The Challenging Conundrum of Diagnosing and Managing *Clostridium difficile* Infection

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Management of patients with *Clostridium difficile* infection (CDI) can be very difficult, especially for the approximately 25% of patients who have had recurrences, and particularly for those who have had multiple recurrences. Following recurrence, patients typically respond to a new course of antimicrobial treatment, usually with vancomycin or fidaxomicin, but often have another recurrence within a few days to months after stopping treatment. Although treatment failure to resolve symptoms is not uncommon when metronidazole is used,[1] failure to resolve symptoms when treated with a new course of antimicrobial treatment with either vancomycin or fidaxomicin is an indication that a condition other than CDI may be the cause of the patient's symptoms.

Patients with CDI recurrences are often managed with long courses of tapered vancomycin dosing followed by pulse dosing on alternate days or every 3 days before stopping. When symptoms recur following multiple treatment attempts, in desperation to prevent further recurrences, patients may be maintained on low-dose vancomycin indefinitely to suppress symptoms. In the current issue of *Mayo Clinic Proceedings: Innovations, Quality & Outcomes*, Tariq et al[2] illustrate the importance of having a specialized clinic to assess and treat these patients.

The authors describe their experience managing patients with recurrent CDI through a specialty clinic set up at their hospital to improve patient care, provide options for diagnostic workup and for treatment, and to allow access to clinical trials and expertise not typically available in a general medical clinic. Considering the prevalence of CDI overall and the complexities in managing patients with recurrent CDI, this concept of providing specialized care and follow-up is a model that should be considered for all institutions that provide care for complex patients in whom CDI is an unfortunate, but common complication.

A critical aspect of this clinic was to thoroughly screen these patients for alternate diagnoses. Emphasis on a thorough history is particularly noteworthy given the prevalence of *C difficile* carriage and potential for misattribution of symptoms to this organism as well as the finding of postinfectious irritable bowel syndrome (IBS) in patients with prior, bona fide CDI. More than 20% of patients seen in this clinic had a diagnosis other than CDI as the cause of their symptoms, the most common of which was postinfectious IBS. We concur with Tariq et al[2] that nonresponse to treatment with vancomycin should be a clue to an alternate diagnosis and not be a trigger to increase the dose of vancomycin, extend the treatment course, or add other agents such as metronidazole to the regimen.

Treatment of CDI in this clinic has been focused on providing fecal microbiota transplants (FMTs), and their criteria for patient selection were reasonable: (1) patients with 3 or more CDI episodes, (2) documentation of diarrhea with a positive stool assay for *C difficile*, and (3) previous treatment with appropriate antibiotic therapies. Although patients were not randomized or offered a standard treatment protocol, cure rates were 87% after 1 FMT and 93% after inclusion of those who responded to a second FMT procedure. The cure rate after antibiotic treatment alone was 60%.

Response rates to FMT have not been as high in randomized controlled trials (RCTs) as in initial observational reports, and the cure rates of comparator or placebo regimens have been higher than expected in RCTs. For example, Hota et al[3] reported an unblinded randomized trial of 14 days of vancomycin therapy followed by randomization to a single FMT via enema vs a 6-week taper and pulse of vancomycin. The study was stopped for futility after enrollment of 30 patients. Patients who received FMT had a cure rate of 44% and those who received vancomycin taper/pulse a cure rate of 58% (P=.70). In another

randomized blinded trial,[4] 46 patients with 3 or more recurrences of CDI were treated with at least a 10-day course of vancomycin for their most recent CDI episode and were randomized to receive FMT with donor stool or placebo (the subject's own stool) administered via colonoscopy. In the donor FMT group, 20 of 22 patients (91%) achieved clinical cure vs 15 of 24 patients (63%) in the placebo FMT group (P=.024).[4] However, response in the placebo patients varied widely between the 2 institutions where this study was performed: 6 of 14 (43%) at one institution and 9 of 10 (90%) at the other. In the Discussion section of this publication, the authors comment that at the institution that had the higher placebo response, many patients had been receiving extended periods of treatment with vancomycin (up to 148 weeks) and fidaxomicin, raising the possibility that some of these patients had already been cured before enrollment. The importance of clear diagnostic criteria for CDI as demonstrated by Tariq et al[2] cannot be emphasized enough in the treatment of recurrent CDI.

We believe that the outcome with antibiotic treatment can be optimized and improved, particularly for those institutions that do not regularly perform FMT. In our experience, most patients with multiple CDI recurrences can be managed with antibiotic therapy. Most of our patients are first managed with a prolonged vancomycin taper and "pulsed" regimen after symptoms have resolved on a standard treatment course of vancomycin.[5] For patients with recurrence of symptoms at the end of their vancomycin pulsed regimen, we have used several post-vancomycin treatment strategies including a post-vancomycin "chaser" with rifaximin[6,7] and, more recently, a taper and "pulsed" regimen with fidaxomicin.[8] In our initial, noncontrolled clinical experience with a fidaxomicin taper and pulse regimen following symptom control with a conventional treatment regimen, we achieved a sustained cure rate of 82% in 12 patients with multiple recurrent CDI (mean of 5 CDI episodes) who were given fidaxomicin 200 mg once daily for a week and once every other day for 3 weeks.[8]

The benefit of prolonged fidaxomicin treatment was also demonstrated in a recent abstract presentation in which patients 60 years or older with CDI were randomized (1:1) to receive fidaxomicin 200 mg oral tablets, twice daily on days 1 to 5, then once daily on alternate days on days 6 to 25, compared with vancomycin 125 mg oral capsules, 4 times daily on days 1 to 10 in the EXTEND trial.[9] Sustained clinical cure (cure of the CDI episode without recurrence over the next 30 days) was the primary end point of this unblinded trial. Of the 356 eligible patients, 36.5% had severe CDI, and 15.4% and 5.6% had had 1 and 2 previous recurrences, respectively. Sustained clinical cure was significantly higher for the extended fidaxomicin regimen compared with the standard vancomycin regimen (70.1% vs 59.2%; P=.03). Most of the sustained clinical cure benefit appeared to be derived from a lower recurrence rate with the extended fidaxomicin regimen.

Fecal microbiome transplants and extended antimicrobial courses are not the only measures that can be used to treat patients with CDI with multiple recurrences. Wilcox et al[10] reported results of 2 phase 3 clinical trials of a monoclonal antibody, bezlotoxumab, given intravenously to patients during CDI treatment to prevent the recurrence of CDI. Results of these 2 very similar trials were comparable and the combined enrollment was 781 patients in the bezlotoxumab arm and 773 in the placebo arm. The recurrence of CDI at 12 weeks was reduced from 27% in the placebo arm to 17% in the bezlotoxumab arm (P<.0001). In the important subgroup of patients who had 2 or more previous CDI episodes, use of bezlotoxumab was associated with a decrease in recurrence rates from 42% to 29%. Bezlotoxumab is currently available for treating patients to prevent recurrence of CDI.

Another approach to prevention of CDI that is not yet available to patients is the oral administration of a strain of nontoxigenic *C difficile*, NTCD-M3, that has undergone a phase 2 randomized clinical trial in 168 patients with a first episode or first recurrence of CDI.[11] The goal with this type of therapy is to replace the toxigenic strain of *C difficile* with a nontoxigenic, harmless strain that would keep the toxigenic strain from recolonizing the gut. In this randomized blinded trial, NTCD-M3 was given orally to patients who had successfully completed antibiotic treatment with

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metronidazole or vancomycin. Oral administration once a day of the liquid NTCD-M3 spores at 2 doses (10 thousand and 10 million spores/d) for 2 durations, 7 or 14 days, was compared with daily oral liquid placebo. The recurrence of CDI at 6 weeks was 30% for placebo and 11% for all doses of NTCD-M3 combined (P=.006). Recurrence was 5% for the best NTCD-M3 dose, 10 million spores/d × 7 days (P=.01). Detection of NTCD-M3 in the stool at any time after administration predicted successful prevention of CDI, indicated by the finding that the recurrence rate was only 2% if NTCD-M3 colonization was detected. Colonization was transient, lasting 22 weeks maximum.

The best management strategy to treat, and obtain sustained clinical cure in patients with CDI is still to be determined, but specialty clinics can be of great assistance in helping to diagnose and appropriately treat these desperately ill patients. We believe that a specialized clinic for management and follow-up of patients with recurrent CDI (similar to the clinics established for the management of HIV and hepatitis C infections) should be considered for any institution that provides tertiary medical care.

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