EDITORIALS

Clostridium difficile — Beyond Antibiotics

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In this decade, the prevention and control of *Clostridium difficile* infection in health care settings has become a global public health challenge. Infection rates have increased dramatically, and several large outbreaks associated with toxinotype III BI/NAP1/027 strains have been described.[1]

One of the major incongruities in the management of *C. difficile* infection is that antibiotics are the mainstay of treatment for this antibiotic-associated condition. Standard therapy with oral metronidazole or vancomycin has not changed since the 1970s. Although antibiotics are effective at inhibiting *C. difficile* and treating symptoms, the use of such drugs does not allow for the reestablishment of normal bowel flora. As a result, 15 to 30% of patients will have recurrent *C. difficile* infection after the cessation of treatment.[1] Many patients will have multiple recurrences. For older, frailer patients, such recurrences may lead to additional complications, as well as perpetuating the spread of *C. difficile* in health care settings. In the community, there are many sufferers of recurrent *C. difficile* infection who have frequent episodes of diarrhea, which has a significant effect on social and occupational functioning.

Various approaches to the management of recurrent *C. difficile* infection have been tried with variable success. Such measures include repeated courses of metronidazole or vancomycin, tapered and pulsed courses of vancomycin, combinations of antibiotics, toxin binders, probiotics, and immunotherapy. Probiotic therapy ranges from the aesthetically very acceptable but probably ineffective use of probiotic drinks and supplements to the less aesthetically acceptable but probably effective fecal transplantation.[2] Intravenous pooled human immunoglobulin products have been used off-label and on an ad hoc basis for passive immunotherapy. However, pharmacokinetic and efficacy data for these products are not available.[1] Active immunization with a *C. difficile* toxoid vaccine is currently being tested in a phase 2, randomized, secondary prevention trial (ClinicalTrials.gov number, NCT00772343).

In this issue of the *Journal*, Lowy et al.[3] present the results of a multicenter, randomized, double-blind, placebo-controlled trial of two novel neutralizing fully human monoclonal antibodies against *C. difficile* toxins A (CDA1) and B (CDB1) for the secondary prevention of *C. difficile* infection. Among 484 eligible patients who were screened at 30 centers in the United States and Canada, 200 were enrolled in the study. These patients were given standard therapy for *C. difficile* infection and were randomly assigned to receive a single intravenous infusion of either CDA1+CDB1 or saline placebo. Patients were followed for 84 days. The primary outcome measure was recurrent *C. difficile* infection.

The trial results are impressive. In the intention-to-treat analysis, recurrent infection developed in 7 of 101 patients (7%) in the antibody group, as compared with 25 of 99 patients (25%) in the placebo group, a relative reduction of 72%. Patients with multiple recurrences were particularly likely to benefit, with a relative reduction of 82% in the recurrence rate, as compared with the placebo group. CDA1+CDB1 had no effect on the duration or severity of initial episodes of infection. The monoclonal antibodies were not immunogenic and had an adverse-event profile similar to that of placebo.

The trial results are consistent with previous studies showing that inadequate circulating antibody levels against *C. difficile* toxins predispose patients to symptomatic and recurrent infection

and with observational data suggesting a benefit associated with passive and active immunization for secondary prevention.[1,4,5] The mechanism by which systemic antibody responses help to minimize toxin-mediated disease in the colon is not well understood. Antitoxin antibodies may be exuded through inflamed colonic mucosa. An alternative mechanism for active transport of antitoxin is provided by the IgG Fc receptor FcRN, which is expressed by adult epithelial cells and facilitates the transport of systemic IgG into the intestinal lumen.[6] Pharmacokinetic data from the study by Lowy et al. indicate that antitoxin monoclonal antibodies have circulating half-lives of 22 days (for CDB1) to 26 days (for CDA1). This is a critical time for protection, since the majority of recurrences in the placebo group occurred within the first 30 days.

The investigators used a combination of monoclonal antibodies against both toxins A and B, since previous studies in animals and humans have shown that this combination optimally protected against recurrence.[7,8] The importance of neutralizing the effects of toxin B as well as toxin A was emphasized in the recent study by Lyras et al.,[9] which showed that toxin B was an essential virulence factor in *C. difficile* infection. The emergence of clinically relevant *C. difficile* strains that are negative for toxin A and positive for toxin B further highlights the importance of therapeutic interventions targeted against both toxins.[1,9]

This novel nonantibiotic approach to secondary prevention is likely to offer hope to physicians and patients battling *C. difficile* infection. Parenteral administration of monoclonal antibodies will be useful for hospitalized patients who may be unable to take oral medications but may be less convenient for outpatients. The mean age of the patients in the study was 64 years (range, 20 to 101).[3] This factor is relevant, since an age of more than 65 years is associated with an increased risk of recurrence by a factor of six, and older patients are likely to benefit most from secondary prevention.[10] The lack of efficacy for monoclonal antibodies in attenuating the severity of initial episodes may be related to the definition of severe infection used by study investigators: the occurrence of at least five unformed stools for at least 2 consecutive days. More conventional markers of disease severity (e.g., serum leukocyte counts, creatinine levels, admission to an intensive care unit, and colectomy rates) were not recorded.[1]

We are entering a new era of novel passive and active immunotherapy for the management of *C. difficile* infection. Passive immunization with monoclonal antibodies may reduce the rate of recurrence in groups of patients who are likely to have a reduced response to active immunization at a critical time in their illness. Studies are needed to determine whether monoclonal antibodies are useful as adjunctive therapy in patients with severe or fulminant *C. difficile* infection or whether there is a role for prophylactic passive immunization of patients at high risk for infections associated with health care settings. It is unlikely that monoclonal antibodies will be used for primary treatment, but they may allow a reduction in the number of days of standard antibiotic therapy for *C. difficile* infection. These novel approaches to breaking the cycle of *C. difficile* infection, along with continued attention to appropriate antibiotic use and infection prevention and control, offer hope in the battle against this increasingly prevalent and difficult-to-manage disease.

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