Treatment of Severe *Clostridium difficile* Colitis: Evidence for the Options

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To-the-Editor

The changing epidemiology of *Clostridium difficile*-associated diarrhea (CDAD) has been dramatic, enigmatic, and challenging in recent years. Notable changes since the year 2000 include the detection of toxin hyperproduction in clinical isolates, a rise in the proportion of cases with severe colitis, and outbreaks with higher case fatality rates.1-4 The emergence of binary toxin (Toxinotype III ribotype 027), the mutation in *tcdC* gene, high-level toxin A and B production in clinical isolates, and the evolution of a *C. difficile* strain with high-level resistance to the newer quinolones (i.e., gatifloxacin and moxifloxacin) have, together, contributed to the rise in CDAD disease severity.5-10 Nonetheless, further characterization of CDAD virulence seems imperative in order to effectively optimize CDAD treatment and prevention strategies.

The majority of patients with fulminant CDAD present with either toxic megacolon, hypotension, bowel perforation, or ileus. In severe *C. difficile* disease, treatment with standard oral or intravenous (IV) drugs has been limited by inadequate achievement of intracolonic drug concentrations and ongoing toxin production.11-13 When oral anti-*C. difficile* drugs are not a therapeutic option, the evidence is limited for selecting a biologically plausible alternative. Parenteral metronidazole drug excretion occurs mainly in the upper gastrointestinal tract with less than 14 percent recovered in the feces.14 Anecdotal reports suggest both poor clinical responses of CDAD to intravenous metronidazole and existent strains with reduced metronidazole susceptibility.11-13,15-18 Parenteral vancomycin has limited penetration of the bowel as well, with stool concentrations of only 6.4 to 10 µg/ml.18-19

Available adjunctive CDAD treatment options include intravenous immunoglobulin (IVIG), administration of intracolonic vancomycin (ICV), and pancolectomy.20-27

In one retrospective study, two patients with persistent *C. difficile* colitis while on metronidazole and vancomycin were given pooled human IVIG (200-300 mg/kg).20 Both patients experienced prompt, dramatic resolution of diarrhea, abdominal distension, and tenderness. Sera of these patients subsequently can neutralize *C. difficile* toxin in cytotoxic assays.

The administration of IV as an adjunctive regimen, may occur via an 18-French Foley catheter or
soft 6-French pigtail catheter as a 60-minute retention enema, lavage or as a component of decompressive colonoscopy. In a review of the archived literature for ICV treatment of CDAD, 83 percent (20/24) of all reported C. difficile cases had clinical and microbiological responses to adjunctive ICV therapy.\textsuperscript{21} As with most observational studies, the duration and dosing interval of ICV varied (2-3 g/day of ICV, with intervals of 4-12 hours), yet the findings suggested that ICV was safe and effective in the majority of ICV recipients.\textsuperscript{21} Lastly, pancolectomy is considered a treatment option for patients with multisystem organ failure, peritonitis, or radiographic evidence of fulminant colitis.\textsuperscript{24-27} Despite surgical intervention, the mortality from fulminant C. difficile colitis has been high in most studies (38-48%).\textsuperscript{26-27} Furthermore, the postoperative long-term sequelae include short gut syndrome, malnutrition, and ostomy care.

As the spectrum of C. difficile has evolved to more case presentations with severe disease, the existing data suggest that adjunctive use of ICV or IVIG should be vigorously studied. Randomized, controlled trials, with and without these adjunctive intervention(s), will contribute to future streamlined treatment options of severe CDAD. Until such data are available, clinicians should carefully select the antimicrobial agent(s) for patients with CDAD and consider the potential benefits of adjunctive therapy.

References


