

# Recommendations for *C. difficile* Infection (CDI) Treatment and Control

by Perry Hookman, Jamie S. Barkin

*C. difficile* (CD) is a gram-positive, anaerobic, spore-forming bacillus that is spread indirectly via the fecal-oral route through spores left on surfaces. It produces two cytotoxins, A and B which binds to receptors on intestinal epithelial cells, leading to inflammation and diarrhea. The toxins loosen the junctions of the epithelial cells that line the colon, allowing for penetration between epithelial cells (1). This begins a cascade of tissue damaging inflammatory processes that involve the release of destructive leukotrienes and cytokines.

Colonization of *C. difficile* is facilitated by the disruption of normal intestinal flora due to antimicrobial therapy. According to Bartlett, the antibiotics most frequently implicated in *C. difficile* associated diarrhea (CDAD) are clindamycin, penicillins, cephalosporins, and fluoroquinolones (2).

There have been dramatic increases in the frequency, severity and refractoriness of *C. difficile* in multiple outbreaks of antibiotic associated diarrhea (AAD), attributed to this hypervirulent strain, NAP1/BI/027 not only in North America, but around the world. Individuals with low or undetectable levels of antibody against *C. difficile* toxin A are more likely to develop diarrhea than those with detectable antibody against the toxin. Careful adherence to infection control policies is critical to the control of *C. difficile*, especially at nursing facilities (SNF's), long-term care and rehabilitation facilities (LTCF) and hospitals, as well as in the community. CDAD primarily occurs in hospitals, where exposure to antimicrobial drugs (the major risk factor for CDAD) and environmental contamination by *C. difficile* spores are more common (3).

Methods of control are discussed as well as contact precautions: for patients with known or suspected *C. difficile*-associated disease and preferences for decontamination are reviewed from the peer reviewed literature.

## INTRODUCTION

**F**rom two previous reviews, Hookman and Barkin (4,5) joined the many who have written about the new more virulent strain of *Clostridium difficile*

Perry Hookman, M.D. and Jamie S. Barkin M.D., University of Miami Miller School of Medicine/Mount Sinai Medical Center, Division of Gastroenterology, Miami, Florida.

that was acknowledged in December 2005 in the National Institutes of Health (NIH)/Center for Disease Control's (CDC) Morbidity and Mortality Weekly Report (MMWR). This CDC report emphasized that, in the past, *C. difficile*-associated diseases (CDAD) usually affected hospital inpatients, but now was appearing in relatively healthy adults, including some who had not even been exposed to a hospital setting.

Two separate reports, by McDonald, et al and Loo, et al, indicated that, not only was the rate of disease associated with *C. difficile* increasing, but a previously uncommon strain of *C. difficile* infection (CDI) had been identified (6,7). This strain of *C. difficile*, which had variations in its toxin genes, was more resistant to fluoroquinolones than prior strains. This newer and more virulent organism has emerged as a cause of geographically-dispersed outbreaks of antibiotic-associated diarrhea (AAD), specifically *C. difficile* diseases (CDD), and *C. difficile*-associated diarrhea (CDAD) associated with *C. difficile*-associated colitis (CDAC).

Bartlett documented that, in the first five years in which CDAD was acknowledged to exist, 1978 through 1983, the most common cause of CDAD was the use of clindamycin (8). The standard diagnostic test was a cytotoxin assay. Standard management was to withdraw the implicated antibiotic and treat with oral vancomycin. Most patients responded well, but 25% relapsed when vancomycin was withdrawn.

Over the next 20 years (1983 through 2003), the most commonly implicated antibiotics were the cephalosporins, which reflected rates of use. Fluoroquinolones now are the major inducing agents, along with cephalosporins, which presumably reflects newly-acquired in vitro resistance and escalating rates of use.

Recently (2003 to 2008), *C. difficile* has been more frequent, more severe, more refractory to standard therapy, and more likely to relapse. This pattern has been widely distributed throughout the United States, Canada, and Europe and is now attributed to a new strain of *C. difficile*, alternatively designated as BI, NAP1, or ribotype 027 (all synonymous terms). This strain appears to be more virulent, because it produces large quantities of toxin. Recent experience has not altered principles of management for the individual patient, but it does serve to emphasize the need 1) for early recognition; 2) for improved methods to manage severe relapsing disease; and 3) for greater attention to infection control and antibiotic restraint.

This new strain, which has been causing virulent outbreaks in hospitals across the US and Europe during this first decade of the 21st century, persists. The emergence of this hypervirulent NAP1/O27 *Clostridium difficile* strain, also known as BI NAP1, has vastly altered the face of the disease, with increased nosoco-

mial outbreaks and concomitant morbidity. Even though the strain had been isolated as far back as 1984, it has emerged as a public concern with the development of fluoroquinolone resistance in our current era of widespread fluoroquinolone use.

In 2007, Blossom and McDonald (9) reported on the increasing incidence and severity of *Clostridium difficile*-associated disease (CDAD) attributable to this hypervirulent strain of *C. difficile* that produces increased levels of toxins A and B, as well as an extra toxin, known as “binary toxin.” This previously uncommon strain now is become epidemic. Also, unusually severe CDI has been reported in populations that previously had been thought to be at low risk, including peripartum women and healthy persons living in the community.

## THE CARRIER STATE

Lawrence has claimed that about twenty percent of hospitalized adults are *C. difficile* carriers; in long-term care facilities, carriage rate may approach 50% (10). Although asymptomatic, these individuals shed pathogenic organisms and serve as a reservoir for environmental contamination. Many patients are colonized with *C. difficile*, but have no symptoms. About 3% of healthy adults and 20%–40% of hospitalized patients are colonized with *C. difficile*, which in healthy persons is metabolically inactive in the spore form. Many patients have *C. difficile* as an asymptomatic organism in their intestine on hospital admission, and it only becomes a problem after they are treated with antibiotics, if, in fact, it ever induces symptoms. Exposure to antibiotics that disrupt the colonic microbial flora appears to be the most important risk factor for CDAD.

## TREATMENT OF CDI

Our current approach to managing recurrent CDI is metronidazole or vancomycin, depending on disease severity, for a standard 14-day course for the first recurrence.

## TREATMENT OF RECURRENT CDI

For a second recurrence, optimal treatment has not been established definitively, but we use the tapering

### A SPECIAL ARTICLE

and pulse-dosing regimen. Adding a probiotic containing either *Lactobacillus* or *S. boulardii* during the final four weeks of vancomycin therapy and for an additional four weeks thereafter, is also an option.

If that too fails, we treat the recurrent symptoms with vancomycin for at least 14 days, after which we discontinue vancomycin, and then administer rifaximin, 200 mg twice daily for 14 days. In remaining patients with recalcitrant CDI, other options, such as prolonged vancomycin therapy or fecal transplantation, can be considered.

### COMPLICATING CO-MORBIDITIES

The Agency for Healthcare Research and Quality (AHRQ) data make clear that one of the challenges in accurately diagnosing CDAD is that it is not unusual for patients to have multiple co-morbidities. The AHRQ found that hospitalized patients with CDAD had over ten diagnoses, versus just six diagnoses for patients without CDAD. According to recent AHRQ data, four out of the top twenty most common principle diagnoses observed with CDAD are infections (sepsis, pneumonia, urinary tract infection, and skin infection) where antibiotic use would be difficult to avoid (11).

PPI therapy also was associated with an increased risk of recurrent *C. difficile* colitis. At a large Veterans Affairs medical center in the US, among patients in whom *C. difficile* colitis was diagnosed between June 2004 and July 2005, patients receiving PPIs were 4.17 times as likely to have recurrence as their counterparts who not receiving them (12).

### SUMMARY OF CONTROL POLICIES

Aggressive CDAD control policies at the best hospitals have successfully decreased the incidence of CDAD. In June 2000, hospital-acquired *C. difficile* (CD) infection rate at the University of Pittsburgh Medical Center–Presbyterian, Pittsburgh, PA increased to 10.4 infections per 1,000 hospital discharges (HDs). The annual rate increased from 2.7 infections per 1,000 HDs to 7.2 infections per 1,000 HDs. This increase was accompanied by an increase in the frequency of severe outcomes. Forty-seven (51%) of 92 HA CD isolates in 2001 were identified as the “epidemic BI strain.”

To combat this epidemic of CDI, a comprehensive CD infection control “bundle” was implemented to control the outbreak (13). This CD infection control bundle consisted of education, increased and early case-finding, expanded infection-control measures, the development of a CD infection management team, and antimicrobial management. Process measures, antimicrobial usage, and hospital-acquired CD infection rates were analyzed, and CD isolates were typed. The rates of compliance with hand hygiene and isolation were 75% and 68%, respectively. The CD management team evaluated a mean of 31 patients per month (11% were evaluated for moderate or severe disease). The use of antimicrobial therapy associated with increased CD infection risk decreased by 41% during the period 2003–2005. The aggregate rate of CD infection during the period 2001–2006 decreased to 4.8 infections per 1,000 HDs; and, by 2006, it was 3.0 infections per 1,000 HDs, a rate reduction of 71%. During the period 2000–2001, the proportion of severe CD cases peaked at 9.4% (37 of 393 CD infections were severe); the rate decreased to 3.1% in 2002 and further decreased to 1.0% in 2006, a 78% overall reduction. In 2005, 13% of CD isolates were type BI (20% were hospital acquired), which represented a significant reduction from 2001. The outbreak of CD infection with the BI strain in hospital was controlled after implementing this CD infection control “bundle” and a CD infection management team. Thus, early identification, coupled with appropriate control measures, reduces the rate of CD infection and the frequency of adverse events.

### RECOMMENDED METHODS OF CONTROL UNDER SUPERVISION OF A CD INFECTION MANAGEMENT TEAM

- Place patients with *C. difficile* in private rooms.
- If private rooms are not available, place these patients in rooms with other patients who have *C. difficile*-associated disease.
- Perform hand hygiene procedures preferably using soap and water. To reduce the transmission of *C. difficile* spores, environmental disinfection with 10% sodium hypochlorite and hand-washing with soap

(continued on page 19)

(continued from page 16)

and water can be effective at removing the spores from hands and surfaces (14).

- Strict antiseptic procedures should be followed by health care workers in contact with the patient, and these procedures should include the use of disposable gloves, and a mask and gown.
- Because alcohol may not be as effective at killing *C. difficile* spores, health care workers must frequently wash their hands with soap and water, rather than with alcohol-based waterless hand sanitizers, especially when caring for CDAD patients (15).
- Patient-care equipment (like blood-pressure cuffs, stethoscopes and thermometers) should either be used only for the infected patient or cleaned well before they are used with another patient (16).
- Enhanced environmental cleaning with dilute bleach should be used to eliminate *C. difficile* spores from all patient contact surface areas, following a regular schedule<sup>17</sup>. These spores may remain on infected surface areas for months or even years (18).

A very important method of controlling outbreaks of *C. difficile*-associated disease should be restricting the use of antimicrobial agents that have been implicated as risk factors for the disease, as recommended by Gerding, et al (19). Davey, et al (20) documented that interventions to improve antibiotic prescribing practices to hospital inpatients can be successful, and that they can reduce antimicrobial resistance and the rates of hospital-acquired infections.

### ADDITIONAL CONTROL STEPS

- Control of Fluoroquinolone Use: Effective surveillance of antibiotic-resistant bacteria and CDAD must be intensified in every healthcare setting, but especially in long-term care and rehabilitation facilities (LTCF). All these facilities must have easy lab access for prompt and active surveillance culturing and *C. difficile* cyto-toxin testing, for both A and B, at the earliest indication of any infection or CDAD (21).
- Lab to unit communication must be improved. At the Mayo Medical School, the time between electronic medical record reporting of a positive result for a test for *C. difficile* toxin in stool and the ordering of antimicrobial therapy was compared during consecutive periods when results were not telephoned (n = 274) and when results were telephoned (n = 90) to the clinical service (22). The mean times to the ordering of antimicrobial therapy were 11.9 and 3.6 hours, respectively (p < .001).
- If your institution experiences an outbreak, consider using only soap and water for hand hygiene when caring for patients with *C. difficile*-associated disease; alcohol-based hand rubs are not as effective against spore-forming bacteria. In addition,
  - Use gloves when entering patients' rooms and during patient care
  - Use gowns if soiling of clothes is likely
  - Dedicate equipment, whenever possible.
- Implement an environmental cleaning and disinfection strategy:
  - Ensure adequate cleaning and disinfection of environmental surfaces and reusable devices, especially items likely to be contaminated with feces and surfaces that are touched frequently
  - Use an Environmental Protection Agency (EPA)-registered hypochlorite-based disinfectant for environmental surface disinfection after cleaning, in accordance with label instructions. Generic sources of hypochlorite (e.g., household chlorine bleach) also may be appropriately diluted and used
  - Follow the manufacturer's instructions for the disinfection of endoscopes and other devices
  - Infection control practices in long-term care and home health settings are similar to those practices taken in traditional health-care settings.

How to clean and disinfect surfaces and devices according to the CDC's evidence-based guidelines for the prevention of CDAD (reported at [http://www.cdc.gov/ncidod/dhqp/id\\_CdiffFAQ\\_HCP.html](http://www.cdc.gov/ncidod/dhqp/id_CdiffFAQ_HCP.html)):

- Surfaces should be kept clean, and body substance spills should be managed promptly, as outlined in the CDC's "Guidelines for Environmental Infection Control in Health-Care Facilities."
- Hypochlorite-based disinfectants have been used with some success for environmental surface disinfection in those patient-care areas where surveillance and epidemiology indicate ongoing transmission of *C. difficile*.
- Consult the aforementioned guidelines for the use conditions for generic sources of hypochlorite-based

A SPECIAL ARTICLE

products (e.g., household chlorine bleach) for disinfection of environmental surfaces.

- Note: EPA-registered hospital disinfectants are recommended for general use whenever possible in patient-care areas. At present, there are no EPA-registered products with specific claims for inactivating *C. difficile* spores, but there are a number of registered products that contain hypochlorite.
- A study by White, et al (23) revealed that all floor cleaning methods reduce the overall microbial load, though high counts and bacterial pathogens occasionally persist despite cleaning. Spray cleaning yielded marginally better results than traditional mopping and vacuuming. Wet scrubbing significantly reduced levels of coagulase-positive staphylococci ( $p = 0.03$ ); which, in combination with routine methods, produced an effect that persisted for at least a week.

CONCLUSIONS

- A sudden change in CDAD incidence in any medical institution should be reported immediately to public health officials.
- Finally, the development of a CD infection management team (CDMT) in each health care facility is strongly recommended to be part of a rapid response team (RRT). ■

References

1. Starr J. *Clostridium difficile* associated diarrhea: diagnosis and treatment. *BMJ*, 2005; 331(7515): 498-501.
2. Bartlett JG. Antibiotic-associated diarrhea. *NEJM*, 2002; 346(5):334-349.
3. Johal SS, Hammond J, Solomon K, et al. *Clostridium difficile* associated diarrhea in hospitalised patients: onset in the community and hospital and role of flexible sigmoidoscopy. *Gut*, 2004; 53(5): 673-677.
4. Hookman P, Barkin J. *C. difficile* Associated Disorders/Diarrhea (CDAD) and *C. difficile* Colitis (CDAC): The Emergence of a More Virulent Era. *Pract Gastroenterol*, 2006;52(4):1071-1075.
5. Hookman P, Barkin J. Guidelines for Prevention, Surveillance, Diagnosis, & Treatment, and, in this New Era of More Virulent Strains of Antibiotic Associated Diarrhea (AAD), *C. difficile*-associated Diseases/Diarrhea [CDAD] and *C. difficile* Colitis [CDAC]. *J Dig Dis Sci*, 2007;65.
6. Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. *NEJM*, 2005; 353(23):2442-2449.
7. McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of *Clostridium difficile*. *NEJM*, 2005; 353(23): 2433-2441.

8. Bartlett JG, Perl TM. The New *Clostridium difficile*—What Does It Mean? *NEJM*, 2005; 353(23): 2503-2505.
9. Blossom DB, McDonald LC. The challenges posed by reemerging *Clostridium difficile* infection. *Clin Infect Dis*, 2007;45(2): 222-227.
10. Lawrence SJ. Contemporary management of *Clostridium difficile*-Associated Disease. *Gastroenterol Endoscopy News Spec Ed*, 2007;35-40.
11. Elixhauser AA, Jhung MA, (Centers for Disease Control and Prevention). *Clostridium difficile*-Associated Disease in U.S. Hospitals, 1993-2005. HCUP Statistical Brief #50. April 2008. Agency for Healthcare Research and Quality, Rockville, MD. 2008.
12. Cadle RM, Mansouri MD, Logan N, et al. Association of proton-pump inhibitors with outcomes in *Clostridium difficile* colitis. *Am J Health Syst Pharm*, 2007;64(22):2359-2363.
13. Muto CA, Blank MK, Marsh JW, et al. Control of an Outbreak of Infection with the Hypervirulent *Clostridium difficile* BI Strain in a University Hospital Using a Comprehensive “Bundle” Approach. *Clin Infect Dis*, 2007;45(1):1274-1276.
14. Gerding DN, Muto CA, Owens RC Jr. Measures to control and prevent *Clostridium difficile* infection. *Clin Infect Dis*, 2008; 46(Suppl 1):S43-S49.
15. Boyce JM, Pittet D. Guidelines for hand hygiene in health-care settings: recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. *Infect Control Hosp Epidemiol*, 2003;23(Suppl):S3-S40.
16. Garner JS. Guideline for isolation precautions in hospitals. *Infect Control Hosp Epidemiol*, 1996;1753-1780.
17. Schulster L, Chinn RY. Guidelines for environmental infection control in health-care facilities: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC). *Morb Mortal Wkly Rep Recomm Rep*, 2003; 55(RR10): 1-42.
18. Barbut F, Petit JC. Epidemiology of *C. difficile* associated infections. *Clin Microb Infect*, 2001;7(8):405-410.
19. Gerding DN, Johnson S, Peterson LR, et al. *Clostridium difficile*-associated diarrhea and colitis. *Infect Control Hosp Epidemiol*, 1995;16(8): 459-477.
20. Davey P, Brown E, Fenelon L, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochran Dat System Rev*, 2005;(4): CD003543.
21. Simor AE, Bradley SF, Strausbaugh LJ, et al. SHEA Position Paper: *Clostridium difficile* in long-term-care facilities for the elderly. *Infect Control Hosp Epidemiol*, 2002; 23(11):696-703.
22. Verdoorn BP, Orenstein R, Wilson JW, et al. Effect of Telephoned Notification of Positive *Clostridium difficile* Test Results on the Time to the Ordering of Antimicrobial Therapy. *Infect Control Hosp Epidemiol*, 2008;29(7):658-660.
23. White LF, Dancer SJ, Robertson C. A microbiological evaluation of hospital cleaning methods. *Int J Environ Health Res*, 2007;17(4):285-295.

PRACTICAL  
GASTROENTEROLOGY  
**REPRINTS**  
Visit our web site at [www.practicalgastro.com](http://www.practicalgastro.com)