Metronidazole for Clostridium difficile–Associated Disease:
Is It Okay for Mom?

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(See the article by Musher et al. on pages 1586–90 and the article by Pépin et al. on pages 1591–7)

The best treatment practices for Clostridium difficile–associated disease (CDAD) have advanced little from what was known 20 years ago, when John Bartlett [1] wrote an excellent editorial about the subject, which addressed virtually all of the issues of current interest. In 1992, Sherwood Gorbach [2], in a tongue-in-cheek editorial about drugs for your mother-in-law but not your mother, included metronidazole among the treatments for CDAD. In 1997, Dr. Gorbach’s then coeditor, Michael Barza [3], recommended the use of metronidazole for most patients with CDAD, because it was inexpensive and was shown to be comparable in efficacy to vancomycin in a randomized, prospective trial by Wenisch et al. [4]. I surmise (but have no data) that the era of widespread use of metronidazole in US hospitals for the treatment of CDAD began in the late 1990s, after publication of the recommendations by the Centers for Disease Control and Prevention’s Healthcare Infection Control Practices Advisory Committee for preventing the spread of vancomycin resistance [5]. Oral vancomycin use was discouraged as treatment for primary antibiotic-associated colitis (AAC) and was recommended only for persons who had severe and potentially life-threatening AAC or did not respond to metronidazole therapy [5]. This was followed by a position statement by the American Society for Health-System Pharmacists on the preferential use of metronidazole for treatment of CDAD, reserving vancomycin therapy for “severe, potentially life-threatening cases or when oral metronidazole cannot be used” [6, p. 1410]. A recent Cochrane Database Review about CDAD treatment concluded that metronidazole (and bacitracin, fusidic acid, teicoplanin, and rifaximin) were as effective as vancomycin for initial symptomatic resolution [7]. The only US Food and Drug Administration (FDA)–approved treatment for CDAD is oral vancomycin. Metronidazole (and bacitracin, fusidic acid, teicoplanin, and rifaximin) have never been subjected to the rigors of an FDA approval process for a CDAD indication.

In this issue of Clinical Infectious Diseases, 2 articles [8, 9], both of which are observational in methodology, suggest that metronidazole may not be as effective for treating CDAD as has been demonstrated in previous prospective, randomized trials [4, 10]. If the allegations of poor clinical response are supportable and generalizable, they have important implications for the treatment of CDAD with metronidazole, especially in view of recent reports of increasing CDAD frequency, mortality rates, and morbidity rates, and they will surely result in increased treatment with oral vancomycin in hospitals on the basis of the assumption that vancomycin, the only alternative to metronidazole, will be more effective.

To try to dissect the observations of the 2 new studies, I have compared them to the only 2 previously published prospective, randomized, controlled studies of metronidazole for CDAD [4, 10]. It is important to note that these prospective clinical trials had specific entry and exclusion criteria, fixed dosing regimens, predefined criteria for success or failure, and the need for informed patient consent, requirements that are not present in the observational trials. In addition, the randomized trials were performed at an earlier time and contained fewer patients. Two clinical outcome end points are critical for comparison: the initial end-of-treatment clinical response of CDAD and the subsequent rate of recurrence of CDAD after successful treatment, which is a long-recognized deficiency for all treatment agents.

In an attempt to make the data more comparable, I took the liberty of recalculating the recurrence rates in the current articles as percentages of initial responders.
and defined patients with true recurrences only as those who were documented to have a new episode of diarrhea and a positive result of a stool toxin test after a successful treatment response. A comparison of recurrence rates was difficult, because one of the prospective trials used a definition of recurrence that excluded patients who received additional antibiotic treatment in the period after successful CDAD treatment, which erroneously lowered the metronidazole recurrence rate to 5% [10]. The follow-up period for recurrence in these studies ranged widely (from 21 to 90 days after CDAD treatment), which was yet another difficulty associated with the comparison.

Recurrence of disease 21 days after the end of therapy could be compared in 2 studies [8, 10], and similar rates were observed (5% [2 of 39 subjects] and 8% [13 of 161 subjects], respectively), despite the flawed recurrence definition in the study by Teasley et al. [10]. The 60-day recurrence rate of 15% (96 of 622 subjects) in Quebec from 1991–2002 [9] is comparable to the ≥30-day recurrence rate of 17% (5 of 29 subjects) in the contemporary 1993–1995 study by Wenisch et al. [4], but both studies had patients whose mean age was less than usual. However, the recurrence rates in 2003–2004 in the studies by Musher et al. [8] (29% at 90 days [47 of 161 subjects]) and Pépin et al. [9] (34% at 60 days [109 of 323 subjects]) were about twice as high as the rates in the earlier studies. Clearly, some of the increase in the study by Musher and colleagues was due to the long 90-day follow-up period, which raises the question of whether some of these recurrences should be considered as new CDAD cases, especially because some of the patients were residents at long-term care facilities, where continued environmental exposure is unavoidable. In Canada, however, the follow-up period was a constant 60 days, and the recurrence rate was more than twice that observed during 1991–2002. Interestingly, for patients who did not respond to treatment with metronidazole and who received “rescue” therapy with vancomycin, the CDAD recurrence rate (proven by results of repeated stool toxin testing) was 33%, which was virtually identical to the rate for patients who responded to initial metronidazole treatment [9].

Pépin et al. [9] also acknowledge that the demographic characteristics of their patients changed dramatically during the course of their study: 37% of patients were ≥65 years old and 47% had hospital-acquired CDAD before 2003, and 68% of patients were ≥65 years old and 75% had hospital-acquired CDAD during 2003–2004. Unfortunately, we have no data about demographic characteristics or CDAD disease frequency from the study by Musher and colleagues. Pépin et al. [9] acknowledge that their hospital harbors a clone identical to one described in US hospitals that produces binary toxin, has a tcdC gene deletion, and is resistant to newer fluoroquinolone antibiotics. It is tempting to attribute the high recurrence rate observed in their study to the epidemic new C. difficile strain that has become entrenched in their hospital environment and is repeatedly infecting older (age, ≥65 years), hospitalized, antibiotic-exposed patients whose immune response to C. difficile is deficient, explaining the high recurrence rate with both metronidazole and vancomycin. Observational data from the study by Pépin et al. [9] do not support this hypothesis, but more definitive answers should be forthcoming with culture, toxino-typing, and susceptibility testing of the strains currently causing CDAD, as well as antibody studies of the patients.

The reduced rates of initial response to metronidazole therapy reported in both recent studies (78% [161 of 207 subjects] [8] and 74% [323 of 435 subjects] [9]) are also worrisome; they are 16%–21% lower than the rates reported in the prospective trials [4, 10]. One possible explanation is the lack of a clinical definition of diarrhea in both studies, which is a weakness of observational studies, because, in my experience, documentation of stool frequency is often absent from medical records, including the electronic medical records used by Musher et al. [8]. Both studies identified patients on the basis of results of laboratory analysis of stool toxin and treatment intervention, which may not always be indicated. In the study by Musher and colleagues, 17% of patients had no diarrhea, and neither study required that diarrhea be included in the case definition. The ratio of the drug level in stool to the MIC of metronidazole is relatively low in persons with diarrhea, and in the absence of diarrhea, the stool drug level is essentially 0, a potential reason for the failure of metronidazole treatment [11]. However, Musher and colleagues did not find that reduced response was associated with absence of diarrhea. Neither study implicates metronidazole resistance as a cause of treatment failure, but neither study reports susceptibility results for clinical failure isolates.

There is an inherent unproven assumption that vancomycin treatment is superior to metronidazole therapy, but this assumption awaits to be proven via prospective trials in the current clinical setting involving a new epidemic strain of C. difficile that may be much more virulent and difficult to treat. We have available some recent information on vancomycin efficacy from the control arms of two phase 2 FDA studies of CDAD [12, 13]. In the trial of the toxin-binding polymer toleran, 80 patients received oral vancomycin (125 mg q.i.d. for 10 days) for mild-to-moderate CDAD and had a response rate of 91% and a recurrence rate of 19% [12]. In a trial of the nonabsorbable antibiotic ramoplanin, 28 patients received the same vancomycin regimen and had a response rate of 86% and a recurrence rate of 21% [13]. Seriously ill patients could not have entered these trials, because of exclusion criteria. These rates are comparable to those reported in earlier vancomycin trials [4, 10].

Do these new observational studies relegate CDAD treatment with metronidazole to secondary status for Mom? Not for
tronidazole and early surgical consultation and enema, coupled with intravenous meclozycin administered via nasogastric tube therapies, including oral vancomycin or vancomycin treatment should precede diarrhea resolution, and any new treatment agents and for comparator agents that are under investigation in randomized clinical trials. If new agents are successful, they will broaden the available CDAD therapeutic options for the first time in 25 years. In the meantime, the best we can do for Mom is to avoid giving her unnecessary antibiotics and to keep her out of the hospital, thus reducing the chance of acquiring CDAD.

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