EDITORIALS

The New *Clostridium difficile* — What Does It Mean?

John G. Bartlett, M.D., and Trish M. Perl, M.D.

Recent experience with influenza, the severe acute respiratory syndrome (also known as SARS), avian influenza, and community-acquired methicillin-resistant *Staphylococcus aureus* has demonstrated how old pathogens can emerge with increased virulence and challenge scientists to explain their rebirth, clinicians to care for patients, and infection-control personnel to prevent their spread. *Clostridium difficile* appears to illustrate these challenges. It already has some distinctive features: it causes disease almost exclusively in the presence of exposure to antibiotics, it is the only anaerobe that poses a nosocomial risk, and it produces toxin in vivo only in the colon.

About 3 percent of healthy adults and 20 to 40 percent of hospitalized patients are colonized with *C. difficile*,[1,2] which in healthy persons is metabolically inactive in the spore form. The assumption is that perturbation of the competing flora promotes a conversion to vegetative forms that replicate and produce toxins. The characteristic clinical expression is watery diarrhea and cramps, and the characteristic pathologic finding is pseudomembranous colitis.

The history of antibiotic-associated colitis began with a multitude of reports early in the antibiotic era, most of them involving surgical patients and generally attributing the condition to *S. aureus*. In 1974, Tedesco et al.[3] reported on a prospective study of 200 consecutive patients given clindamycin, of whom 41 had diarrhea and 20 (10 percent of all those receiving clindamycin) had pseudomembranous colitis. *C. difficile* was reported as the cause of pseudomembranous colitis in 1978,[4] and within three years, toxins A and B were described, the cytotoxin assay became the standard diagnostic test, clinical studies showed that nearly any antibiotic with an antibacterial spectrum could cause this complication, and oral vancomycin became the standard treatment. Studies showed that toxins A and B act by disrupting the actin-cytoskeleton of fibroblasts in tissue culture[5] and in intestinal epithelial cells by uridine 5′-diphosphate glucose dependent glucosylation of Rho proteins.[6] In the past 20 years, *C. difficile* has become the most commonly recognized microbial cause of nosocomial diarrhea, reflecting high rates of colonization in hospitalized patients[3] and the frequent use of antimicrobial agents. The most commonly implicated agent in the 1970s was clindamycin, and in the 1980s it was cephalosporins, but the recent surge of cases suggests that fluoroquinolones may now play a prominent role.[6]

Many previous reports of *C. difficile*–induced disease concerned epidemics, but the reports were generally restricted to single institutions or wards. Recently, however, there appears to be a wider distribution. An example is a regional outbreak in Sherbrooke, Quebec, in 2002, in which there were reports of more disease and more serious disease. A retrospective chart review of 1721 cases of *C. difficile*–associated diarrhea occurring over 13 years showed that the rate of this complication increased by a factor of 4 during this period and that the cases were also increasingly severe; major risk factors were age over 65 years and receipt of fluoroquinolones.[7] A similar experience was reported in Pittsburgh[8] and at other hospitals in the United States.[9] The question is whether these were isolated events or whether there was something different about medical practice, the pathogen, or the antibiotic use involved in them.

This issue of the *Journal* includes two large studies that, taken together, describe a new strain of *C. difficile* and implicate a possible role of flu-

oroquinolone use as driving its emergence. The report by McDonald et al.[9] is an extensive microbial analysis of 187 isolates obtained from patients with *C. difficile*–associated enteric disease from eight outbreaks at U.S. health care facilities occurring between 2000 and 2003. Notable is the quality of the microbial analysis and the availability of 6000 control strains of *C. difficile*. Recently collected isolates showed that the epidemic strain was BI/NAP1 of toxinotype III, was positive for binary toxin, contained an 18-base pair *tcdC* deletion, and was universally resistant to fluoroquinolones. The binary toxin is similar to the iota toxin of *Clostridium perfringens* type E and plays an uncertain role in the pathogenesis of *C. difficile*–associated enteric disease. Because the *tcdC* gene is a negative regulator of the production of toxins A and B, this deletion could augment the production of toxins.[10] This hypothesis is supported by recent studies showing that this *C. difficile* strain produces 16 to 23 times more toxins A and B in vitro than do other strains.[11] The BI/NAP1 strain accounted for 51 percent of the current cases of infection but only 17 percent of the historic control isolates.[11]

The other report, by Loo et al.,[12] provides a similar microbial analysis that is augmented with important clinical and epidemiologic data. They report on a prospective review of *C. difficile*–associated enteric disease in 1703 patients at 12 hospitals in Quebec over a period of 5.5 months in 2004. The reported incidence of 22.5 per 1000 admissions and an attributable mortality of 6.9 percent are strikingly high. Of particular concern is the very high incidence and mortality associated with increasing age: the incidence among patients over 90 years of age was 74.4 per 1000 admissions and the mortality was 14 percent. Analysis of the isolates showed that most strains were resistant to fluoroquinolones, and 84 percent of the implicated strains had binary toxin and the *tcdC* gene deletion. Fluoroquinolones were implicated either alone or with other antibiotics as the inducing agent in 52 percent of cases. These data support the concept that a more virulent strain of *C. difficile* is causing epidemic disease at selected locations and is associated with more frequent and more severe disease, as indicated by higher rates of toxic megacolon, leukemoid reaction, shock, requirement of colectomy, and death.[7,8,12]

What should we do? Control hinges on prevention, recognition of cases, and optimal management of disease. Physicians and infection-control personnel need to monitor for an increasing incidence of *C. difficile*–associated disease on the basis of some classic features: the administration of antibiotics complicated by diarrhea, fever, leukocytosis, sometimes with a leukemoid reaction, and hypoalbuminemia or toxic megacolon, or both. Standard stool assays available in most laboratories will not identify this epidemic strain, but the strain might be suspected on the basis of the number and severity of cases. Treatment consists of the prompt discontinuation of the implicated antimicrobial agent and the administration of oral metronidazole; for severely ill patients and those who do not have a prompt response to metronidazole, oral vancomycin should be considered. Prevention efforts should include fastidious use of barrier precautions, isolation of the patient, careful cleaning of the environment with sporicidal agents active against *C. difficile*, and fastidious use of hand hygiene. This last requirement should include washing hands with soap and water as a supplement to the use of alcohol-based sanitizers, since such sanitizers do not eradicate *C. difficile*. Particularly important is antibiotic stewardship with restraint in the use of epidemiologically implicated antimicrobial agents, usually second- and third-generation cephalosporins, clindamycin, or fluoroquinolones, or a combination of the three.

From the Department of Medicine, Johns Hopkins University School of Medicine, Baltimore.

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Febuxostat — Treatment for Hyperuricemia and Gout?

Larry W. Moreland, M.D.

Gout is a relatively common cause of legendary, severe pain as well as tophi, joint deformities, and nephropathy. Unlike most noninfectious diseases, frequently a pharmacologic "cure" for gout is attained. Shortcomings in the management of gout — due to poor patient education and compliance, substandard medical management, and drug toxicity — can perpetuate its adverse effects. The burden of gout is substantial, and recent epidemiologic studies suggest that it is increasing. This increase is probably due to risk factors related to lifestyle.[1,2]

Acute and chronic arthritis, tophi, and renal disease are manifestations of gout that reflect the magnitude and duration of hyperuricemia, which is the biochemical hallmark of gout.[3,4] Treatment of an acute attack of gout differs from treatment aimed at preventing attacks and other manifestations by reducing the serum urate level. Prevention with the use of a new drug, febuxostat, for the management of hyperuricemia is the focus of the article by Becker and colleagues in this issue of the *Journal*.[5] The emergence of a new medication to lower serum urate levels is welcome inasmuch as none have been approved for use in the United States since the introduction of allopurinol, in 1964, and the drugs that are available have limitations owing to inefficacy or toxicity.

Hyperuricemia results from inadequate renal excretion of uric acid relative to its production; the imbalance is most often due to a defect in the complex excretory mechanisms of the kidney. The overproduction of urate owing to hereditary disorders of purine metabolism or other clinical disorders, as well as exogenous factors including diet, alcohol, and certain medications, can overwhelm these excretory mechanisms.[3,6]

The drugs available for the treatment of hyperuricemia in patients with gout are uricosuric agents (e.g., probenecid), which increase the excretion of uric acid, and allopurinol and its metabolite oxypurinol, which inhibit the oxidation of xanthine to uric acid. Use of the uricosuric drugs probenecid and sulfinpyrazone is limited by their inefficacy in patients whose creatinine clearance is less than 50 ml per minute per 1.73 m^2 of body-surface area; this excludes most patients older than 60 years of age. Xanthine oxidase inhibitors such as allopurinol are effective in patients with renal insufficiency, but these patients may require a reduction in dose because its clearance is performed primarily by renal mechanisms. The advantages and disadvantages of currently available hypouricemic drugs are outlined in Table 1. Allopurinol is the most frequently used antihyperuricemic agent[6,7] because of its efficacy regardless of the cause of hyperuricemia and because of the convenience of once-daily dosing.

Approximately 20 percent of patients who use allopurinol report adverse events, with 5 percent discontinuing use.[8] The most common side effects are gastrointestinal intolerance and skin rashes. If the rash is not severe and is not thought to be vasculitic, allopurinol can be withheld temporarily, until the rash resolves, and then resumed.

More serious adverse events associated with allopurinol include fever, toxic epidermal necrolysis, alopecia, bone marrow suppression, hepatitis, and vasculitis. The most serious adverse event is allopurinol hypersensitivity syndrome, which can be lethal and consists of fever, skin rash, eosinophilia, hepatitis, and progressive renal insufficiency.[6] Although oxypurinol has been used in patients who are sensitive to allopurinol, its use has been limited because of poor gastrointestinal absorption and high prevalence of hypersensitivity reactions among patients. Oxypurinol