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Narrative Review: The New Epidemic of *Clostridium difficile*–Associated Enteric Disease

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Antibiotic-associated diarrhea and colitis were well established soon after antibiotics became available. Early work implicated *Staphylococcus aureus*, but in 1978 *Clostridium difficile* became the established pathogen in the vast majority of cases. In the first 5 years (1978 through 1983), the most common cause was clindamycin, the standard diagnostic test was the cytotoxin assay, and standard management was to withdraw the implicated antibiotic and treat with oral vancomycin. Most patients responded well, but 25% relapsed when vancomycin was withdrawn. During the next 20 years (1983 through 2003), the most commonly implicated antibiotics were the cephalosporins, which reflected the rates of use; the enzyme immunoassay replaced the cytotoxin assay because of speed of results and technical ease of performance; and metronidazole replaced vancomycin as standard treatment, and principles of containment hospitals became infection control and antibiotic control. During the recent past (2003 to 2006), *C. difficile* has been more frequent, more severe, more refractory to standard therapy, and more likely to relapse. This pattern is widly distributed in the United States, Canada, and Europe and is now attributed to a new strain of *C. difficile* designated BI, NAP1, or ribotype 027 (which are synonymous terms). This strain appears more virulent, possibly because of production of large amounts of toxins, and fluoroquinolones are now major inducing agents along with cephalosporins, which presumably reflects newly acquired in vitro resistance and escalating rates of use. The recent experience does not change principles of management of the individual patient, but it does serve to emphasize the need for better diagnostics, early recognition, improved methods to manage severe disease and relapsing disease, and greater attention to infection control and antibiotic restraint.

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Diarrhea and colitis due to *Clostridium difficile* are well-recognized and extensively studied iatrogenic complications of antibiotic use and have been for nearly 30 years. Important risks for infection include hospitalization, advanced age, gastrointestinal surgery or gastrointestinal procedures, and antibiotic exposure. The most common inducing agents have been clindamycin or broad-spectrum cephalosporins, but nearly all agents with an antibacterial spectrum may be responsible. The cytotoxin assay that originally led to the detection of *C. difficile* in 1978 remains the most sensitive diagnostic test, but the enzyme immunoassay is now used by most laboratories because of ease of processing, cost, and speed of results. Standard treatment of *C. difficile* infection includes withdrawal of the inducing agent and use of oral metronidazole or oral vancomycin; metronidazole is preferred in guidelines, but vancomycin is probably more effective, especially in seriously ill patients. The major complications of treatment are failure to respond, primarily because of advanced disease with ileus, and relapse or reinfection after treatment is discontinued. Prevention principles include hospital infection control and antibiotic restraint.

Against this background, there is a new epidemic of *C. difficile* infection that is occurring more frequently and is more serious and more refractory to therapy. Evidence of the severity of the infection includes high rates of toxic megacolon, leukemoid reactions, severe hypoalbuminemia, requirement for colectomy, shock, and death. These complications are most common in elderly patients, and the inducing agents are often fluoroquinolones and cephalosporins. Analysis of outbreaks in North America implicates a unique strain of *C. difficile* that produces large amounts of toxin in vitro, produces a binary toxin of uncertain clinical significance, and is resistant to fluoroquinolones in vitro. Successful management of patients with this strain requires early detection of infection, rapid treatment, and implementation of infection control, sometimes including antibiotic control.

Clostridium difficile was identified as the major cause of antibiotic-associated diarrhea and the nearly exclusive cause of pseudomembranous colitis in 1978. Subsequent work in the following 2 years defined the clinical features, methods of laboratory diagnosis, epidemiology, principles of infection control, and treatment of *C. difficile*–associated disease. *Clostridium difficile* infection is an important and frequent iatrogenic complication, but it has been relatively easy to manage, with the exception of occasional institutional outbreaks and a nagging problem of relapsing disease following treatment. However, during the past 5 years, an unanticipated increase in infection has been recognized, particularly in some locations where *C. difficile*–associated disease has become more frequent, more serious, and more refractory to standard therapy. It now seems that this change is explained by a unique strain of *C. difficile* that has unusual virulence factors, which may account for increased severity, and fluoroquinolone resistance, which

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Clostridium difficile is the most common identifiable bacterial cause of diarrhea in the United States.

Tissue culture assay is the best diagnostic test to detect the cytotoxin; enzyme immunoassay is the test used in most hospitals, but it has a sensitivity of only about 75%.

A new epidemic strain of *C. difficile* has emerged that causes more frequent and more serious disease.

Features of severe disease include ileus, toxic megacolon, pseudomembrane formation, leukemoid reactions, hyperalbuminemia, requirement for colectomy, sepsis, and death.

Risk factors are use of antibiotics (especially broad-spectrum cephalosporins and fluoroquinolones), advanced age, hospitalization, and gastrointestinal surgery or gastrointestinal procedures.

Oral vancomycin is the preferred treatment for seriously ill patients.

Infection control and antibiotic control are important preventive measures.

may account for increased frequency. These recent observations have resulted in renewed interest in an "old pathogen." This review updates the status of *C. difficile*–associated enteric disease and its management in light of these new observations.

Initial Studies (1974 to 2003)

Antibiotic-associated enterocolitis was generally attributed to *Staphylococcus aureus* in the first 25 years of the antibiotic era (1, 2). In 1974, Tedesco and colleagues (3) reported results of a prospective study of 200 patients given clindamycin who underwent endoscopy after reporting diarrhea. In this study, 41 (20.5%) patients had diarrhea and 20 (10%) had pseudomembranous colitis (3). Despite the ease of recovering *S. aureus* in stool, tests to detect the organism yielded negative results. This led our group and others to pursue an alternative putative agent by using the hamster model (4) for correlations with observations in patients. *Clostridium difficile* was reported as the agent of antibiotic-associated pseudomembranous colitis in 1978 (5).

During the ensuing 25 years, researchers established essential data documenting associated risks, clinical features, diagnosis, and management of *C. difficile*–associated diarrhea that became widely accepted.

Risk Factors

Almost all studies include the 3 major risks for infection with *C. difficile*: antibiotic exposure, advanced age, and hospitalization (6–8). With regard to antibiotic exposure, any antimicrobial agent with an antibacterial spectrum can be the cause, but there is a hierarchical list of agents that has been subject to change. Clindamycin followed by ampicillin or amoxicillin played prominent roles in the 1970s, but these were largely supplanted by cephalosporins in the 1980s (9, 10). Researchers from Sweden showed that advanced age was a risk in population-based analyses indicating that the rate per 100 000 persons older than 65 years of age was 20 times higher than that in persons younger than 20 years of age (11). The risk associated with hospitalization and chronic care facilities is attributed to high rates of *C. difficile* colonization. Studies have shown a 20% to 40% rate of colonization in hospitalized adults compared with 2% to 3% in healthy adults (12, 13), reflecting widespread contamination of hospital environments, especially in areas associated with infection (6, 7, 14, 15). Gastrointestinal surgery and gastrointestinal procedures are also risks.

Clinical Expression

Clinical disease and *C. difficile* toxin are present almost exclusively in patients with recent antibiotic exposure (6, 7, 12, 16), with rare exceptions (17, 18). A recent report implicates gastric acid–suppressive agents as a risk for disease (19), but this has not been consistently observed (20). Clinical expression of infection almost always includes diarrhea, but severity of this and constitutional symptoms (6–8, 16, 17) varies widely. Common findings in patients with infection include colitis with cramps, fever, fecal leukocytes, and inflammation on colonic biopsy. Pseudomembranous colitis represents an advanced stage of disease, and although considered "nonspecific," it is nearly diagnostic of *C. difficile* infection (17). The disease is almost always restricted to the colon (21). *Clostridium difficile* infection is a protein-losing enteropathy that is often associated with hypoalbuminemia and sometimes with anasarca (3). Most patients have leukocytosis, and this infection is now recognized as a prominent cause of leukemoid reactions (22).

Diagnosis

The standard test for infection is detection of *C. difficile* toxin in stool. The initial report in 1978 (5) used the tissue culture assay, and no subsequent test has proven superior in terms of sensitivity or specificity (23–25). The main limitations of the test are the 24 to 48 hours required for results, work intensity, and cost (25). Most laboratories now use enzyme immunoassay to detect toxin A or toxins A and B, but several studies show that these are only about 75% sensitive compared with tissue culture assays (23–25) so that repeated tests or empirical treatment may be required (26). Alternative methods of detection include detection of *C. difficile* by culture, by polymerase chain reaction testing, or by analysis for the "common antigen" of *C.*

Table. **Treatment Recommendations for *Clostridium difficile*–Associated Diarrhea***

Initial treatment
- Discontinue implicated antimicrobial agent or agents
- Institute supportive care: hydration and electrolyte replacement, if appropriate
- Avoid antiperistaltics, including narcotics and loperamide
- Begin antimicrobial therapy:
  - Oral vancomycin, 125–250 mg 4 times daily for 10 d
    - Advantages: ideal pharmacologic profile; unbeaten in clinical trials; only FDA-approved treatment; in vitro activity vs. all strains
    - Disadvantages: high relapse or reinfection rate; promotion of acquisition of vancomycin-resistant *Enterococcus faecalis*; high cost
  - Oral metronidazole, 250 mg 4 times daily or 500 mg 3 times daily for 10 d
    - Advantages: comparable to vancomycin in most clinical trials; preferred according to IDSA, CDC, and SHEA guidelines; low cost
    - Disadvantages: poor pharmacologic profile; in vitro resistance for some strains; high relapse or reinfection rate; less effective than vancomycin in some studies

Infection control: Nosocomial cases
- Single room with bathroom; barrier precautions; hand hygiene with soap and water; avoidance of rectal thermometers; terminal room cleaning with 1:10 household bleach
- Consider antibiotic restrictions based on epidemiologic associations if *C. difficile* is epidemic or endemic

Complications
- Inability to take medications by mouth: IV metronidazole† (500 mg 4 times daily) and vancomycin (500 mg every 6 h by retention enema or nasogastric tube)
- Delayed response and critical illness: consider IVIG (400 mg/kg of body weight)† or surgical consultation for possible colectomy, especially if leukemoid reaction (leukocyte count $> 20 \times 10^9$ cells/L), renal failure, septic shock, or any combination of these occurs
- Need for concurrent antibiotics
  - Withdraw inducing agent
  - Substitute agent or agents unlikely to cause *C. difficile*–associated diarrhea, avoiding clindamycin, broad-spectrum cephalosporins, and fluoroquinolones
- Relapsing disease
  - Repeat treatment with metronidazole or vancomycin using standard regimens
  - Oral vancomycin in tapering or pulse dosing (125 mg every other day for 4–6 wk)
  - Biotherapy: Oral lactobacilli, such as Lactinex (Becton–Dickinson, San Diego, California) (1 g 4 times daily), or *Lactobacillus* GG (Culturelle, Bloomfield, Connecticut) (1 tablet or 10^{10} CFU twice daily for 4–6 wk), or *Saccharomyces boulardii* (two 250-mg capsules twice daily for 4–6 wk)
  - Anion exchange resin: oral cholestyramine (4-g packet 3 times daily)†
  - Fecal transplant (30–50 g fresh stool from healthy donor in normal saline delivered by enema or nasogastric tube)
  - IVIG (400 mg/kg ± repeat in 3 wk)†
  - Combinations of above, but do not give vancomycin concurrently with lactobacilli (vancomycin is active against lactobacilli) or vancomycin with cholestyramine (cholestyramine binds vancomycin)

* CDC = U.S. Centers for Disease Control and Prevention; CFU = colony-forming unit; FDA = U.S. Food and Drug Administration; IDSA = Infectious Diseases Society of America; IV = intravenous; IVIG = intravenous immunoglobulin; SHEA = Society for Healthcare Epidemiology of America.
† Supporting data are anecdotal.

difficile (25, 27, 28). An inherent problem with detection of the organism rather than the toxin is that 10% to 30% of hospitalized patients are colonized without disease (13). Some laboratories use 1 of these last methods to screen stool samples, with subsequent testing for the cytotoxin in samples with positive results (25, 28).

Infection Control

Standard recommendations of the Society for Healthcare Epidemiology of America for infection control include the following: patient isolation in a single room, preferably with a bathroom; contact precautions; room cleansing with a 1:10 dilution of bleach; avoidance of rectal thermometers; and soap and water for handwashing rather than alcohol-based hand hygiene (14). Alcohol-based hand cleaning is considered inferior because clostridia spores survive alcohol. This is important because health care workers can transmit *C. difficile* via their hands. Antibiotic control of clindamycin or cephalosporins has sometimes been necessary during epidemics (29, 30). Attempts to prevent infection with prophylactic metronidazole or oral vancomycin may actually increase the rate of *C. difficile* carriage (31).

Treatment

Recommendations for treatment are supportive care, withdrawal of the implicated antibiotic, and avoidance of unnecessary use of drugs with antiperistaltic activity (**Table**). When continued antibiotic treatment is necessary, it is best to use agents with a low probability of causing *C. difficile*–associated disease, such as urinary antiseptics, tetracyclines, narrow-spectrum betalactams, macrolides, sulfonamides, aminoglycosides, vancomycin, metronidazole, and trimethoprim–sulfamethoxazole (32). It is not clear whether mild cases require antibiotic treatment against *C. difficile* (33). When symptoms are at least moderately severe or persistent despite withdrawal of the implicated antimicrobial agent, the usual options are oral vancomycin or oral metronidazole (6–8, 14, 16, 34). Oral vancomycin is the only drug approved by the U.S. Food and Drug Administration for *C. difficile* enteric infection. It has ideal pharmacologic properties for treating a pathogen that is completely restricted to the colonic lumen because the drug is not absorbed and is found at levels in the colonic lumen that are more than 100 times higher than the highest minimum inhibitory concentration reported (31, 35, 36).

Metronidazole is the preferred treatment agent in guidelines from the Society for Healthcare Epidemiology of America, Infectious Diseases Society of America (IDSA), and the U.S. Centers for Disease Control and Prevention (16), presumably because of its low cost and because of the possibly erroneous conclusion that vancomycin promotes fecal colonization with vancomycin-resistant enterococci more than metronidazole does (37). The pharmacologic properties of metronidazole are poor for treating a pathogen in the colonic lumen because its absorption is nearly complete and at detectable levels in stool only in the presence of diarrhea (31, 35, 36) and because some strains of *C. difficile* are resistant to metronidazole in vitro (38). Comparative trials of vancomycin versus metronidazole have shown that the drugs are equivalent (39, 40), but

there is some evidence that oral vancomycin is preferred in seriously ill patients because of relatively high failure rates of metronidazole in recent reports (41), poor response to metronidazole when antibiotics for the initial condition need to be continued (42), and a slower clinical response compared with oral vancomycin treatment (43).

The expected response to treatment is rapid defervescence in patients who are febrile and resolution of diarrhea over 4 to 6 days (44). In my experience (45) with 189 patients with *C. difficile* enteric infection, including 100 with endoscopic evidence of pseudomembranous colitis, 96% responded to oral vancomycin. For patients who are seriously ill and cannot take oral medications, it is recommended that vancomycin be delivered by nasogastric tube or by enema (46). This may be augmented with intravenous metronidazole, but evidence of efficacy of intravenous metronidazole treatment is poor (47). Another option, based on previous studies showing a correlation between clinical expression and serum levels of IgG antibody versus *C. difficile* (48), is intravenous immunoglobulin (49, 50). Results using intravenous immunoglobulin in acutely ill patients are variable and anecdotal (49, 50). Some patients with advanced disease, especially those with ileus or toxic megacolon, require colectomy. However, the frequency of patients with advanced disease was only 0.4% at The Johns Hopkins Hospital in the early 1990s (51). Patients with serious disease who do not respond to standard therapy should be considered for colectomy (51–53). The mortality rate in reports of 94 patients who had colectomy for *C. difficile*–associated colitis was 45% (51–53).

The major complication of antibiotic treatment of *C. difficile* infection has been relapse, which is seen in about 20% of patients treated with metronidazole or vancomycin (39, 40, 45). The clinical features of relapse are highly characteristic: The patient reports a recurrence of symptoms identical to those of the initial illness, usually within 1 week but up to 6 to 8 weeks after vancomycin or metronidazole is withdrawn (45, 54). These patients usually respond well to retreatment, but some have additional relapses and a small portion have repeated relapses necessitating several courses of antibiotics (45, 54, 55). Relapse is caused by the initial strain of *C. difficile*, but nearly half of patients experiencing relapse may be infected with new strains of *C. difficile* (56). These observations illustrate the paradox that oral vancomycin and metronidazole both cause and cure antibiotic-associated diarrhea. The postulated cause of recurrence is failure to mount an immune response as indicated by low serum levels of IgG versus toxin A (50, 57). Several methods are used to treat relapsing disease, including biotherapy or probiotics (such as *Saccharomyces boulardii* and *Lactobacillus rhamnosus* GG) (58–61), stool implants (62), immunotherapy (intravenous immunoglobulin) (48, 49), and tapering or pulse dosing of oral vancomycin (54, 61).

THE NEW EPIDEMIC OF *CLOSTRIDIUM DIFFICILE*

History

Investigators from Québec, Canada, noted an increase in the frequency and severity of *C. difficile*–associated diarrhea in the early 2000s (20, 63–65). A review of 1771 case-patients from 1991 through 2003 in Sherbrooke, Québec, showed that the incidence of *C. difficile* enteric disease per 100 000 people increased 4-fold for the entire region and 10-fold for persons older than 65 years of age. Among those admitted to the hospital in the region, the incidence increased from 3 to 12 per 1000 persons in 1991 to 2002 to 25 to 43 per 1000 persons in 2003 to 2004 (63). Furthermore, the disease seemed to be more serious and refractory to therapy, as indicated by increased rates of toxic megacolon, disease requiring colectomy, associated shock, or death (20, 63, 66). Indeed, the attributable mortality rate was an astonishing 16.7% (66). Five variables were associated with these complications: age older than 65 years, acquisition of infection at a hospital, peripheral leukocyte count higher than 20×10^9 cells/L, renal failure, and immunosuppression (66). The implication is that the disease was more frequent, more severe, more refractory to therapy, and subject to high rates of relapse (63–68).

While these developments were occurring in Canada, McDonald and colleagues (68, 69) at the Centers for Disease Control and Prevention noted reports of increasing frequency and severity of *C. difficile* from U.S. physicians, including 8 hospital outbreaks in 6 states (68, 69). An analysis of the International Classification of Diseases, Ninth Revision (ICD-9) coding in the United States showed an increase 82 000 cases in 1996 to 178 000 in 2003 (69). There were also other reports of *C. difficile* causing more disease and more serious disease in the United States (70, 71) and in other areas of the world (72). Thus, this seemed to be an experience that was widespread and possibly global.

Clinical Observations

Clinical features of the epidemic disease are similar to the historical experience but more severe. Prominent complications include toxic megacolon, leukemoid reactions, septic shock, requirement for colectomy, and death (20, 62–71). The newly implicated class of antibiotics was fluoroquinolones for most of the recent outbreaks, although cephalosporins still accounted for a substantial portion (20, 63, 68, 71).

Epidemic Strain

This epidemic, with a large increase of patients with infection, many experiencing severe complications, raised the possibility of a new strain of *C. difficile* that had unique properties accounting for enhanced virulence. This suspicion was confirmed by analysis of epidemic strains from Québec and 8 U.S. sites. Results of the analysis showed a highly characteristic strain, designated BI/NAP1, that has been rare historically and is responsible for the majority of these outbreaks (20, 68, 73). This strain has several appel-

lations, according to the biological property tested: NAP1 by pulsed-field gel electrophoresis, BI on restriction-endonuclease analysis, toxinotype III, and ribotype 027 on polymerase chain reaction. With regard to unique features, 5 factors have been found in nearly all strains that may contribute to the clinical observations.

The first of the 5 factors are toxins A and B, which are the classic toxins associated with *C. difficile*–associated disease. Most strains of *C. difficile* produce both toxins, but the epidemic strain has been shown to produce substantially more toxins A and B in vitro (73). The second factor is toxinotype III. Toxinotyping is based on analysis of the region of the *C. difficile* genome known as the pathogenicity locus (PaLoc) that includes genes that encode for toxin A (*tcdA*) and toxin B (*tcdB*) and the neighboring regulatory genes. All BI/NAP1 strains are toxinotype III, but more than 80% of other strains are toxinotype 0 (68, 73). The third factor is the deletion of *tcdC*, which is an 18 base-pair sequence in the pathogenicity locus (PaLoc) responsible for downregulation of toxin production (68, 74). The fourth factor is binary toxin, an iota-like toxin similar to that produced by *Clostridium perfringens* type E (75). The binary toxin is present in the epidemic strain, but its role in the pathogenesis of *C. difficile*–associated disease is unclear. It causes fluid accumulation in rabbit ileal loops, but *C. difficile* strains that possess binary toxin without toxins A and B fail to cause disease in hamsters (76). The final factor is resistance in vitro to fluoroquinolones, which is infrequently observed in strains collected before 2001 and may be an important factor in the increased frequency of disease rather than contributing to its virulence (20, 66, 68, 77).

Diagnosis and Treatment

There is no test available to clinical laboratories for detection of the BI/NAP1 strain of *C. difficile*. This would require stool culture for isolation of *C. difficile*, which is not done in most laboratories, and referral to a research laboratory to detect the strain. This is best justified in an epidemic of severe disease. Clinical clues to serious disease include toxic megacolon, leukemoid reactions, requirement for treatment in an intensive care unit, renal failure, sepsis, and requirement for colectomy. Management of the infection and associated disease should follow the recommendations noted earlier, although early diagnosis is stressed and there may be preferential use of oral vancomycin (**Table**). Prevention is best accomplished by judicious use of antibiotics and stringent application of infection control policies.

SUMMARY

There seems to be a new epidemic strain of *C. difficile* that is associated with increased frequency and severity of enteric disease and resistance to fluoroquinolones. It is not easy for physicians to know if this strain is the pathogen in an individual patient or even for an epidemic within a hospital setting because methods to detect the strain are not standard in most laboratories. Nevertheless, a pathogen should be suspected if there is an increase in the occurrence of infection and more severe associated disease as indicated by high rates of serious complications, including toxic megacolon, leukemoid reactions, requirement for colectomy, shock, or death. Fastidious attention to infection control is required because infection with this strain may be a major nosocomial complication, especially in elderly patients. Outbreaks may require restriction of antibiotic use with attention to antibiotics implicated in the epidemic, which now include fluoroquinolones, clindamycin, and cephalosporins. Traditional treatment, including oral metronidazole or oral vancomycin, is recommended. These drugs seem to be similar in clinical trials, but many authorities now prefer oral vancomycin for more serious disease and for patients who do not respond rapidly to metronidazole.

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