The incidence of *Clostridium difficile*-associated disease (CDAD) has increased over the past few years and more severe cases of CDAD have been reported. This changing epidemiology is possibly a result of the emergence of a more virulent strain of *C difficile* that is more resistant to fluoroquinolones and is associated with increased morbidity and mortality. Because of advanced age and frequent courses of antibiotic therapy, patients in long-term care facilities are at increased risk of *C difficile* infection. In addition to beta-lactams and clindamycin, the fluoroquinolones have recently been associated with increased rates of CDAD. Early identification of *C difficile* infection and prompt initiation of therapy with the most appropriate agent are critical to minimize morbidity and mortality in this era of increasingly severe CDAD. Metronidazole and vancomycin have been the mainstays of therapy, and recent data support the expanding role of vancomycin in the treatment of severe CDAD. Adjunctive therapy with probiotics, intravenous immunoglobulin, or rifampin has been used in refractory or recurrent CDAD. Adherence to the recommended infection control measures and the judicious use of antibiotics should also be part of the global management of CDAD in long-term care facilities. (J Am Med Dir Assoc 2007; 8: 290–299)

**Keywords:** *Clostridium difficile*-associated disease; CDAD; diarrhea; pseudomembranous colitis; *C difficile* colitis; fluoroquinolones; vancomycin; metronidazole; long-term care

The process of selecting articles for this review was as follows. References were identified by searching Medline, PubMed, and Medscape from 1980 to the present, along with abstracts of the 44th Annual Meeting of the Infectious Diseases Society of America (IDSA). Keywords used were *C difficile* colitis, *C difficile* diarrhea, long-term care, nursing home, fluoroquinolones, vancomycin, metronidazole, antibiotic-associated colitis, antibiotic-associated diarrhea, pseudomembranous colitis, and contact isolation.

**INTRODUCTION**

*Clostridium difficile* is a spore-forming gram-positive bacteria that produces two exotoxins, toxins A (a cytotoxin) and B (an enterotoxin).1,2 The organism is known to cause diarrhea and colitis and accounts for 15% to 25% of all episodes of antibiotic-associated diarrhea.3 *C difficile* causes a spectrum of diarrheal syndromes that vary widely in severity and are referred to by different names, including *C difficile*-associated diarrhea, *C difficile*-associated colitis, and pseudomembranous colitis.4 Pseudomembranous colitis has been the hallmark of disease; however, clinical presentation may range from asymptomatic colonization to toxic megacolon, perforation, and, on rare occasions, death.5–7 Thus, clinicians have recently begun to refer to infection with this organism as *C difficile*-associated disease (CDAD).

Over the past few years an increase has occurred in both the incidence and severity of CDAD, possibly because of the emergence of a strain of *C difficile* that has increased virulence, increased microbial resistance, or both. This strain has the ability to produce greater quantities of toxins A and B, is more resistant to the fluoroquinolones, and is associated with increased rates of morbidity and mortality. Residents of long-term care facilities (LTCFs) are particularly at risk because of extended stays in the LTCF, advanced age, frequent hospitalizations, and the widespread use of antibiotics in LTCFs.8

This article reviews the changing epidemiology of CDAD, characteristics of the newly identified strain, characteristics of
C DIFFICILE IN LONG-TERM CARE

C difficile is the most common infectious cause of acute diarrhea in nursing homes. A retrospective review from July 2001 through December 2003 in 200 LTCFs affiliated with major medical centers found that the incidence of CDAD ranged from 0 to 2.62 cases per 1000 resident-days. The highest rates of CDAD were noted in residents of subacute care units where the majority of patients were admitted from hospital settings.

In the absence of an outbreak of CDAD, the incidence of asymptomatic colonization with C difficile in LTCFs has ranged from 4% to 20%. A study of a 233-bed LTCF over a 6-month period found that almost one third of residents acquired C difficile within 2 weeks of antibiotic therapy, although the minority actually experienced diarrhea. A significant proportion of residents may already be carrying C difficile on admission to the LTCF, and up to 20% may acquire the organism during a stay. The risk of acquiring C difficile colitis in colonized patients was assessed through rectal swabs taken weekly for 9 weeks from patients with long-term stays (at least 7 days) in 3 hospital wards. Of 282 patients, 21% had a positive culture for C difficile during their hospital stay. Of these patients, 21% (51 patients) were symptom-free excretors. In a similar study, of 229 stool cultures collected from LTCF residents, 7.1% were positive for C difficile. However, none of these residents were symptomatic. There does not appear to be an increased risk of developing subsequent clinical illness in asymptomatic carriers compared with patients who are not colonized, and treatment of such carriers does not decrease the risk of developing CDAD.

CHANGING EPIDEMIOLOGY

McDonald and colleagues at the Centers for Disease Control and Prevention (CDC) analyzed national hospital discharge data from 1996 to 2003 to determine whether CDAD is increasing in acute care hospitals and to identify epidemiologic factors associated with the changing rates. The National Hospital Discharge Survey (NHDS) is conducted annually by the National Center for Health Statistics of the CDC and consists of diagnostic and demographic data collected from a national probability sample of discharge records. The estimated population-based rates of discharges with either a primary or a secondary diagnosis of CDAD during this period demonstrated that CDAD is increasing in the United States. From 2000 to 2003, the increase in CDAD listed as either the primary or secondary diagnosis on discharge was significantly higher than the prior period from 1996 to 2000 (Figure 1).

Along with the increased incidence of CDAD, there has been an increase in both morbidity and mortality associated with this infection. At a university medical center, the incidence of CDAD among hospitalized surgical patients with C difficile colitis increased from 0.68% in 1989 through 1999 to 1.2% in 2000; during these same time periods, overall morbidity and mortality doubled from 1.6% to 3.2%. From 1989 to 2000, 44 patients required colectomies and 20 died as a direct result of C difficile colitis.

In a second study, the length of stay and mortality among 161 hospitalized inpatients with nosocomial CDAD were compared with 656 control subjects without CDAD in a recent outbreak in Quebec during 2003 and 2004. Compared with the control group, patients with CDAD spent an average of 6.7 additional days in the hospital on first admission, and overall almost 10% of patients required admission to the intensive care unit and 2.5% required emergency colectomy. The 30-day mortality was 23% in patients with CDAD compared with 7% in the control group (P < .001), and the cumulative attributable mortality rate 12 months after diagnosis represented a dramatic increase in the severity of CDAD at this institution.

The changing epidemiology of CDAD may be the result of changes in antimicrobial use, practitioner prescribing habits, inadequate infection control practices, the emergence of a strain of C difficile with increased virulence and resistance, and a general aging of the overall population.

PATHOGENESIS AND RISK FACTORS

Originally, it was thought that the administration of antimicrobial therapy following asymptomatic colonization resulted in C difficile–associated diarrhea. However, Johnson and Gerding derived an alternative model of the pathogenesis for infection with C difficile. In this hypothesis, when patients are admitted to a hospital they are at negligible risk for CDAD until they are administered antimicrobial therapy. If a patient is exposed to C difficile during or after such treatment, either the patient will become colonized without diarrhea, will develop CDAD, or will not become infected at
all (Figure 2). The importance of the host immune response in the pathogenesis of *C. difficile* also has been explored. Kyne and colleagues24 conducted a prospective study to determine the immune response to *C. difficile*. Of 271 patients, 84 (31%) became colonized at some point during their hospital stay. Of these 84 patients, 47 (17%) developed active infection and 37 (14%) remained asymptomatic carriers and reservoirs of infection. Baseline immunoglobulin G (IgG) antibody levels to toxins A and B were similar in patients who later became colonized with *C. difficile* compared with those who did not acquire the organism. After acquiring the organism, however, those who became asymptomatic carriers had significantly greater increases in serum levels of IgG antibodies against toxin A than those in whom *C. difficile* infection developed. These patients also appeared to be protected by these higher IgG antibody levels.

Antibiotic exposure within the prior 2 months appears to be the most important risk factor for the development of *C. difficile* infection.35 Antibiotics, as well as other agents, have been associated with the development of *C. difficile* infection; traditionally, however, clindamycin,3,26,27 the penicillins, and cephalosporins25 have been identified as classic offenders. The use of cephalosporins or trimethoprim-sulfamethoxazole has been identified as a significant risk factor for the development of asymptomatic carriage of *C. difficile* in LTCFs.15 Recent reports suggest that the fluoroquinolones may play a major role in the development of CDAD.9

Antibiotic use in the LTC setting is common. Studies reviewing antibiotic use in LTCFs reveal that from 50% to 75% of residents are exposed to 1 or more courses of antibiotics over a 12-month period28–32 and approximately 50% of these antibiotic courses were administered for unknown indications.33 One study of 2408 patients receiving 9373 courses of antibiotics determined that the majority of antibiotics given in these 22 LTCFs were for either respiratory tract or urinary tract infections.28 Therefore, optimizing antibiotic prescribing practices could have an impact on the development of *C. difficile* infection in this setting.

Other risk factors associated with the development of CDAD include contact with a carrier, an infected patient, or a contaminated environment; advanced age; long length of stay in a health care facility; and gastrointestinal surgery or manipulation.34–38 Retrospective data have also identified a patient’s albumin level as a major risk factor for CDAD, with 68% of patients with CDAD having an albumin level less than 3 g/dL.39 Patients with immunosuppression and those with severe underlying illnesses may also be at risk for developing CDAD.8

One recent study identified the concomitant use of gastric acid suppressive therapy as a possible risk factor for the development of CDAD. A case-controlled study in England reported that the use of proton pump inhibitors was associated with an increased risk (adjusted rate ratio 2.9; 95% confidence interval [CI], 2.4–3.4) of community-acquired *C. difficile* infections.40 Another retrospective review of 53 nursing home patients identified the use of proton pump inhibitors as a significant risk factor when compared with a control group (60% versus 32%, respectively; *P* < .05).39 In contrast, in the Canadian study by Pépin, proton pump inhibitors were not found to be associated with CDAD.41 These data should be further investigated in the United States to better characterize the role of gastric acid suppressive therapy in the development of CDAD.

**EPIDEMIC STRAIN OF *C. DIFFICILE***

Recent reports suggest that the increasing incidence and increasing severity of CDAD in the United States may be associated with the emergence of a new strain of *C. difficile* with increased virulence, antibiotic resistance, or both. A total of 187 *C. difficile* isolates were collected from 8 health care facilities in 6 states where outbreaks occurred between 2000 and 2003.42 Isolates were characterized by restriction endonuclease analysis (REA), pulsed-field gel electrophoresis (PFGE), and toxinotyping and then compared with a database of more than 6000 isolates obtained before 2001. Isolates that belonged to one REA group (BI) and the same PFGE type (NAP1) were identified at all 8 facilities. This epidemic strain, identified as BI/NAP1, is distinct from other outbreak strains reported during the late 1980s (the so-called J strain). All BI/NAP1 isolates were of toxinotype III, and resistance to the 8-methoxyfluoroquinolones (gatifloxacin and moxifloxacin) was more common in the current isolates than in non-BI/NAP1 isolates (100% vs 42%; *P* < .001).

The epidemic strain is also associated with the presence of binary toxin (referred to as binary toxin CDT), which is similar to the iota toxin found in *C. perfringens*.43 Previously found in only 2% to 3% of hospital isolates, the production of this additional toxin may represent a potential virulence factor in the BI/NAP1 strain of *C. difficile*.44 An 18-base pair (bp) deletion in the tcdC gene has been identified in the epidemic strain. This gene is believed to function as a negative regulator of toxin production such that deletions in the gene result in unsuppressed toxin production. Concentrations of toxins A and B produced in vitro by this epidemic strain were 16 and 23 times higher, respectively, than those measured in isolates of 12 different types.44 Hyperproduction of
toxins A and B may contribute to the development of more severe cases of CDAD.

Figure 3 shows the geographic distribution of outbreaks of CDAD in the United States. Listed are the 22 states where outbreaks have been definitively defined by the CDC as of January 2007 (personal communication with McDonald LC, CDC, January 26, 2007).42,45 Outbreaks caused by BI/NAP1 strains in 3 additional states (Arizona, Indiana, and Minnesota) have been confirmed by Dale N. Gerding, MD, at the Hines VA Clostridium difficile Research Lab, which have not yet been confirmed by the CDC. (See note added in Acknowledgements).

ROLE OF FLUOROQUINOLONES

Gaynes and colleagues46 conducted a retrospective, case-controlled study of 612 LTCF residents to determine the cause of increased rates of CDAD reported from October 2001 to June 2002. The rate of CDAD increased from 0.44 per 1000 patient-days during January to September 2001 to 1.32 per 1000 patient-days during the outbreak period (October 2001 through June 2002) (P < .01). The increased rate of CDAD coincided with a formulary change from levofloxacin to gatifloxacin in October 2001 (Figure 4). This increase subsequently resolved during the last time period shown, when the formulary was changed back from gatifloxacin to levofloxacin in July 2002.

A case-controlled study of 1719 episodes of nosocomial CDAD at 12 hospitals in Quebec determined that patients with C difficile infection were more likely than matched controls to have received fluoroquinolones (odds ratio [OR] = 3.9) or cephalosporins (OR = 3.8) compared with clindamycin (OR = 1.6) or macrolides (OR = 1.3).47 Of these isolates, 82% were identified as being the epidemic strain, which were resistant to fluoroquinolones and had the binary toxin gene present.

From 1999 to 2000–2001, the incidence of nosocomial cases of CDAD in a Pittsburgh hospital increased from 2.7 to 6.8 cases per 1000 discharges (P < .001) and the number of severe cases also increased. This increased incidence led to a retrospective review of 2334 patients hospitalized with C difficile colitis from January 1989 to December 2000 and involved a case-controlled study to identify risk factors for nosocomial C difficile infection and the evaluation of trends in antibiotic use before and during the outbreak.48 No obvious changes occurred in the patient population or infection control practices; however, the outbreak was preceded by the addition of levofloxacin to the formulary. An independent risk factor for the development of C difficile infection was exposure to ceftriaxone or clindamycin. A more significant risk factor that may have contributed substantially to the outbreak was exposure to levofloxacin. Antibiotic trend analysis demonstrated that cephalosporin and clindamycin use did not change significantly but the addition of levofloxacin to the formulary was accompanied by a significant increase in fluoroquinolone use (P < .001), which preceded the C difficile outbreak by 9 months.

Pépin and colleagues49 performed a retrospective cohort study of hospitalized patients during an epidemic in Quebec (January 2003 through June 2004) and evaluated 293 incident cases of CDAD. More than 50% of patients were older than 80 years of age and received fluoroquinolone therapy, and 21.5% died within 30 days of the initial diagnosis. Fluoroquinolones were identified as the most important risk factor for CDAD during this large epidemic (adjusted hazard ratio [AHR] = 3.44). Drug-specific AHRs were also measured among patients who received a fluoroquinolone and tended to be lower among patients who received levofloxacin (AHR = 2.52) compared with those who received ciprofloxacin (AHR = 3.74). A small number of patients received the newer respiratory fluoroquinolones; however, the risk associated with

**Fig. 3.** Outbreaks of Clostridium difficile in the 22 states definitively defined by the Centers for Disease Control and Prevention and the 3 identified at the Hines VA Clostridium difficile Research Lab.42,45 (Courtesy of L. Clifford McDonald, MD, Centers for Disease Control and Prevention.)

**Fig. 4.** Fluoroquinolone treatment and rates of Clostridium difficile–associated disease (CDAD). In October 2001, the formulary changed from levofloxacin to gatifloxacin, and an associated increase in CDAD may be observed. This increase subsequently resolved during the last time period shown, when the formulary was changed back from gatifloxacin to levofloxacin. (Adapted from Gaynes R, Rimland D, Killum E, et al. Outbreak of Clostridium difficile infection in a long-term care facility: association with gatifloxacin use. Clin Infect Dis 2004;38:640–645.)
gatifloxacin (AHR = 6.10) appeared higher than with moxifloxacin (AHR = 2.04).

Fluoroquinolones have become the most widely prescribed class of antibiotics in the United States.\textsuperscript{50} Prospective studies need to confirm the recent observations that support the association of the fluoroquinolones with increased rates of CDAD. In an effort to control the spread of CDAD, clinicians should include this class of antibiotics as part of any antimicrobial stewardship program.

**DIAGNOSIS**

**Clinical Presentation**

The diagnosis of CDAD is largely based on clinical suspicion and recognition of epidemiologic characteristics. The clinical features of CDAD can range from mild diarrhea to life-threatening colitis. The most common clinical symptoms include watery diarrhea, fever that may be low grade, loss of appetite, nausea, and abdominal pain or distension.\textsuperscript{8} Early recognition of these signs and symptoms and prompt empiric treatment are essential to prevent complications such as toxic megacolon, leukemoid reactions, septic shock, requirement for colectomy, and death (rarely).\textsuperscript{19,20,42,51–53} CDAD caused by an epidemic strain generally has a more rapid onset and more pronounced clinical signs and symptoms. Clinicians must recognize the potential markers of severe disease such as admission to an intensive care unit, the presence of a high serum creatinine level,\textsuperscript{51} sepsis,\textsuperscript{8} marked leukocytosis,\textsuperscript{53,54} or a significantly decreased serum albumin level.\textsuperscript{26} Because of the increasing incidence and severity of CDAD and the increased rates of mortality and morbidity, health care professionals should suspect CDAD in any patient in a hospital or LTCF who has diarrhea and has recently received antibiotics.\textsuperscript{6}

**Laboratory Testing**

The most commonly used laboratory tests to diagnose CDAD include toxin testing, antigen detection assays, and stool culture. The advantages and disadvantages of the common diagnostic testing methods are shown in Table 1.\textsuperscript{55–60} Stool culture may be the most sensitive test but may be the least specific because it does not distinguish between toxin-producing strains and those associated with colonic colonization.\textsuperscript{5,36,57} It is also labor-intensive and costly, and results are not available to the clinician for up to 72 hours after collection. Stool culture is best used for the molecular typing of isolates during outbreaks of \textit{C difficile}.

Antigen detection is a rapid method (less than 1 hour) that detects the presence of \textit{C difficile} antigen by latex agglutination or immunochromatographic assay. Antigen detection tests must be combined with toxin testing to verify the diagnosis because nontoxigenic strains of \textit{C difficile} can be found in up to 20% of patients.\textsuperscript{57}

The gold standard for diagnosis of \textit{C difficile} infection is tissue cytotoxic assay for \textit{C difficile} in stool.\textsuperscript{58–60} Although it is the most sensitive test available, tissue culture assay requires technical expertise, is costly, requires up to 48 hours for a final result,\textsuperscript{8,57,60} and detects only toxin B.\textsuperscript{8}

Same-day results can be obtained from toxin testing using an enzyme immunoassay (EIA) that detects toxin A, or toxins A and B. However, EIA is less sensitive than tissue culture assay.\textsuperscript{8} EIAs that detect only toxin A will not detect A–B–

| Table 1. Advantages and Disadvantages of Diagnostic Testing Methods for \textit{Clostridium difficile}* |
|---------------------------------|-----|--------------------|-------------------------|---------------------|
| Diagnostic Test                | Turnaround Time | Sensitivity, % | Advantages | Disadvantages |
| Endoscopy                        | 2 h          | 51               | Diagnostic of pseudomembranous colitis. | Low sensitivity. |
| Anaerobic culture               | 72 h         | 89–100           | Results useful for molecular typing. | Does not distinguish toxin-producing strains. |
| ELISA: toxin A                  | 2 h          | 80–95            | Easy to use. | Does not detect A–B+ strains. |

* Based on data from Kelly et al,\textsuperscript{56} Wilkins and Lyerly,\textsuperscript{57} and Gerding et al.\textsuperscript{61}
isolates, which may also cause clinical disease and be cross-transmitted in health care institutions. ELAs that detect both toxins provide increased sensitivity for those specimens that contain only low levels of toxins A and B.\(^5\)

A test is now commercially available to determine whether an institution has been contaminated by the NAP1 strain of \textit{C difficile} (DiversiLab Clostridium Kit, Spectral Genomics, Inc., Houston, TX). Currently, the test may be used solely to compare a \textit{C difficile} isolate to virulent epidemic strains such as PFGE-type NAP1 but not to establish the diagnosis of CDAD in a patient. The test may also provide additional information such as differentiation of toxinotypes, the presence or absence of the binary toxin CDT, and deletions in the tcdC gene.

Because laboratory testing for the BI/NAP1 strain in patients is not yet possible, the clinician must rely on clinical suspicion to provide appropriate antibiotic therapy. However, there are general principles of diagnostic testing for \textit{C difficile}. When collecting stool samples for diagnostic testing, generally 1 or 2 samples are sufficient. Obtaining more specimens does not significantly increase the yield. Testing should only be performed on watery or loose stool, and samples should be stored in the refrigerator and collected promptly by the laboratory.\(^6\) High clinical suspicion of CDAD should always override a negative result.\(^9\) Stool samples should not be tested in asymptomatic patients unless an outbreak investigation is under way and “test of cure” cultures after a treatment course should not be performed in previously symptomatic patients.

To determine the presence of pseudomembranous colitis, an advanced stage of the disease, direct visualization of the colonic mucosa using sigmoidoscopy or colonoscopy is necessary. Full colonoscopy usually is performed with caution when fulminant colitis is suspected because of the concern of colonic perforation. Abdominal imaging studies, including computed tomography scans, may reveal “thumbprinting” of the colonic mucosa, suggesting the presence of mucosal edema. On occasion, massive colonic wall thickening or ascites is seen in patients with severe \textit{C difficile} colitis.\(^5\)

### TREATMENT OF CDAD IN LONG-TERM CARE

#### First Occurrence

Whenever possible, the offending agent should be discontinued in patients with suspected CDAD. Intravenous fluid replacement and mild antidiarrheals such as bismuth subsalicylate may be sufficient to cause resolution of symptoms in mild cases of CDAD. Antiperistaltics (such as atropine/diphenoxylate [Lomotil] and loperamide [Imodium]) and opioid analgesics should be avoided because they may precipitate toxic megacolon.\(^7\)\(^8\) For moderate to severe infection, oral antibiotic therapy directed against \textit{C difficile} is required.\(^9\)

According to the Guidelines from the American College of Gastroenterology (ACG), the Society for Healthcare Epidemiology of America (SHEA), and the American Society of Health System Pharmacists (ASHP), acceptable treatment options for patients with symptomatic CDAD are metronidazole and vancomycin.\(^6\)\(^9\)\(^11\)

Prospective, comparative studies between metronidazole and oral vancomycin have enrolled small numbers of patients and shown comparable response (>90%) and relapse rates (5% to 20%).\(^6\)\(^2\) Resolution of diarrhea occurs more rapidly in patients treated with oral vancomycin (3 days) compared with metronidazole (4.6 days).\(^1\)\(^5\) A prospective, randomized trial comparing metronidazole with oral vancomycin was recently presented at the 44th Annual Meeting of the Infectious Diseases Society of America (IDSA).\(^6\) Patients were stratified based on severity of CDAD (mild/moderate versus severe CDAD). Of 81 patients with mild CDAD, both the cure rates (98% with vancomycin versus 90% with metronidazole; \(P = 0.36\)) and relapse rates (5% relapse with oral vancomycin versus 8% with metronidazole; \(P = 0.67\)) were similar. However, of 69 patients with severe CDAD, the cure rate was 97% for vancomycin compared with 76% for metronidazole (\(P = 0.02\)) and there was no statistical difference in relapse rates (10% vancomycin versus 21% relapse with metronidazole; \(P = 0.30\)). The authors concluded that oral vancomycin is superior to metronidazole in the treatment of severe but not mild CDAD and that vancomycin should be considered as first-line therapy in severe CDAD. Treatment guidelines for CDAD are currently being revised by IDSA and SHEA and are expected to be published in the Fall of 2007 (http://www.idsociety.org/Content/NavigationMenu/Practice_Guidelines/Standards_Practice_Guidelines_Statements/H11022/Standards_Practice_Guidelines_Statements.htm).

Given the higher cost of oral vancomycin and guidelines of the Hospital Infection Control Practices Advisory Committee (HICPAC) for appropriate use of vancomycin,\(^6\) oral metronidazole has historically been the preferred agent for mild to moderate disease. Prior use of intravenous vancomycin was identified as a major contributor to the risk of vancomycin-resistant enterococcal (VRE) infection or colonization in a review of 18 case-controlled studies;\(^6\) however, another study failed to find an association between oral vancomycin therapy for \textit{C difficile} and culture positivity for VRE.\(^6\) Recent data also suggest that other antimicrobials may influence VRE colonization. Data demonstrate that most antimicrobials with antianaerobic activity, including metronidazole and vancomycin, promote the overgrowth of VRE in stool.\(^7\)

Because of this concern about the emergence of gram-positive resistance, oral vancomycin has generally been reserved for patients who are intolerant to metronidazole, have severe or fulminant CDAD, or have failed metronidazole therapy. A recent prospective, randomized, controlled trial comparing oral metronidazole and oral vancomycin supports the use of vancomycin in patients with severe CDAD and white blood cell counts higher than 20,000/mm\(^3\).\(^6\)\(^7\)\(^1\)

Regardless of which treatment course is selected, it is preferable to administer the agent orally to provide the highest concentration of drug at the site of infection. In severely ill patients, however, the oral route may not be available. Anecdotal experience suggests that intravenous metronidazole is effective in the treatment of CDAD, and bactericidal fecal concentrations can be achieved in acute disease when metronidazole is delivered by this route.\(^7\)\(^2\)\(^7\) Vancomycin can also be administered via a nasogastric tube or a percutaneous endoscopic gastrostomy tube, as well as by enema.
Recurrent and Refractory Disease

There have been recent reports of therapeutic failures and an increased rate of recurrence with the use of oral metronidazole in the treatment of CDAD. Up to 45% of patients who have an initial relapse are likely to experience subsequent episodes. Relapse or re-infection with C difficile will occur in 12% to 24% of patients within 2 months of the initial episode; up to 65% of patients who have suffered 2 or more episodes will have another recurrence.

Recent reports of metronidazole and vancomycin treatment outcomes have noted a marked increase in metronidazole treatment failures since 2000. A prospective, observational study of 207 patients treated with metronidazole for CDAD determined that 103 patients (50%) were cured by the initial course of therapy and had no disease recurrence. It was also noted, however, that 46 patients (22%) continued to have symptoms for at least 10 days despite ongoing therapy and 58 (28%) had an initial response but then a recurrence of infection within 90 days of completing therapy. The mortality rate was higher among patients who did not respond fully to an initial course of therapy compared with those who did respond initially (33% versus 21%; P < .05). A retrospective review of patients with CDAD treated with metronidazole in Quebec from 1991 to 2004 was conducted to determine the rates of treatment failure and relapse. From 1991 to 2002, treatment failures with metronidazole were reported to be 9.6% and the rate of recurrence at less than 60 days as 20.8%. From 2003 to 2004, however, treatment failure rates with metronidazole increased to 25.7% and relapses at less than 60 days increased to 47.2% (P < .001 for all comparisons) (Figure 5).

A retrospective review of 99 patients treated for CDAD during hospitalization from January 2000 to September 2001 reported 61 metronidazole responders (62%) and 38 treatment failures (38%). An albumin level of less than 2.5 g/dL and a stay in the intensive care unit were identified as predictors of failure of metronidazole therapy for CDAD.

Prior observations suggest that more than 90% of initial recurrences can be retreated with the same agent used for initial treatment because the first recurrence does not appear to be related to in vitro resistance. In patients who have multiple recurrences or who are refractory to treatment, various strategies have been used with variable success. There are reports of tapered or pulse dosing of vancomycin resulting in positive outcomes. Adjunctive therapies with probiotics, intravenous immunoglobulin, and corticosteroids have also been used. In clinical trials evaluating probiotics such as Saccharomyces boulardii or Lactobacillus for the adjunctive treatment of CDAD, the beneficial effect has been limited to a subgroup of patients with recurrent CDAD or in patients with severe CDAD receiving high-dose oral vancomycin. Probiotics are safe and easy to administer; however, current data fail to provide sufficient evidence for the routine use of probiotics in the treatment of CDAD.

Intravenous immunoglobulin and corticosteroids have also been used in a limited number of patients; however, no randomized, controlled data exist to support their routine use in patients with CDAD. In patients with severe disease who develop toxic megacolon or ileus, traditional treatment with oral or intravenous agents may not be successful because fecal concentrations of antibiotics are inconsistent. Adjunctive intracolonic vancomycin administration has been shown to prevent recurrence and complications in a small series of patients with severe CDAD.

The addition of rifampin to an existing C difficile antibiotic regimen such as metronidazole or vancomycin has also been evaluated. There have been anecdotal reports of treatment success with the use of the combination therapy with vancomycin and rifampin. In an early study of 7 patients with multiple pathological and clinical relapses who were treated with this combination, diarrhea and abdominal pain resolved in all. A recent prospective, randomized trial evaluated oral metronidazole and rifampin in the treatment of 39 patients with an initial episode of CDAD. Combination therapy with metronidazole and rifampin did not reduce the median time to resolution of symptoms nor did it reduce the likelihood of relapse when compared with metronidazole alone. Significantly more deaths occurred in the combination group than in the metronidazole-alone group (6 of 19 versus 1 of 20; P = .04). The authors concluded that there is no role for the routine use of rifampin as adjunctive therapy.

Treatment with donor stool administered by way of a nasogastric tube has been used successfully in patients with recurrent CDAD. In this procedure, the normal colonic flora that has been disrupted by C difficile and antibiotic therapy is replaced. No controlled data exist, however, and the process is not esthetically pleasing.

PREVENTION AND CONTROL

Transmission of C difficile can occur on several levels. Hand carriage by health care workers can result from direct contact with stool when patients are infected or colonized with C difficile and is an effective way of cross-transmitting the organism to other patients. C difficile spores may also contaminate inanimate surfaces in the patient’s environment such as bed rails, over-bed tables, other furniture, toilets, bedpans, mops, and weight scales. Medical equipment such as stetho-
scopes and electronic rectal thermometers may play a role in the cross-transmission of the organism. Friction-based hand hygiene and appropriate infection control–based barrier use have been shown to be effective in preventing nosocomial transmission of C. difficile. Because alcohol-based hand gels are not sporicidal, friction-based hand hygiene with soap and water is required to remove spores on skin surfaces.

Cleaning and disinfecting environmental surfaces and reusable equipment with a 10% bleach solution has been shown to be an effective method of disinfection. In a before-and-after interventional study, patients in 3 units were evaluated to determine if unbuffered 1:10 hypochlorite solution (10% bleach solution) used routinely as an environmental disinfectant was effective in reducing the incidence of CDAD. The introduction of a 10% bleach solution for routine cleaning was effective in reducing the incidence of CDAD from 8.6 to 3.3 cases per 1000 patient-days in patients who had received bone marrow transplantation (hazard ratio, 0.37; 95% CI, 0.19–0.74) when compared with a quaternary ammonium solution. In another study, surface contamination with C. difficile was decreased with the use of an unbuffered hypochlorite solution but the use of a phosphate-buffered hypochlorite solution was most effective. It is difficult to determine the benefit of environmental disinfection because multiple infection control procedures have generally been employed simultaneously. Although it appears that cleaning with bleach is more effective at reducing the levels of environmental C. difficile spores, it is uncertain whether long-term use, particularly at high concentrations, is sustainable given the corrosive nature of bleach.

Based on the mode of transmission, patients with CDAD and fecal incontinence should be cared for in private rooms. A private room should be considered for any resident with CDAD until diarrhea has resolved. In residents with active diarrhea, health care workers should employ contact isolation procedures, which require the use of gloves and other appropriate barriers when contact with the resident or the resident’s environment occurs. Medical equipment such as stethoscopes and blood pressure cuffs should not be shared with other residents.

Because antibiotic exposure is an important risk factor for the development of CDAD, antibiotic prescribing habits in facilities should be reviewed for appropriateness of empiric and ongoing therapy. Targeted restriction of high-risk agents may be of some value in decreasing the rates of CDAD. A systematic review of antimicrobial prescribing in hospitals reported that several antibiotic interventions are effective in the control of CDAD. For example, institutional antibiotic policies involving the restriction of clindamycin or third-generation cephalosporins have been associated with a subsequent decrease in the incidence of C. difficile–associated diarrhea. Conversely, data have also demonstrated increased rates of CDAD following unrestricted use of extended-spectrum antibiotics. As previously discussed, fluoroquinolone therapy has been linked to an increased risk of CDAD. Widespread use of the fluoroquinolones may have contributed to increased rates of CDAD caused by the spread of a C. difficile strain that is more resistant to fluoroquinolones. Sparing the use of fluoroquinolones should be among the practices of interest to control nosocomial cases of CDAD.

SUMMARY

A dramatic increase has been observed in both the incidence and severity of CDAD. Additionally, an expanding spectrum of diseases associated with C. difficile has been noted. The causes and mechanisms of the increased virulence of the epidemic strain of C. difficile are currently under investigation. Residents of LTCFs are particularly at risk because of frequent hospital stays, advanced age, exposure to multiple courses of antibiotics, and numerous comorbidities. Optimal management of CDAD is dependent on prompt diagnosis, early treatment with the appropriate antibiotics, effective infection control measures, and the judicious use of antibiotics. Addressing all of these management strategies is important to minimize the morbidity and mortality associated with CDAD in LTCFs.

ACKNOWLEDGMENT

Staci Pacetti, PharmD, assisted in the researching and writing of this article.

Note: As of April 3, 2007, outbreaks of Clostridium difficile infection in two additional states (Minnesota and Rhode Island) have been confirmed by the Centers for Disease Control and Prevention. The Hines VA Clostridium difficile Research Lab has identified outbreaks in Arizona, Indiana, and the District of Columbia. [Centers for Disease Control and Prevention. Data and Statistics about Clostridium difficile Infections. www.cdc.gov/ncidod/dhqp/id_Cdiff_data.html. Accessed June 1, 2007.]

REFERENCES


