Relatively Poor Outcome after Treatment of *Clostridium difficile* Colitis with Metronidazole

Daniel M. Musher,1,2,3 Saima Aslam,1 Nancy Logan,1 Srikanth Nallacheru,1 Imran Bhaila,4 Franziska Borchert,1 and Richard J. Hamill1,2

1Medical Service, Infectious Diseases Section, Michael E. DeBakey Veterans Affairs Medical Center, and Departments of 2Medicine and 3Molecular Virology and Microbiology, Baylor College of Medicine, Houston, Texas; and 4Aga Khan University, Karachi, Pakistan

(See the editorial commentary by Gerding on pages 1598–1600 and the article by Pépin et al. on pages 1591–7)

**Background.** *Clostridium difficile* is a frequent cause of serious nosocomial infection. Earlier reports have suggested that treatment with metronidazole cured nearly 90% of patients, with only a modest rate of recurrence of infection. In recent years, the rate of response to treatment with this drug has appeared to be much lower.

**Methods.** We undertook a prospective, observational study of 207 patients who were treated with metronidazole for *C. difficile* colitis.

**Results.** A total of 103 patients (50%) were cured by the initial course of therapy and had no recurrence of disease. Forty-six patients (22%) continued to have symptoms of colitis for \(\frac{10}{11}\) days despite treatment, and 58 (28%) responded initially but had a recurrence within the ensuing 90 days. The mortality rate among patients who developed *C. difficile* colitis was 27%, and it was higher among patients who did not respond fully to an initial course of therapy, compared with those who did (33% vs. 21%; \(P < .05\)).

**Conclusions.** Because of the relatively poor response to therapy, additional approaches to prevention and/or treatment of *C. difficile* colitis appear to be warranted.

*Clostridium difficile* has become an important cause of nosocomial infection, producing a syndrome of colitis that is associated with substantial morbidity [1–3]. Soon after the recognition of this disease, oral vancomycin was found to provide effective treatment, with a clinical response rate that approached 90% [4, 5]. A randomized trial comparing metronidazole with vancomycin to treat *C. difficile* colitis revealed response rates of 88% for vancomycin and 90% for metronidazole, with recurrence rates of 12% and 5%, respectively, for the 2 drugs [6]. In 1 large case series [7], 98% of 632 patients responded to treatment with metronidazole, and only 7% had recurrent disease. Because the response to metronidazole was equivalent to the response to vancomycin, and because vancomycin is far more costly than metronidazole and its use in the hospital may be associated with selection of vancomycin-resistant bacteria, metronidazole has become the preferred drug for treating *C. difficile* colitis [1, 3, 8].

In contrast, our recent experience suggested that *C. difficile* colitis does not respond so readily to treatment. Nair et al. [9] reported that 8 (22%) of 36 patients did not respond to metronidazole and that an additional 7 (19%) had recurrent disease within 3 months after completing therapy, and Noren et al. [10] found a 25% rate of recurrent disease among patients nearly all of whom were treated with metronidazole. A recent survey of infectious diseases specialists suggested that antibiotic failure has become more frequent among patients who received treatment for treating *C. difficile* colitis [11]. Explanations include the presence, in hospitals, of patients who are older and sicker than they were in the past, increasing use of broad-spectrum antibiotics, such as the newer cephalosporins [12] and fluoroquinolones [12–14], and the possibility that more virulent and/or more highly antibiotic-resistant strains of *C. difficile* have emerged [15, 16]. Accordingly, we undertook a prospective, observational study to examine the rates of failure and recurrence after treatment for *C. difficile* colitis in a medical center where very good follow-up data are available on virtually all patients.
METHODS

Site of study. The Michael E. DeBakey Veterans Affairs Medical Center (Houston, TX) provides complete medical care for ~137,000 adults of all ages. Patients characteristically have no medical insurance and rely exclusively on this medical center for their medical care. Computerized medical records document every encounter between a patient and any component of the system. Thus, follow-up data are accessible and remarkably complete. The records also list all medication orders and medications that have been prescribed for outpatients and administered to inpatients.

Patient inclusion, data collection, and treatment. Patients with a fecal ELISA (Premier Clostridium difficile toxins A and B kits; Meridian Diagnostics) positive for C. difficile toxin between 1 October 2003 and 31 May 2004 were included in this study if they received ≥7 days of treatment with oral metronidazole at a dose ≥1.5 g/day. The medical record was reviewed for 6 weeks before the onset of colitis and for 3 months after completion of treatment. Doctors’ and nurses’ notes were studied for evidence of symptoms or signs of C. difficile colitis, such as diarrhea, abdominal pain, fever, leukocytosis, and pseudomembranous colitis.

During the time of this study, the use of oral vancomycin was restricted by hospital policy, and no patient received this drug as primary therapy for treatment of C. difficile colitis. Patients who did not respond to metronidazole therapy were treated in accordance with the preference of primary care physicians, who were free to select metronidazole or oral vancomycin.

Response to therapy. Patients were stratified into 1 of the following 4 categories on the basis of their response to treatment: the complete response group was comprised of patients with symptoms or signs of C. difficile colitis that resolved ≤9 days after beginning treatment and did not recur during the ensuing 3 months; the refractory-to-treatment group was comprised of those with symptoms or signs of C. difficile colitis that persisted for ≥10 days after the beginning of treatment; the documented recurrence group consisted of those with symptoms or signs of C. difficile infection that reappeared after an initial clinical response and for whom C. difficile toxin was again demonstrated in feces; and the clinical recurrence group was comprised of those with symptoms or signs that reappeared after an initial clinical response and without documentation of C. difficile toxin in feces, either because the toxin assay was not done or because it was done and the result was negative.

Statistical analysis. The independent Student’s t test and Fisher’s exact test were used for continuous and categorical variables, respectively. A P value < .05 was considered to be statistically significant. The statistical package used was Epi Info, version 3.3 (Centers for Disease Control and Prevention).

Approval. This study was approved by the Institutional Review Board at the Baylor College of Medicine (Houston) and by the Research and Development Committee at the Michael E. DeBakey Veterans Affairs Medical Center.

RESULTS

Patients. Between 1 October 2003 and 31 May 2004, a total of 207 patients qualified for this study, all of whom had had a fecal ELISA positive for C. difficile toxin and had received ≥7 days of metronidazole therapy at a dosage of ≥1.5 g/day (figure 1). Symptoms of C. difficile infection included diarrhea in 171 patients (83%), abdominal discomfort in 27 (13%), and fever (temperature, ≥37.6°C) in 109 (53%) (table 1). Eighty-one patients had leukocytosis (WBC count, >11,500 cells/mm³); the median WBC count among those with leukocytosis was 17,400 cells/mm³. Pseudomembranous colitis was documented by sigmoidoscopy or colonoscopy in 4 patients; this low number reflected the emphasis on clinical diagnosis and the rarity of requests for gastroenterology consultation. There were no differences in the frequency of any of these symptoms or signs between patients who responded completely to the first course of treatment with metronidazole and patients who were refractory to treatment or had recurrent disease (table 1; P > .45 for all comparisons, by Fisher’s exact test).

Response to metronidazole. Of the 207 patients, 103 (50%) had a complete clinical cure during the initial treatment with metronidazole (figure 1). Forty-six patients (22%) who had persistent symptoms and/or signs of colitis were regarded as refractory to therapy. Fifty-eight (28%) responded initially to metronidazole therapy with a complete resolution of their symptoms and signs of colitis but had a recurrence of disease within 90 days after completion of therapy. In 47 of these 58 patients, C. difficile toxin was again documented in ≥1 fecal sample; such findings were considered to be documented recurrences. Thirteen of these 47 patients had early recurrence, with reappearance of colitis symptoms within 21 days after completing metronidazole therapy; 34 had recurrence of symptoms >21 days after therapy was completed (figure 1). In the remaining 11 (5%), fecal samples were either not submitted for study or were ELISA negative for toxin; such findings were called clinical recurrences. These patients had a total of 270 episodes of C. difficile colitis. There were 63 documented recurrences, with a mean of 1.34 episodes per patient.

Duration of metronidazole treatment and response. On the basis of our inclusion criteria, all patients received ≥1.5 g of metronidazole daily for at least 7 days. The duration of treatment in this observational study was 7 days for 48 (23.2%) of 207 patients, 8–10 days for 61 (29.5%), 11–14 days for 60 (29%), and ≥14 days for 38 (18.4%). Treatment for 7 days was more likely than longer courses of therapy to be associated with a cure (P < .05, by Fisher’s exact test), probably reflecting the tendency of health care professionals to prescribe therapy for
Figure 1. Study flow and rate of response to therapy for 207 patients who were treated initially with metronidazole for Clostridium difficile colitis

7 days and then to extend the duration of treatment for patients who did not respond satisfactorily.

**Intensity of antibiotic therapy and response to treatment.**
The mean number of antibiotic-days during the 6 weeks preceding the diagnosis of C. difficile colitis (determined by adding the number of days a patient received each antibiotic) was 17.1 for those who had a complete response and 17.9 for those who did not respond to therapy (P = .7). The mean number of antibiotic-days during the time that patients received treatment with metronidazole was 6.5 among those with a complete response and 8.4 in those who were refractory to therapy or who had recurrent disease (P = .12). The 70 patients who did not receive additional antibiotic treatment after metronidazole was begun to treat C. difficile colitis were evenly divided among those who had a complete response to therapy and those who did not. The use of cefepime or parenteral vancomycin alone or together in the 6 weeks preceding the diagnosis of C. difficile colitis was more likely to be associated with metronidazole failure than was treatment with other antibiotic regimens (P < .05).

**Antibiotic susceptibility of C. difficile.** Antibiotic susceptibility testing of C. difficile isolates was not done as a routine microbiological procedure at our medical center during the time that this study was in progress. Since completion of the study, however, 18 C. difficile isolates from patients who were not included in this series have been studied, and all were fully susceptible to metronidazole (MIC, 0.125–1.0 μg/mL). Two of these patients had recurrent disease. PFGE of the 18 isolates showed 4 major clones and several minor ones, suggesting that a single epidemic strain was not responsible for the failure of therapy.

**Treatment of refractory and recurrent infection.** Among 46 patients with refractory disease, prolonged metronidazole therapy (i.e., ≥2 weeks) eventually was associated with a complete resolution of symptoms in 15 (50%) of 30 cases. Sixteen patients with refractory disease were treated with vancomycin, of whom 5 (31%) responded; the difference in the rate of response to prolonged metronidazole therapy was not significantly different from that for vancomycin therapy (P = .35). Recurrent C. difficile in 44 patients was treated successfully with an additional course of metronidazole in 31 (70%). Vancomycin was used to treat recurrence of C. difficile colitis in 9 patients, of whom 7 (78%) had no subsequent recurrence; the difference between the efficacy of metronidazole therapy was not significantly different from that for vancomycin therapy (P > .9). During the time of treatment and the 90-day period thereafter, 56 (27%) of 207 patients died; the mortality rate was 33% among those who did not respond to therapy and 21% among those who were cured (P < .05).

**DISCUSSION**

C. difficile colitis has emerged as a prominent cause of disease in hospitalized patients. The reported rate of infection is 3.4–8.4 cases per 1000 hospital admissions [15], and both the rate and severity of infection appear to be increasing [14, 17, 18]. Earlier studies suggested that ~90% of patients responded to treatment with metronidazole or vancomycin; 10%–15% developed recurrent disease. In contrast, more-recent reports have shown a much higher rate of treatment failure [9, 10, 19], and a recent survey has confirmed that this is the prevailing experience among infectious diseases physicians [11]. Our goal was to use our exceptional ability to track patients to examine the hypothesis that the response to metronidazole was not as
good as had been previously reported. We found that only one-half of the patients who are treated for *C. difficile* colitis are promptly cured by their first course of therapy. Symptoms and/or signs of *C. difficile* colitis in 22% of patients persist for \( \geq 10 \) days after initiation of metronidazole therapy, and an additional 27% have recurrent disease after an initial response to therapy.

Intense antibiotic therapy was not responsible for metronidazole failure. The mean number of antibiotic-days before the disease or during treatment for the first episode of disease was similar in patients who were and patients who were not cured. Although new exposure to antibiotic therapy, especially to antibiotics from \( \geq 1 \) class, has been shown to be a significant risk factor for recurrence of disease [9, 20], we were unable to document such an association. In the absence of a group of control subjects, we were unable to determine whether receipt of a particular antibiotic predisposed to *C. difficile* infection [21]. The association between previous use of cefepime and/or parenteral vancomycin and a poor response to metronidazole therapy may relate to the generally increased level of illness, because these antibiotics tended to be the empirical antibiotic treatments of choice for ill patients at the time of this study. However, the use of third-generation cephalosporins has been specifically associated with *C. difficile* colitis [12, 22].

An increased rate of treatment failure and recurrence of disease among hospitalized persons may reflect that current patients are older and sicker than past patients [23]; one prospective cohort study has shown a strong association between the severity of underlying diseases and the susceptibility to *C. difficile* infection [24]. The present study emphasizes that *C. difficile* infection is associated with substantial morbidity and mortality rates. The mortality rate among our 207 patients was 27%. Deaths were generally attributed to the underlying medical conditions of the patient and not to the *C. difficile* infection, although colitis probably contributes to general debility of patients and, therefore, to death. The high mortality rate even among patients who responded to treatment is consistent either with a debilitating effect of colitis or with the view that *C. difficile* colitis is a marker for serious underlying disease.

Increased use of certain antibiotics, such as third-generation cephalosporins or fluoroquinolones, may also contribute to the rate of therapy failure [13, 14, 22, 25]. Specific resistance to metronidazole was probably not a factor, because strains of *C. difficile* resistant to this drug have not been identified at our medical center. Finally, an epidemic clone of *C. difficile* that is now causing severe colitis in some hospitals [16] was not a problem at our medical center, because PFGE of a sample of strains isolated at our medical center showed no predominant strain.

The host immune response plays an important role in protection against *C. difficile* colitis. Asymptomatic carriers have a greater increase in serum levels of antibody to toxin A after colonization than do symptomatic patients [26, 27]; such carriers are at decreased risk of subsequently developing *C. difficile* disease [28]. For patients who develop *C. difficile* colitis, a higher level of anti-toxin antibody after treatment is associated with a decreased risk of recurrence of disease [19, 29]. It is possible that, in our patients, all of whom had numerous comorbidities and many of whom were in a long-term care facility at our medical center, a poor immune response contributed to the high rate of treatment failure.

In our patients, the best response rate was observed with 7 days of treatment. Longer courses of therapy, however, may have been a marker for more-severe disease and/or for treatment failure. Among patients treated for recurrent disease, the rate of response to vancomycin or metronidazole appears to be approximately the same. Because of the fear of selecting vancomycin-resistant bacterial pathogens in our hospital population and the absence of clear evidence to favor vancomycin therapy over metronidazole therapy, we continue to restrict the use of vancomycin, as do other institutions [15]. Clearly, new modalities of treatment need to be sought, and these include other drugs, such as nitazoxanide or tinidazole; probiotics, such as *Saccharomyces boulardii* and *Lactobacillus* species [30]; immunotherapy, for example, using monoclonal antibodies to neutralize *C. difficile* toxin [31]; and immunophylaxis with vaccines [32, 33].

### Acknowledgments

**Financial support.** This work was funded in part by the Department of Veterans Affairs through the Merit Review Program.

**Potential conflicts of interest.** D.M.M., R.J.H., and N.L. are investigators in a study of nitazoxanide for treating *Clostridium difficile* colitis, funded by Romark Laboratories. All other authors: no conflicts.

### References


