<sup>100</sup> repetitive element sequence PCR,<sup>101</sup> and PCR ribotyping.<sup>102</sup> Sequence-based techniques consist presently of multilocus sequence typing<sup>103</sup> and multilocus variable-number tandem-repeat analysis.<sup>104,105</sup> A recent international comparative study of 7 different typing methods (multilocus sequence typing, multilocus variable-number tandem-repeat analysis, PFGE, restriction endonuclease analysis, PCR-ribotyping, amplified fragment-length polymorphism analysis, and surface layer protein A gene sequence typing) assessed the discriminatory ability and typeability of each technique, as well as the agreement among techniques in grouping isolates according to allele profiles defined by toxinotype, the presence of the binary toxin gene, and deletion in the *tcdC* gene.<sup>106</sup> All the techniques were able to distinguish the current epidemic strain of *C. difficile* (NAP1/BI/027) from other strains. Restriction endonuclease analysis, surface layer protein A gene sequence typing, multilocus sequence typing, and PCR ribotyping all included isolates that were toxinotype III, positive for binary toxin, and positive for an 18-base pair deletion in *tcdC* (ie, the current epidemic strain profile) in a single group that excluded other allelic profiles.

## II. WHAT IS THE BEST TESTING STRATEGY TO DIAGNOSE CDI IN THE CLINICAL LABORATORY AND WHAT ARE ACCEPTABLE OPTIONS?

### Recommendations

5. Testing for *C. difficile* or its toxins should be performed only on diarrheal (unformed) stool, unless ileus due to *C. difficile* is suspected (**B-II**).

6. Testing of stool from asymptomatic patients is not clinically useful, including use as a test of cure. It is not recommended, except for epidemiological studies (**B-III**).

7. Stool culture is the most sensitive test and is essential for epidemiological studies (**A-II**).

8. Although stool culture is not clinically practical because of its slow turnaround time, the sensitivity and specificity of stool culture followed by identification of a toxigenic isolate (ie, toxigenic culture), as performed by an experienced laboratory, provides the standard against which other clinical test results should be compared (**B-III**).

9. Enzyme immunoassay (EIA) testing for *C. difficile* toxin A and B is rapid but is less sensitive than the cell cytotoxin assay, and it is thus a suboptimal alternative approach for diagnosis (**B-II**).

10. Toxin testing is most important clinically, but is hampered by its lack of sensitivity. One potential strategy to overcome this problem is a 2-step method that uses EIA detection of glutamate dehydrogenase (GDH) as initial screening and then uses the cell cytotoxicity assay or toxigenic culture as the confirmatory test for GDH-positive stool specimens only. Results appear to differ based on the GDH kit used; therefore, until more data are available on the sensitivity of GDH testing, this approach remains an interim recommendation. (**B-II**)

11. Polymerase chain reaction (PCR) testing appears to be rapid, sensitive, and specific and may ultimately address testing concerns. More data on utility are necessary before this methodology can be recommended for routine testing. (**B-II**)

12. Repeat testing during the same episode of diarrhea is of limited value and should be discouraged (**B-II**).

### Evidence Summary

Accurate diagnosis is crucial to the overall management of this nosocomial infection. Empirical therapy without diagnostic testing is inappropriate if diagnostic tests are available, because even in an epidemic environment, only approximately 30% of hospitalized patients who have antibiotic-associated diarrhea will have CDI.<sup>13</sup> Efficiently and effectively making the diagnosis of CDI remains a challenge to the clinician and the microbiologist.

Since the original observations that *C. difficile* toxins are responsible for antibiotic-associated colitis, most diagnostic

tests that have been developed detect the toxin B and/or toxin A produced by *C. difficile*. Using an animal model and isogenic mutants of *C. difficile*, toxin B was demonstrated to be the primary toxin responsible for CDI.<sup>107</sup> Initial tests were performed using cell culture cytotoxicity assays for toxin B. Subsequent tests have used antigen detection with EIA. Tests detecting *C. difficile* common antigen (ie, GDH) have been improved using EIA, compared with the older latex agglutination assays.<sup>108-110</sup> Because of cost and turnaround time, the focus of diagnostic testing has been on antibody-based tests to identify the toxins. These tests are also easier to perform in the clinical laboratory. The sensitivity of these tests is suboptimal when compared with more time-intensive methodologies. Furthermore, toxin EIAs have suboptimal specificity, which means that, because the great majority of diagnostic samples will not have toxin present, the positive predictive value of the results can be unacceptably low.<sup>111,112</sup> Culture followed by detection of a toxigenic isolate (ie, toxigenic culture) is considered the most sensitive methodology, but it routinely takes 2–3 days and could take up to 9 days to obtain results.<sup>113-115</sup> Thus the optimal strategy to provide timely, cost-effective, and accurate results remains a subject of controversy.

**Specimen collection and transport.** The proper laboratory specimen for the diagnosis of *C. difficile* infection is a watery, loose, or unformed stool promptly submitted to the laboratory.<sup>116,117</sup> Except in rare instances in which a patient has ileus without diarrhea, swab specimens are unacceptable, because toxin testing cannot be done reliably. Because 10% or more of hospitalized patients may be colonized with *C. difficile*,<sup>116</sup> evaluating a formed stool for the presence of the organism or its toxins can decrease the specificity of the diagnosis of CDI. Processing a single specimen from a patient at the onset of a symptomatic episode usually is sufficient. Because of the low increase in yield and the possibility of false-positive results, routine testing of multiple stool specimens is not supported as a cost-effective diagnostic practice.<sup>118</sup>

**Detection by cell cytotoxicity assay.** Detection of neutralizable toxin activity in stools from patients with antibiotic-associated colitis was the initial observation that led to the discovery that *C. difficile* is the causative agent of this infection.<sup>119</sup> The presence or absence of the pathogenicity locus (PaLoc), a 19-kilobase area of the *C. difficile* genome that includes the genes for toxins A and B and surrounding regulatory genes, accounts for the fact that most strains of *C. difficile* produce either both toxins or neither toxin, although an increasing number of strains are found to lack production of toxin A.<sup>120</sup> Numerous cell lines are satisfactory for detection of cytotoxin, but most laboratories use human foreskin fibroblast cells, on the basis of the fact that it is the most sensitive cell line for detecting toxin at low titer (1 : 160 or less).<sup>121</sup>

Using a combination of clinical and laboratory criteria to

establish the diagnosis of CDI, the sensitivity of cytotoxin detection as a single test for the laboratory diagnosis of this illness is reported to range from 67% to 100%.<sup>2,9,122</sup>

**Detection by EIA for toxin A or toxins A and B.** Commercial EIA tests have been introduced that either detect toxin A only or detect both toxins A and B. Compared with diagnostic criteria that included a clinical definition of diarrhea and laboratory testing that included cytotoxin and culture, the sensitivity of these tests is 63%–94%, with a specificity of 75%–100%. These tests have been adopted by more than 90% of laboratories in the United States because of their ease of use and lower labor costs, compared with the cell cytotoxin assay. The toxin A/B assay is preferred because 1%–2% of strains in the United States are negative for toxin A.<sup>123</sup>

**Detection by culture.** Along with cytotoxin detection, culture has been a mainstay in the laboratory diagnosis of CDI and is essential for the epidemiologic study of isolates. The description of a medium containing cycloserine, cefoxitin, and fructose (CCFA medium) provided laboratories with a selective culture system for recovery of *C. difficile*.<sup>124</sup> Addition of taurocholate or lysozyme can enhance recovery of *C. difficile*, presumably because of increased germination of spores.<sup>125</sup> Optimal results require that culture plates be reduced in an anaerobic environment prior to use. The strains produce flat, yellow, ground glass–appearing colonies with a surrounding yellow halo in the medium. The colonies have a typical odor and fluoresce with a Wood's lamp.<sup>115</sup> Additionally, Gram stain of these colonies must show typical morphology (gram-positive or gram-variable bacilli) for *C. difficile*. Careful laboratory quality control of selective media for isolation of *C. difficile* is required, as there have been variations in the rates of recovery with media prepared by different manufacturers. With experience, visual inspection of bacterial colonies that demonstrate typical morphology on agar and confirmation by Gram stain usually is sufficient for a presumptive identification of *C. difficile*. Isolates not fitting these criteria can be further identified biochemically or by gas chromatography.

**Detection by tests for *C. difficile* common antigen (GDH).** The initial test developed to detect GDH was a latex agglutinin assay. It had a sensitivity of only 58%–68% and a specificity of 94%–98%.<sup>2,122</sup> The latex test for *C. difficile*–associated antigen, therefore, is not sufficiently sensitive for the routine laboratory detection of CDI, even though it is rapid, relatively inexpensive, and specific. Use of this test provides no information regarding the toxigenicity of the isolate, nor does it yield the isolate itself, which would be useful for epidemiologic investigations.

Several assays for GDH have been developed using EIA methodology. These newer assays show a sensitivity of 85%–95% and a specificity of 89%–99%. Most importantly, these tests have a high negative predictive value, making them useful for rapid screening, if combined with another method that detects toxin.<sup>126,127</sup> Several 2-step algorithms have been

TABLE 2. Summary of Infection Control Measures for the Prevention of Horizontal Transmission of *Clostridium difficile*

Variable	Strength of recommendation	Reference(s)
Hand hygiene	A-II	
Contact precautions		
Glove use	A-I	Johnson et al <sup>150</sup>
Gowns	B-III	
Use of private rooms or cohorting	C-III	
Environmental cleaning, disinfection, or use of disposables		
Disinfection of patient rooms and environmental surfaces	B-II	
Disinfection of equipment between uses for patients	C-III	Brooks et al <sup>79</sup>
Elimination of use of rectal thermometers	B-II	Mayfield et al, <sup>76</sup> Wilcox et al <sup>78</sup>
Use of hypochlorite (1,000 ppm available chlorine) for disinfection	B-II	

developed that are based on the use of this test.<sup>110,115,126,128,129</sup> They all use the GDH test for screening in which a stool sample with a negative assay result is considered negative for the pathogen but a positive assay result requires further testing to determine whether the *C. difficile* strain is toxigenic. The confirmatory test has primarily been a cell cytotoxin assay.<sup>110,115,129</sup> It is also possible to use a toxin A/B EIA or culture with cytotoxin testing as the confirmatory test, although the limited sensitivity of the toxin EIA is problematic. One of the more recent studies performed 2-step testing of 5,887 specimens at 2 different hospitals. The GDH test result was positive for 16.2% of specimens at one hospital and 24.7% of specimens at the other. Therefore, 75%–85% of the samples did not require that a cell cytotoxin assay be performed, at a cost savings of between \$5,700 and \$18,100 per month.<sup>110</sup> Another recent study tested 439 specimens using GDH screening with cell cytotoxicity assay for confirmation.<sup>130</sup> The comparator test in this study was culture with cell cytotoxin assay. The GDH test identified all samples that were culture positive. The sensitivity of the 2-step algorithm was 77%, and the sensitivity of culture was 87%. Another recent study comparing GDH EIA with culture, PCR, and toxin EIA found that only 76% of specimens that were culture positive for *C. difficile* and only 32% of culture-positive specimens in which toxin genes were detected tested positive for GDH using an insensitive confirmatory toxin A assay.<sup>130</sup> Although most studies have shown a high negative predictive value for the GDH assay, some studies have questioned its sensitivity. PCR tests for toxigenic *C. difficile* in stool samples are now available commercially from several manufacturers, and this may be a more sensitive and more specific approach, but more data on utility are necessary before this methodology can be recommended for routine testing. Currently there is no testing strategy that is optimally sensitive and specific and, therefore, clinical suspicion and consideration of the patient risk factors are important in making clinical decisions about whom to treat.

**Other test methodologies.** Pseudomembranous colitis can only be diagnosed by direct visualization of pseudomembranes on lower gastrointestinal endoscopy (either sigmoidoscopy or

colonoscopy) or by histopathologic examination. However, direct visualization using any of these techniques will detect pseudomembranes in only 51%–55% of CDI cases that are diagnosed by combined clinical and laboratory criteria that include both a culture positive for *C. difficile* and a positive stool cytotoxin test result.<sup>9</sup> Pseudomembranous colitis has been used as a marker of severe disease, as has CT scanning. Abdominal CT scanning may facilitate the diagnosis of CDI but this methodology is neither sensitive nor specific.<sup>13</sup>

### III. WHAT ARE THE MOST IMPORTANT INFECTION CONTROL MEASURES TO IMPLEMENT IN THE HOSPITAL DURING AN OUTBREAK OF CDI?

#### A. Measures for Healthcare Workers, Patients, and Visitors

##### Recommendations

13. Healthcare workers and visitors must use gloves (**A-I**) and gowns (**B-III**) on entry to a room of a patient with CDI.

14. Emphasize compliance with the practice of hand hygiene (**A-II**).

15. In a setting in which there is an outbreak or an increased CDI rate, instruct visitors and healthcare workers to wash hands with soap (or antimicrobial soap) and water after caring for or contacting patients with CDI (**B-III**).

16. Accommodate patients with CDI in a private room with contact precautions (**B-III**). If single rooms are not available, cohort patients, providing a dedicated commode for each patient (**C-III**).

17. Maintain contact precautions for the duration of diarrhea (**C-III**).

18. Routine identification of asymptomatic carriers for infection control purposes is not recommended (**A-III**) and treatment of such identified patients is not effective (**B-I**).

##### Evidence Summary

Prevention of *C. difficile* acquisition can be categorized into 2 strategies: preventing horizontal transmission, to minimize

exposure; and decreasing the risk factors for patients to develop *C. difficile* infection, if exposure has occurred.<sup>131</sup> This section will focus on prevention of horizontal transmission. There are 3 ways in which patients may be exposed to *C. difficile* in the hospital milieu: (1) by contact with a healthcare worker with transient hand colonization, (2) by contact with the contaminated environment, or (3) by direct contact with a patient with CDI. The rate of acquisition during hospitalization increases linearly with time and can be as high as 40% after 4 weeks of hospitalization.<sup>132</sup> There may not be a single method that is effective in minimizing exposure to *C. difficile*, and a multifaceted approach is usually required.<sup>133-136</sup> Different methods may be more or less effective in different institutions, depending on the local epidemiology and the available resources (Table 2).

**Hand hygiene.** Hand hygiene is considered to be one of the cornerstones of prevention of nosocomial transmission of *C. difficile*, as it is for most nosocomial infections. Several studies have documented the reduction of rates of hospital-acquired infection by improvement in the compliance with hand washing by healthcare workers between episodes of contact with patients.<sup>137</sup> Unfortunately, many studies have also documented low rates of hand washing by healthcare workers.<sup>137,138</sup> The advent of alcohol-based hand antiseptics was greeted with great optimism as a breakthrough for improving compliance with hand hygiene.<sup>139,140</sup> These alcohol-based antiseptics are popular because of their effectiveness in reducing hand carriage of most vegetative bacteria and many viruses, their ease of use at the point of care, and their ability to overcome the relative inaccessibility of hand washing facilities in many institutions.

However, *C. difficile*, in its spore form, is also known to be highly resistant to killing by alcohol.<sup>141</sup> Indeed, exposing stool samples to ethanol in the laboratory facilitates isolation of *C. difficile* from these specimens.<sup>142</sup> Therefore, healthcare workers who decontaminate their hands with alcohol-based products may simply displace spores over the skin surface, as opposed to physically removing *C. difficile* spores by mechanical washing with soap and running water. This could potentially increase the risk of transferring this organism to patients under their care. Several studies have not demonstrated an association between the use of alcohol-based hand hygiene products and increased incidence of CDI. Gordin et al<sup>143</sup> assessed the impact of using an alcohol-based hand rub on rates of infection with methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and CDI 3 years before and after implementation. After implementation, a 21% reduction was observed in the rate of methicillin-resistant *S. aureus* infection, and a 41% decrease in the rate of vancomycin-resistant *Enterococcus* infection. The incidence of CDI was essentially unchanged and did not increase with the implementation of alcohol-based hand rub.

A recent study compared use of alcohol-based products with other methods of hand hygiene.<sup>144</sup> This study assessed the efficacy of different hand washing methods for removal

of a nontoxigenic strain of *C. difficile*. Although there is a theoretical potential for alcohol-based hand hygiene products to increase the incidence of CDI because of their relative ineffectiveness at eliminating spores from the hands, there has not been any clinical evidence to support this thus far.

McFarland et al<sup>1</sup> suggested that chlorhexidine containing antiseptic was more effective than plain soap for removing *C. difficile* from the hands of healthcare workers. They found that *C. difficile* persisted on the hands of 88% of personnel (14 of 16) who had washed with plain soap (as determined by culture). Washing with 4% chlorhexidine gluconate reduced the rate to 14% (1 of 7 personnel). Another study involving experimental hand seeding with *C. difficile* showed no difference between bland soap and chlorhexidine gluconate in removing *C. difficile* from hands.<sup>145</sup>

**Contact precautions.** The use of additional isolation techniques (contact precautions, private rooms, and cohorting of patients with active CDI) has been employed for control of outbreaks, with varied success.<sup>28,146-148</sup> Contact precautions include the donning of gowns and gloves when caring for patients with CDI.<sup>149</sup> These measures are based on the premise that patients with active CDI are the primary reservoir for spread of disease within the institution. There is ample evidence for the contamination of personnel's hands with *C. difficile* spores.<sup>1,66</sup> Hence, the use of gloves in conjunction with hand hygiene should decrease the concentration of *C. difficile* organisms on the hands of healthcare personnel. A prospective controlled trial of vinyl glove use for handling body substances showed a significant decline in CDI rates, from 7.7 cases per 1,000 discharges before institution of glove use to 1.5 cases per 1,000 discharges after institution of glove use ( $P = .015$ ).<sup>150</sup> In addition, the use of gowns has been promoted because of potential soiling and contamination of the uniforms of healthcare personnel with *C. difficile*. *C. difficile* has been detected on nursing uniforms, but a study found no evidence of the uniforms being a source of transmission to patients.<sup>151</sup>

Cartmill and colleagues<sup>136</sup> achieved a reduction in the number of new *C. difficile* cases by using an aggressive policy of increasing the number of diarrheal stools cultured for *C. difficile*, instituting contact precautions early, treating CDI patients with vancomycin, and disinfecting environmental surfaces with a hypochlorite solution. Placing the focus for control measures on clinically symptomatic patients with CDI was successful in this institution, which supports the hypothesis that patients with diarrhea, who are known to have the highest number of organisms in their stools and in their immediate hospital environment, are the most likely source of nosocomial transmission.

**Facilities.** Improving the hospital layout can enhance the effectiveness of infection control measures. In a cohort study of nosocomial acquisition of CDI, there were higher acquisition rates in double rooms than in single rooms (17% vs 7%;  $P = .08$ ) and a significantly higher risk of acquisition after exposure to a roommate with a positive culture result.<sup>1</sup>

The importance of adequate hospital facilities was highlighted in a study comparing CDI rates in 2 Norwegian hospitals.<sup>152</sup> These 2 hospitals were comparable in size and had similar clinical departments. However, the hospitals differed in their physical infrastructure, bed occupancy rate, and antibiotic utilization pattern. The older hospital had fewer single rooms and a higher bed occupancy rate but a lower rate of use of broad-spectrum antibiotics, compared with the modern hospital. The incidence of CDI was lower in the modern hospital than in the older hospital. However, this study was limited by a lack of description of patient demographic characteristics and other risk factors that may impact CDI rates. Furthermore, there may have been a higher rate of case finding in the older institution than in the modern hospital, because the incidence of patient testing was consistently higher in the older hospital during the study period.

In a systematic review of the architecture of hospital facilities and nosocomial infection rates, there was a lack of compelling evidence that a reduction in nosocomial infections could be attributable to improvement in hospital patient rooms.<sup>153</sup> In 8 studies reviewed, 3 studies documented a statistically significant decrease in the incidence of nosocomial infections after the architectural intervention, whereas 5 studies showed no difference.<sup>153</sup> It is difficult to assess the effect of improvements in hospital design and renovation on the incidence of nosocomial infections. These studies are often nonrandomized, historical cohort studies that examine the incidence of specific nosocomial infections before and after the intervention. The American Institute of Architects recommends single-patient rooms in new construction, as well as in renovations.<sup>154</sup>

**Healthcare worker carriage.** Cases of nosocomial acquisition of *C. difficile* by healthcare workers have been reported.<sup>155,156</sup> Two prospective studies indicate, however, that *C. difficile* poses little risk to the healthcare worker. In a 1-year prospective case-control study in which 149 patients with CDI were identified, rectal swab specimens from 68 personnel (54 nurses and 14 physicians) revealed only 1 employee (1.5%) colonized with *C. difficile*.<sup>9</sup> A colonization rate of 1.7% was found among medical house staff.<sup>157</sup> Therefore, it is rare that healthcare workers acquire *C. difficile*; nevertheless, they can serve as primary transmitters of *C. difficile* by way of transient hand contamination.

**Identification and treatment of asymptomatic patient carriers.** In institutions with higher rates of CDI (7.8–22.5 cases per 1,000 discharges), the number of asymptotically colonized patients has been found to be considerably higher than the number with CDI.<sup>1,150,158</sup> The rationale for identifying and treating these asymptomatic patients is that they potentially serve as a reservoir for horizontal spread of *C. difficile* to other patients, either by way of the environment or by way of the hands of medical personnel. Delmee et al<sup>159</sup> demonstrated a significant reduction in new *C. difficile* infections in a leukemia unit after institution of oral vancomycin treatment (500 mg 4 times daily for 7 days) for asymptotically

colonized patients, combined with extensive environmental renovation and cleaning. In contrast, metronidazole therapy was ineffective in reducing the incidence of CDI when administered to all *C. difficile* carriers in a chronic-care facility, even when contact precautions and antibiotic restriction were used concurrently.<sup>160</sup>

One prospective trial showed no significant reduction in the incidence of *C. difficile* carriage after therapy with oral metronidazole, compared with placebo, whereas 9 of 10 patients treated with vancomycin became culture negative for *C. difficile* after treatment.<sup>161</sup> On day 70 of follow-up, however, 4 of 6 patients who had initial clearance with vancomycin treatment were positive for *C. difficile* (including 1 patient who developed CDI), whereas only 1 of 9 placebo-treated patients remained positive for the pathogen ( $P < .05$ ).

Thus, treatment of asymptomatic *C. difficile* carriers is effective when vancomycin is used, but patients treated with vancomycin may be at increased risk for reinfection or prolonged carriage after treatment is stopped. The efficacy of using vancomycin treatment for asymptomatic carriers as a control measure to interrupt hospital transmission has not been established. Similarly, it has been suggested that identification of asymptomatic carriers and institution of more stringent barrier precautions may be useful in interrupting an outbreak, but there are no available data to support such a measure.

## B. Environmental Cleaning and Disinfection

### Recommendations

19. Identification and removal of environmental sources of *C. difficile*, including replacement of electronic rectal thermometers with disposables, can reduce the incidence of CDI (**B-II**).
20. Use chlorine-containing cleaning agents or other sporicidal agents to address environmental contamination in areas associated with increased rates of CDI (**B-II**).
21. Routine environmental screening for *C. difficile* is not recommended (**C-III**).

### Evidence Summary

The true extent of the contribution of the healthcare environment to infection transmission remains controversial. However, for bacteria that resist desiccation, there is much evidence that the environment is an important source of nosocomial infection.<sup>162</sup> *C. difficile* spores can survive in the environment for months or years and can be found on multiple surfaces in the healthcare setting.<sup>1,66,163,164</sup> The rate of recovery of *C. difficile* from the environment is increased if media that encourage spore germination—for example, media containing lysozyme—are used.<sup>125</sup> Interestingly, epidemic strains of *C. difficile* have a greater sporulation capacity in vitro than do nonoutbreak strains.<sup>165</sup> Studies have found that the rate of environmental contamination by *C. difficile* increases according to the carriage and symptom status of the patient(s): it was lowest in

rooms of culture-negative patients (fewer than 8% of rooms), intermediate in rooms of patients with asymptomatic *C. difficile* colonization (8%–30% of rooms), and highest in rooms of patients with CDI (9%–50% of rooms).<sup>1,164</sup> Also, a study found that the incidence of *C. difficile* infection correlated significantly with the environmental prevalence of *C. difficile* on one hospital ward ( $r = 0.76$ ;  $P < .05$ ) but not another ( $r = 0.26$ ;  $P > .05$ ), possibly because of confounding factors.<sup>77</sup> Environmental contamination has been linked to the spread of *C. difficile* by way of contaminated commodes,<sup>1,75,77</sup> blood pressure cuffs,<sup>166</sup> and oral and rectal thermometers.<sup>79,167,168</sup> Replacement of electronic thermometers with single-use disposable thermometers has been associated with significant reductions in CDI incidence.<sup>79,167,168</sup>

There is evidence that the environmental prevalence of *C. difficile* can affect the risk of CDI, and may not simply reflect the prevalence of symptomatic disease. Samore and colleagues<sup>75</sup> showed that the environmental prevalence of *C. difficile* correlated with the extent of contamination of healthcare workers hands by this bacterium. Furthermore, there are several reports that interventions to reduce environmental contamination by *C. difficile* have decreased the incidence of infection.<sup>76,78</sup> Kaatz and colleagues<sup>169</sup> found that phosphate buffered hypochlorite (1,600 ppm available chlorine; pH, 7.6) was more effective than unbuffered hypochlorite (500 ppm available chlorine) at reducing environmental levels of *C. difficile*. Introduction of cleaning with a hypochlorite-based solution (5,000 ppm available chlorine) was also associated with reduced incidence of CDI in a bone marrow transplant unit where there was a relatively high infection rate.<sup>76</sup> The incidence of CDI increased almost to the baseline level after the reintroduction of use of the original quaternary ammonium compound cleaning agent. However, the environmental prevalence of *C. difficile* was not measured in this study, and the results were not reproducible with patients on other units, possibly because of the low prevalence of infection. Wilcox et al<sup>78</sup> used a 2-year crossover study design to demonstrate a significant correlation between the use of a cleaning agent containing chlorine (dichloroisocyanurate; 1,000 ppm available chlorine) and a reduction in the incidence of CDI on 1 of the 2 hospital wards that were examined. Although it is likely that higher concentrations of available chlorine within the range of 1,000–5,000 ppm are more reliably sporicidal than lower concentrations, the potential disadvantages (eg, causticity to surfaces, complaints from personnel about the odor, and possible hypersensitivity) should be balanced against the potential advantages in particular settings (eg, environmental cleaning interventions may have their greatest impact in settings with the highest baseline rates). Therefore, depending on such factors, the concentration of available chlorine should be at least 1,000 ppm and may ideally be 5,000 ppm. A recent report highlighted the use of vaporized hydrogen peroxide to reduce the level of environmental contamination by *C. difficile*. The prevalence of *C. difficile* was significantly reduced (to a recovery level of 0) after hydrogen

peroxide use, albeit from a low level (5%), possibly because of former hypochlorite based cleaning; the incidence of CDI decreased, although not significantly.<sup>170</sup> Unfortunately, practical considerations (the need to seal rooms and to have access to specialized equipment) and the cost limit the applicability of this approach to environmental decontamination.

A wide range of disinfectants suitable for decontamination of instruments (eg, endoscopes) or the environment have in vitro activity against *C. difficile* spores.<sup>141,165,171–173</sup> With the exceptions noted above, comparative data on the in situ efficacy of these disinfection options are lacking. The efficacy of cleaning is critical to the success of decontamination in general, and thus user acceptability of disinfection regimens is a key issue. Endoscopes have not been implicated in the transmission of *C. difficile*, but spread by means of this mechanism is preventable by careful cleaning and disinfection with 2% alkaline glutaraldehyde.<sup>171</sup> In vitro data show greater *C. difficile* sporicidal activity as the concentration of free chlorine increases with acidified bleach, but practical issues may limit the use of such products for routine cleaning. A study found that working-strength concentrations of 5 different cleaning agents inhibited growth of *C. difficile* cultures in vitro.<sup>165</sup> However, only chlorine-based cleaning agents used at the recommended working concentrations were able to inactivate *C. difficile* spores. Also, in vitro exposure of epidemic *C. difficile* strains, including NAP1/BI/027, to subinhibitory concentrations of non-chlorine-based cleaning agents (detergent or hydrogen peroxide) significantly increased sporulation capacity; this effect was generally not seen with chlorine-based cleaning agents.<sup>125,167</sup> These observations suggest the possibility that some cleaning agents, if allowed to come into contact with *C. difficile* in low concentrations, could promote sporulation and, therefore, the persistence of the bacterium in the environment.

Use of chlorine-containing cleaning products presents health and safety concerns, as well as compatibility challenges that need to be assessed for risk. However, current evidence supports the use of chlorine-containing cleaning agents (with at least 1,000 ppm available chlorine), particularly to address environmental contamination in areas associated with endemic or epidemic CDI. Routine bacteriological surveillance of the environment is generally unhelpful, largely because it has not been possible to establish threshold levels associated with increased risk of clinical infection, but it may be useful for ascertaining whether cleaning standards are suboptimal, notably in a setting experiencing an outbreak or where *C. difficile* is hyperendemic.

### *C. Antimicrobial Use Restrictions*

#### Recommendations

22. Minimize the frequency and duration of antimicrobial therapy and the number of antimicrobial agents prescribed, to reduce CDI risk (A-II).
23. Implement an antimicrobial stewardship program

(A-II). Antimicrobials to be targeted should be based on the local epidemiology and the *C. difficile* strains present, but restricting the use of cephalosporin and clindamycin (except for surgical antibiotic prophylaxis) may be particularly useful (C-III).

### Evidence Summary

Most studies have determined that the great majority of patients with CDI have had prior exposure to antimicrobial agents. In a recent study, 85% of patients with CDI had received antibacterial therapy within the 28 days prior to the onset of symptoms.<sup>174</sup> The widespread use of antimicrobial agents and the propensity for polypharmacy means that the accurate quantification of the CDI risk associated with specific antibiotics is very difficult. An greater number of antimicrobial agents administered, a greater number of doses, and a greater duration of administration have been associated with increased risk of CDI.<sup>9,89,158,175-177</sup> Antibiotic risk studies and prescribing intervention studies frequently do not consider exposure to *C. difficile* when assessing outcomes. Thus, efforts to demonstrate the effects of restriction of antibiotics may be confounded by infection control interventions that affect the risk of acquiring *C. difficile*.

Limitation or restriction of use of antimicrobial agents that are found to be associated with increased CDI rates is an intuitively attractive approach to reducing infection rates. However, there are few sound studies that clearly demonstrate the successful implementation of antibiotic prescribing interventions, notably in terms of their effectiveness at reducing CDI. A recent Cochrane systematic review by Davey and colleagues<sup>178</sup> examined the effectiveness of interventions to improve antibiotic prescribing practices for hospital inpatients. It analyzed relevant randomized and quasi-randomized controlled trials, controlled before-and-after studies, and interrupted time-series studies (with at least 3 data points before and after implementation of the intervention). Of 66 identified intervention studies that contained interpretable data, 5 (all interrupted time-series) reported outcome data regarding occurrence of CDI.<sup>179-183</sup> Three of these found significant reductions in CDI incidence,<sup>179-181</sup> and 2 interrupted time-series showed weak or nonsignificant evidence for a decrease in incidence.<sup>182,183</sup>

Climo et al<sup>180</sup> observed a sustained decrease in the incidence of CDI after the prescribing of clindamycin was restricted (11.5 cases per month prior to restriction, compared with 3.33 cases per month after restriction;  $P < .001$ ). By contrast, the incidence of CDI was increasing by 2.9 cases per quarter before the restriction of clindamycin use. Similarly, Pear and colleagues<sup>179</sup> found that, before clindamycin restriction, the CDI rate was increasing (mean incidence, 7.7 cases per month;  $P < .001$ ), and after restriction the incidence suddenly decreased (mean incidence, 3.68 cases per month ( $P = .041$ ), and there was a sustained reduction averaging 0.32 cases per month ( $P = .134$ ). Furthermore, regression analysis showed a significant relationship between the amount of clin-

damycin being prescribed per unit time and the incidence of CDI. Carling et al<sup>181</sup> examined the effectiveness of an antimicrobial management team that focused on 3 interventions to alter prescribing patterns: choice, shorter duration of antibiotic therapy (ie, stop therapy after 2–3 days if there was no confirmed infection), and switching from intravenous to oral formulations. Prescribing of third-generation cephalosporins (and aztreonam) was targeted, and over 6 years it decreased from 24.7 to 6.2 defined daily doses per 1,000 patient-days ( $P < .0001$ ). The multidisciplinary antibiotic stewardship program had no impact on the prevalence rates of vancomycin-resistant *Enterococcus* infection or methicillin-resistant *S. aureus* infection but did significantly reduce the rates of CDI ( $P = .002$ ) and antibiotic-resistant gram-negative bacterial infections ( $P = .02$ ).

However, it is important to emphasize that, for a significant decrease in the incidence of CDI to be realized, reducing the use of antimicrobial agents that are associated with a high CDI risk is necessary, as opposed to simply making lower-risk agents available on the formulary. One study found that introduction of piperacillin-tazobactam onto the formulary for a large Elderly Medicine unit was not associated with a significant reduction in the CDI rate.<sup>184</sup> However, once cefotaxime was replaced by piperacillin-tazobactam, CDI rates decreased in 4 of 5 wards and overall by 52% ( $P < .008$ ). Unintentional restriction of piperacillin-tazobactam, consequent to manufacturing difficulties, led to a 5-fold rise in cefotaxime prescribing, and CDI rates increased from 2.2 to 5.1 cases per 100 admissions ( $P < .01$ ). Similar observations that a piperacillin-tazobactam shortage led to increased prescribing of cephalosporins (ceftriaxone and cefotetan) and higher CDI rates have also been reported elsewhere.<sup>185</sup>

As reports of increasing incidence and more-severe CDI associated with the highly fluoroquinolone-resistant NAP1/BI/027 strain continue to mount, several investigators have addressed the issue of antimicrobial restriction as a means of controlling this strain. A reduction in overall antimicrobial use has played a role in controlling at least 2 large institutional outbreaks caused by this strain.<sup>48,186</sup> However, other outbreaks appear to have come under control through the application of infection control measures alone.<sup>25</sup> There are limited data on whether restriction of a specific fluoroquinolone, or restriction of the entire class, can favorably impact increased rates of CDI due to NAP1/BI/027. In an early single-hospital outbreak caused by NAP1/BI/027 and reported by Gaynes et al,<sup>187</sup> it appeared that a switch from levofloxacin to gatifloxacin as the formulary drug of choice precipitated the outbreak; when the formulary drug of choice was switched back to levofloxacin, the outbreak ceased. Moreover, a case-control study showed an association between CDI and gatifloxacin exposure, leading the authors to propose that gatifloxacin is a higher-risk antimicrobial than levofloxacin. However, in a similar scenario in which an outbreak occurred following a formulary switch from levofloxacin to moxifloxacin as the drug of choice, reverting to levofloxacin was not associated

with a decrease in CDI.<sup>188</sup> Given that the NAP1/BI/027 strain has increased resistance to fluoroquinolones as a class, rather than to one specific agent, it is unlikely that restricting the use of a specific fluoroquinolone would reduce CDI rates to the same level that could be achieved if use of all members of the class were restricted. Nonetheless, there is currently insufficient evidence to recommend restriction of use of a specific fluoroquinolone or the fluoroquinolone class for the control of CDI, other than as part of a reduction in overall antimicrobial use.<sup>186</sup>

#### D. Use of Probiotics

##### Recommendation

24. Administration of currently available probiotics is not recommended to prevent primary CDI, as there are limited data to support this approach and there is a potential risk of bloodstream infection (C-III).

##### Evidence Summary

For many years, administration of probiotics has been advocated as a preventive measure for patients receiving antibiotics. Until recently, no individual study had shown probiotics to be effective in the prevention of CDI. It is doubtful whether meta-analyses are acceptable, given the diversity of probiotics used in various studies. Additional problems are the lack of standardization of such products, variations in the bacterial counts in such products according to the duration of storage, and the possibility of inducing bacteremia or fungemia. A recent randomized trial showed, for the first time, that ingestion of a specific brand of yogurt drink containing *Lactobacillus casei*, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus* reduced the risk of CDI in patients more than 50 years of age who were prescribed antibiotics and were able to take food and drink orally.<sup>189</sup> However, this conclusion was based on a small number of patients in a highly selected population that excluded patients receiving high-risk antibiotics. There was also an extraordinarily high rate of CDI among patients in the placebo group, who were given a milkshake in place of the yogurt drink (9 of 53 patients in the placebo group developed CDI, compared with 0 of 56 patients in the intervention group). The Expert Panel believes that larger trials are required before this practice can be recommended.

#### IV. DOES THE CHOICE OF DRUG FOR TREATMENT OF CDI MATTER AND, IF SO, WHICH PATIENTS SHOULD BE TREATED AND WITH WHICH AGENT?

##### Recommendations

25. Discontinue therapy with the inciting antimicrobial agent(s) as soon as possible, as this may influence the risk of CDI recurrence (A-II).

26. When severe or complicated CDI is suspected, ini-

tiate empirical treatment as soon as the diagnosis is suspected (C-III).

27. If the stool toxin assay result is negative, the decision to initiate, stop, or continue treatment must be individualized (C-III).

28. If possible, avoid use of antiperistaltic agents, as they may obscure symptoms and precipitate toxic megacolon (C-III).

29. Metronidazole is the drug of choice for the initial episode of mild-to-moderate CDI. The dosage is 500 mg orally 3 times per day for 10–14 days. (A-I)

30. Vancomycin is the drug of choice for an initial episode of severe CDI. The dosage is 125 mg orally 4 times per day for 10–14 days. (B-I)

31. Vancomycin administered orally (and per rectum, if ileus is present) with or without intravenously administered metronidazole is the regimen of choice for the treatment of severe, complicated CDI. The vancomycin dosage is 500 mg orally 4 times per day and 500 mg in approximately 100 mL normal saline per rectum every 6 hours as a retention enema, and the metronidazole dosage is 500 mg intravenously every 8 hours. (C-III)

32. Consider colectomy for severely ill patients. Monitoring the serum lactate level and the peripheral blood white blood cell count may be helpful in prompting a decision to operate, because a serum lactate level rising to 5 mmol/L and a white blood cell count rising to 50,000 cells per  $\mu$ L have been associated with greatly increased perioperative mortality. If surgical management is necessary, perform subtotal colectomy with preservation of the rectum. (B-II)

33. Treatment of the first recurrence of CDI is usually with the same regimen as for the initial episode (A-II) but should be stratified by disease severity (mild-to-moderate, severe, or severe complicated), as is recommended for treatment of the initial CDI episode (C-III).

34. Do not use metronidazole beyond the first recurrence of CDI or for long-term therapy because of potential for cumulative neurotoxicity (B-II).

35. Treatment of the second or later recurrence of CDI with vancomycin therapy using a tapered and/or pulse regimen is the preferred next strategy (B-III).

36. No recommendations can be made regarding prevention of recurrent CDI in patients who require continued antimicrobial therapy for the underlying infection (C-III).

##### Evidence Summary

For 25 years, metronidazole and oral vancomycin have been the main antimicrobial agents used in the treatment of CDI. Two randomized controlled trials conducted in the 1980s and 1990s that compared metronidazole therapy and vancomycin therapy found no difference in outcomes but included fewer than 50 patients per study arm.<sup>190,191</sup> Fusidic acid or bacitracin have not been widely adopted for treatment, partially because comparative studies showed a trend toward higher frequency

of recurrence of CDI or lower efficacy.<sup>191,192</sup> Treatment with teicoplanin is probably not inferior to treatment with metronidazole or vancomycin, but this drug remains unavailable in the United States.<sup>193</sup> Vancomycin is the only agent with an indication for CDI from the US Food and Drug Administration. The use of vancomycin for initial treatment of CDI markedly decreased following the 1995 Centers for Disease Control and Prevention's recommendation that the use of vancomycin in hospitals be reduced, to decrease the selection pressure for the emergence of vancomycin-resistant enterococci.<sup>194</sup> Since then, metronidazole has generally been recommended for first-line treatment of CDI, with oral vancomycin being used mainly after metronidazole is found to be ineffective or if it is contraindicated or not well tolerated.<sup>13,14,195</sup> Prospective trials of metronidazole (and vancomycin) therapy have not compared regimens with durations longer than 10 days. However, it is recognized that some patients may respond slowly to treatment and may require a longer course (eg, 14 days). The oral formulation of vancomycin is much more expensive than metronidazole, and to reduce costs, some hospitals use the generic intravenous formulation of vancomycin for oral administration. Some patients report a bad taste after taking this intravenous formulation by mouth.

Recent reports from Canada and the United States, in the context of the emergence of a hypervirulent strain of *C. difficile*, have prompted a reassessment of the comparative efficacy of metronidazole and vancomycin, especially when used to treat patients with severe CDI, primarily on the basis of studies done prior to the emergence of the epidemic strain. When administered orally, metronidazole is absorbed rapidly and almost completely, with only 6%–15% of the drug excreted in stool. Fecal concentrations of metronidazole likely reflect its secretion in the colon, and concentrations decrease rapidly after treatment of CDI is initiated: the mean concentration is 9.3 µg/g in watery stools but only 1.2 µg/g in formed stools.<sup>196</sup> Metronidazole is undetectable in the stool of asymptomatic carriers of *C. difficile*.<sup>161</sup> Consequently, there is little rationale for administration of courses of metronidazole longer than 14 days, particularly if diarrhea has resolved. In contrast, vancomycin is poorly absorbed, and fecal concentrations following oral administration (at a dosage of 125 mg 4 times per day) reach very high levels: 64–760 µg/g on day 2 and 152–880 µg/g on day 4.<sup>197</sup> Doubling the dosage (250 mg 4 times per day) may result in higher fecal concentrations on day 2.<sup>198</sup> Fecal levels of vancomycin are maintained throughout the duration of treatment. Given its poor absorption, orally administered vancomycin is relatively free of systemic toxicity.

Historically, metronidazole resistance in *C. difficile* has been rare; minimal inhibitory concentrations (MICs) of nearly all strains have been less than or equal to 2.0 mg/L.<sup>199–203</sup> In a recent report from Spain, the MIC<sub>90</sub> of 415 isolates was 4.0 mg/L, and 6.3% of isolates had metronidazole MICs of 32 mg/L or higher.<sup>204</sup> These levels of resistance have not been

reported elsewhere. In the United Kingdom, recently recovered isolates belonging to ribotype 001 had geometric mean MICs of 5.94 µg/mL, compared with 1.03 µg/mL for historic isolates (recovered before 2005) of the same ribotype.<sup>205</sup> There is no evidence that the epidemic NAP1/BI/027 strain is more resistant to metronidazole than are nonepidemic strains or historic isolates.<sup>25,206</sup> However, given the relatively low fecal concentrations achieved with metronidazole, even a modest decrease in susceptibility might be clinically relevant, and continued surveillance for metronidazole resistance will be important. The MIC<sub>90</sub> of vancomycin against *C. difficile* is 1.0–2.0 µg/mL, and the highest MIC ever reported is 16 µg/mL,<sup>200–203,207</sup> but considering the high fecal concentrations achieved with oral vancomycin, emergence of resistance is likely not a concern.

Three main outcomes should be considered when evaluating drugs used in the treatment of CDI: time to symptom resolution (or the proportion of patients who respond within 7–10 days); recurrences after initial symptom resolution; and the frequency of major complications, such as death within 30 days of diagnosis, hypovolemic or septic shock, megacolon, colonic perforation, emergency colectomy, or intensive care unit admission.

**Treatment of a first episode of CDI.** Three factors may indicate a severe or complicated course and should be considered when initiating treatment: age, peak white blood cell count (leukocytosis), and peak serum creatinine level.<sup>25,80</sup> The influence of greater age probably reflects a senescence of the immune response against *C. difficile* and its toxins, and greater age has been consistently related to all adverse outcomes. Leukocytosis likely reflects the severity of colonic inflammation; complications are more common among patients who had leukocytosis with a white blood cell count of 15,000 cells/µL or higher than among patients with a normal white blood cell count, and the course of the disease is truly catastrophic in patients with a white blood cell count of 50,000 cells/µL or higher.<sup>208</sup> An elevated serum creatinine level may indicate severe diarrhea with subsequent dehydration or inadequate renal perfusion.

The time to resolution of diarrhea might be shorter with vancomycin than with metronidazole therapy.<sup>209</sup> A recent observational study showed that patients treated with vancomycin in the years 1991–2003 were less likely to develop complications or die within 30 days after diagnosis than were patients treated with metronidazole.<sup>80</sup> However, extension of this case series up through 2006 showed that for the years 2003–2006, when infection with the NAP1/BI/027 strain predominated, vancomycin no longer was superior to metronidazole therapy.<sup>210</sup> Thus, the potential superiority of vancomycin therapy in avoiding complications of CDI, especially among patients infected with the NAP1/BI/027 strain, requires further study.

A recent randomized controlled trial showed, for the first time, that vancomycin at a dosage of 125 mg 4 times per day was superior to metronidazole at a dosage of 250 mg 4 times per day in a subgroup of patients with severe disease, as

assessed by a severity score incorporating 6 clinical variables.<sup>211</sup> The patients were recruited in the years 1994–2002, probably before the emergence of the NAP1/BI/027 strain in the United States. A more recent study conducted since the emergence of the NAP1/BI/027 strain, reported in abstract form, confirms the superiority of vancomycin over metronidazole for treatment of severe CDI.<sup>212</sup> There is no evidence to support administration of combination therapy to patients with uncomplicated CDI. Although hampered by its low statistical power, a recent trial did not show any trend toward better results when rifampin was added to a metronidazole regimen. There is no evidence to support use of a combination of oral metronidazole and oral vancomycin.

The criteria proposed in Table 3 for defining severe or complicated CDI are based on expert opinion. These criteria may need to be reviewed in the future, on publication of prospectively validated severity scores for patients with CDI.

**Treatment of severe, complicated CDI.** Ileus may impair the delivery of orally administered vancomycin to the colon, but intravenously administered metronidazole is likely to result in detectable concentrations in feces and an inflamed colon. Even though it is unclear whether a sufficient quantity of the drug reaches the right and the transverse colon, intracolonic administration of vancomycin seems useful in some cases.<sup>28,213</sup> If colonic perforation is demonstrated or colectomy is imminent, it may be prudent to stop oral or rectal therapy with any antimicrobial agent, but, short of these complications, the emphasis should be on delivery of effective therapy to the colon. Despite the lack of data, it seems prudent to administer vancomycin by oral and rectal routes at higher dosages (eg, 500 mg) for patients with complicated CDI with ileus. Use of high doses of vancomycin is safe, but high serum concentrations have been noted with long courses of 2 g per day, with

renal failure. It would be appropriate to obtain trough serum concentrations in this circumstance. Passive immunotherapy with intravenous immunoglobulins (150–400 mg/kg) has been used for some patients not responding to other therapies,<sup>214</sup> but no controlled trials have been performed.

Colectomy can be life-saving for selected patients.<sup>208</sup> Colectomy has usually been performed for patients with megacolon, colonic perforation, or an acute abdomen, but the procedure is now also performed for patients with septic shock.<sup>208,215</sup> Among patients with a lactate level of 5 mmol/L or greater, postoperative mortality is 75% or higher, when possible colectomy should be performed earlier.<sup>208</sup>

**Treatment of recurrent CDI.** The frequency of further episodes of CDI necessitating re-treatment remains a major concern. Historically, 6%–25% of patients treated for CDI have experienced at least 1 additional episode.<sup>28,216,217</sup> Recurrences correspond to either relapse of infection the original strain or re-infection of patients who remained susceptible and are exposed to new strains.<sup>218,219</sup> In clinical practice, it is impossible to distinguish these 2 mechanisms. Recent reports documented an increase in the frequency of recurrences after metronidazole therapy, especially in patients aged 65 years or more. More than half of patients aged 65 years or more in a Canadian center experienced at least 1 recurrence,<sup>220</sup> while in Texas, half of patients treated with metronidazole either did not respond to the drug or experienced a recurrence.<sup>206</sup> Other risk factors for a recurrence are the administration of other antimicrobials during or after initial treatment of CDI, and a defective immune response against toxin A.<sup>69,221</sup>

Using either metronidazole or vancomycin treatment of a first recurrence does not alter the probability of a second recurrence,<sup>222</sup> but use of vancomycin is recommended for the first recurrence in patients with a white blood cell count of

TABLE 3. Recommendations for the Treatment of *Clostridium difficile* Infection (CDI)

Clinical definition	Supportive clinical data	Recommended treatment	Strength of recommendation
Initial episode, mild or moderate	Leukocytosis with a white blood cell count of 15,000 cells/ $\mu$ L or lower and a serum creatinine level less than 1.5 times the premorbid level	Metronidazole, 500 mg 3 times per day by mouth for 10–14 days	A-I
Initial episode, severe <sup>a</sup>	Leukocytosis with a white blood cell count of 15,000 cells/ $\mu$ L or higher or a serum creatinine level greater than or equal to 1.5 times the premorbid level	Vancomycin, 125 mg 4 times per day by mouth for 10–14 days	B-I
Initial episode, severe, complicated	Hypotension or shock, ileus, megacolon	Vancomycin, 500 mg 4 times per day by mouth or by nasogastric tube, plus metronidazole, 500 mg every 8 hours intravenously. If complete ileus, consider adding rectal instillation of vancomycin	C-III
First recurrence	...	Same as for initial episode	A-II
Second recurrence	...	Vancomycin in a tapered and/or pulsed regimen	B-III

<sup>a</sup> The criteria proposed for defining severe or complicated CDI are based on expert opinion. These may need to be reviewed in the future upon publication of prospectively validated severity scores for patients with CDI.

15,000 cells/ $\mu$ L or higher (or a rising serum creatinine level), since they are at higher risk of developing complications.

A substantial proportion of patients with a second recurrence will be cured with a tapering and/or pulsed regimen of oral vancomycin. Metronidazole should not be used beyond the first recurrence or for long-term therapy because of the potential for cumulative neurotoxicity.<sup>223</sup> Various regimens have been used and are similar to this one: after the usual dosage of 125 mg 4 times per day for 10–14 days, vancomycin is administered at 125 mg 2 times per day for a week, 125 mg once per day for a week, and then 125 mg every 2 or 3 days for 2–8 weeks, in the hope that *C. difficile* vegetative forms will be kept in check while allowing restoration of the normal flora. Management of patients who do not respond to this course of treatment or experience a further relapse is challenging. There is no evidence that adding cholestyramine or rifampin to the treatment regimen decreases the risk of a further recurrence.<sup>224</sup> It should be noted that cholestyramine, colestipol, and other anion-exchange resins bind vancomycin, which make these a specific contraindication. A recent uncontrolled case series of patients with multiple recurrences of CDI documented that oral rifaximin therapy (400 mg 2 times per day for 2 weeks) cured 7 of 8 patients when it was started immediately following the last course of vancomycin and before symptom recurrence.<sup>225</sup> Caution is recommended with use of rifaximin because of the potential for isolates to develop an increased MIC during treatment.<sup>225,226</sup>

Studies of the probiotic *Saccharomyces boulardii* have been inconclusive, but in a subset analysis of a randomized controlled trial, administration of *S. boulardii* in combination with a high dosage of vancomycin appeared to decrease the number of recurrences. Administration of *S. boulardii* has, however, been associated with fungemia in immunocompromised patients and in patients with central venous lines, and it should be avoided in critically ill patients.<sup>227</sup> There is no compelling evidence that other probiotics are useful in the prevention or treatment of recurrent CDI.<sup>228</sup>

Considering that disruption of the indigenous fecal flora is likely a major risk for infection with *C. difficile* and, particularly, for recurrent infection, instillation of stool from a healthy donor has been used with a high degree of success in several uncontrolled case series.<sup>229,230</sup> The availability of this treatment is limited, however. If “fecal transplant” is considered, the donor should be screened for transmissible agents, and logistic issues need to be considered, including the timing, the collection and processing of the specimen from the donor, the preparation of the recipient, and the route and means of administration (ie, by nasogastric tube or by enema).

Other potential options for treatment include alternative antimicrobial agents, such as nitazoxanide,<sup>7</sup> intravenous immunoglobulins (150–400 mg/kg).<sup>230–233</sup>

**Prevention of recurrent CDI in patients requiring antimicrobial therapy.** Some patients need to receive other anti-

timicrobials during or shortly after the end of CDI therapy, either to complete the treatment of the infection for which they had received the inciting antibiotics or to treat a new incidental infection. These patients are at high risk of a recurrence and its attendant complications.<sup>69,221</sup> Many clinicians prolong the duration of treatment of CDI in such cases, until after the other antimicrobial regimens have been stopped. Whether this reduces the risk of CDI recurrence is unknown, and the Expert Panel offers no specific recommendation, but if the duration of CDI treatment is prolonged, oral vancomycin is the preferred agent, given the absence of therapeutic levels of metronidazole in the feces of patients who no longer have active colitis.

## RESEARCH GAPS

The initial step in developing a rational clinical research agenda is the identification of gaps in information. The process of guideline development, as practiced by SHEA and the IDSA, serves as a natural means by which such gaps are identified. Thus, these guidelines identify important clinical questions and identify the quality of evidence supporting those recommendations. Clinical questions identified by the SHEA-IDSA Expert Panel and by members of the IDSA Research Committee that could inform a *C. difficile* research agenda are listed below.

### Epidemiology

*What is the epidemiology of CDI?* What is the incubation period of *C. difficile*? What is the infectious dose of *C. difficile*? How should hospital rates be risk-adjusted for appropriate interhospital comparisons? Does administration of proton pump inhibitors increase the risk of CDI and, if so, what is the magnitude of risk? What are the sources for *C. difficile* transmission in the community? Is exposure to antimicrobials (or equivalent agents, such as chemotherapy drugs) required for susceptibility to CDI? What is the role of asymptomatic carriers in transmission of *C. difficile* in the healthcare setting? What are the validated clinical predictors of severe CDI? At what age and to what degree is *C. difficile* pathogenic among infants?

### Diagnostics

*Is GDH detection in stool sufficiently sensitive as a screening test for *C. difficile* colitis?* How well does this method correlate with culture for toxigenic *C. difficile* and cell culture cytotoxicity assay? Which of these “gold standard” assays (culture for toxigenic *C. difficile* or cell culture cytotoxicity assay) is optimal as a reference test for diagnosis of CDI? Is screening by GDH test, coupled with confirmatory testing for toxigenic *C. difficile* by cell culture cytotoxicity assay or real time PCR for toxin B, as sensitive as primary testing of stool using real-time PCR? What is the best diagnostic method for hospital laboratories that do not have PCR technology available?

Which commercial PCR assay for toxin B performs best, compared with culture for toxigenic *C. difficile*? Is PCR testing for toxin B too sensitive for clinical utility? How do individual laboratory-derived PCR assays for *C. difficile* compare with commercial PCR assays?

Is there any role for repeated *C. difficile* stool testing during the same episode of illness?

After initial diagnosis of CDI, should testing be repeated for any reason other than recurrence of symptoms following successful treatment?

## Management

If a validated severity-of-illness tool for CDI is developed, how will treatment recommendations for primary CDI be modified?

What is the best treatment for recurrent CDI? What is the best way to restore colonization protection of intestinal microbiota? What is the role of fecal transplant? What is the role of administration of passive antibodies (immunoglobulins or monoclonal antibodies) or active immunization (with vaccines)?

What is the best approach to treatment of fulminant CDI? What are the criteria for colectomy in a patient with fulminant CDI? What is the role of treatment with vancomycin or other antibiotics alone or in combination in fulminant infection? What is the role of treatment with passive antibodies (immunoglobulin or monoclonal antibody therapy) in fulminant infection?

## Prevention

What preventive measures can be taken to reduce the incidence of CDI? Can administration of probiotics or biotherapeutic agents effectively prevent CDI? What are the most effective antimicrobial stewardship strategies to prevent CDI? What are the most effective transmission prevention strategies (ie, environmental management and isolation) to prevent CDI in inpatient settings? What is the incremental impact of each? Can vaccination effectively prevent CDI, and what would be the composition of the vaccine and the route of administration? What are systemic or mucosal serologic markers that predict protection against CDI?

## Basic Research

What is the biology of *C. difficile* spores that leads to clinical infection? What induces spore germination and where does it occur in the human gastrointestinal tract? How do spores interact with the human gastrointestinal immune system? What are the triggers for sporulation and germination of *C. difficile* in the human gastrointestinal tract? What is the role of sporulation in recurrent *C. difficile* disease?

What is the basic relationship of *C. difficile* to the human gut mucosa and immune system? Where in the gut do *C. difficile* organisms reside? What enables *C. difficile* to colonize patients? Is there a *C. difficile* biofilm in the gastrointestinal tract? Is mucosal adherence necessary for develop-

ment of CDI? Is there a nutritional niche that allows *C. difficile* to establish colonization? What is the role of mucosal and systemic immunity in preventing clinical CDI? What causes *C. difficile* colonization to end? Do *C. difficile* toxins enter the circulation during infection?

## PERFORMANCE MEASURES

Performance measures are tools to help guideline users measure both the extent and the effects of implementation of guidelines. Such tools or measures can be indicators of the process itself, outcomes, or both. Deviations from the recommendations are expected in a proportion of cases, and compliance in 80%–95% of cases is generally appropriate, depending on the measure.

- Infection control practices should be consistent with guideline recommendations, including compliance with recommended isolation precautions and adequacy of environmental cleaning. Data exist supporting the conclusion that use of these measures has led to control of outbreaks of CDI.
- Treatment of the initial episode of CDI should be consistent with the guidelines. In particular, patients with severe CDI (provisionally identified as leukocytosis with a white blood cell count greater than 15,000 cells/ $\mu$ L or an increase in the serum creatinine level to 1.5 times the pre-morbid level) should be treated with vancomycin. Evidence suggests treatment with this agent has significantly better outcomes than does treatment with metronidazole.
- Appropriate testing for the diagnosis of CDI includes submitting samples only of unformed stool. Additionally, no more than 1 stool sample should be obtained for routine testing during a diarrheal episode. Stool should not be submitted for test of cure.

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Pharmaceutical, Romark Laboratories, and Acambis. V.G.L. reports that she has served as a consultant for Genzyme. J.P. reports that he has served on advisory boards for Pfizer and Novartis; as an advisor for Viropharma, Acambis, Wyeth Pharmaceuticals, and Bayer; and as speaker for Wyeth Pharmaceuticals. C.P.K. reports that he has served as scientific advisor and consultant to Actelion, Cubist Pharm, MicroBiotix, Salix Pharm, Sanofi-Pasteur, ViroPharma, and Wyeth Pharm and has received research support from Actelion and MicroBiotix. M.H.W. and L.C.M. report no conflicts relevant to this guideline.

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It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. SHEA and the IDSA consider adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

The findings and conclusions in this report are those of the author(s), writing on behalf of SHEA and the IDSA, and do not necessarily represent the views of the Centers for Disease Control and Prevention, or the United States Department of Veterans Affairs.

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