The pathogenesis of colitis due to Clostridium difficile is closely linked to the elaboration of 2 large, single-unit glucosyltransferases referred to as toxin A (TcdA) and toxin B (TcdB). Clinical isolates from patients with symptomatic C. difficile infection (CDI) invariably produce both TcdA and TcdB or TcdB alone. Vaccination of experimental hamsters against both toxins prevents fatal C. difficile cecitis, and isogenic mutants of C. difficile in which both toxin genes are inactivated are rendered avirulent [1]. Debate remains about the relative importance and specific roles of these 2 toxins, but both toxins, which are very similar in structure and function, are likely involved [2].

Infection with C. difficile is usually manifest as colitis, with rare reports of bacteremia and extracolonic infections, such as hepatic or splenic abscess. Although the infection is typically limited to the colon, CDI is not infrequently severe and accompanied by systemic complications, including fever, hypotension, and shock. The epidemiology of CDI in North America has changed significantly in the last decade, with increased rates of disease throughout the United States and Quebec, Canada [3, 4]. In parallel with increased rates of disease, the relative severity of illness has also increased. During the multihospital CDI outbreak in Quebec in 2004, the directly attributable CDI mortality was 6.9%, and CDI contributed to death in another 7.5%; these rates are in contrast to an overall CDI mortality rate of 1.5% in Canada 7 years earlier [4]. While progress has been made in the management of recurrent CDI, there has been little improvement in the management of severe CDI, and most treatment and strategies are empirical or based on anecdotal observations. Rational treatments for severe CDI await a better understanding of the pathogenesis of severe disease.

Steele and colleagues [5] report in this issue of the Journal their findings correlating the detection of TcdA and TcdB in serum of piglets and mice infected with C. difficile and the development of systemic disease. Bartlett and colleagues [6] first reported toxemia in clindamycin-treated hamsters in 1978. Blood from all 20 hamsters in that study were positive for a cytotoxin neutralized by antitoxin to Clostridium sordellii, and the authors speculated that death in the hamsters was a result of absorption of the toxin(s) produced by C. difficile. This observation, however, has not been repeated or extended until recently. While mortality is nearly 100% in clindamycin-treated hamsters, morbidity and mortality following CDI in other animal models is variable. Steele and colleagues were able to use gnotobiotic piglets and mice to test the hypothesis that toxemia correlates with systemic disease and mortality. The authors used 2 substrains of the epidemic BI/NAP1/027 C. difficile strain responsible for the recent CDI outbreaks in Quebec and the United States [3, 4] to infect the animals, as well as a novel immunocytotoxicity (ICT) assay to detect TcdA in tissue culture. This assay, based on antibody enhancement of TcdA toxicity in cells expressing Fc-γ receptor I, allows enhanced detection of TcdA, which is inherently less cytotoxic than TcdB for most cell lines. The authors found toxin by the ICT assay in approximately one-third of the serum samples from the infected piglets and mice, as well as in the pleural fluid and ascites from these animals. Rac1 glycosylation assays corroborated these findings, and neutralization of both toxins in the in vitro assays by anti-TcdA plus anti-TcdB antiserum indicated the presence of TcdA and TcdB. Furthermore, 67% of serum samples (12/18) from piglets with systemic CDI and none of the serum samples (0/25) from the piglets with nonsystemic CDI were positive for toxin, and 85% of the serum samples (23/27) from mice with severe CDI and none of the serum samples (0/34) from mice with nonsystemic CDI were positive. Both of these results were highly significant. The authors were also able to prevent toxemia and systemic CDI in vivo by administering neutralizing anti-TcdA.
and anti-TcdB antibodies systemically in mice. Finally, they were able to show increased levels of proinflammatory cytokines, interleukin (IL)–1β and IL-6, in piglets and mice with systemic CDI.

*C. difficile* cytotoxin (primarily a measure of TcdB activity) has been reported in the serum samples from 2 children with fatal pseudomembranous colitis, 1 with leukemia (postmortem serum was positive) and 1 with Hirschsprung’s disease (premortem serum was positive) [7]. It is known that TcdB is a potent cardiotoxin experimentally [8], and systemization of TcdB in these patients potentially contributed to the fatal outcome. If systemization of TcdA and TcdB is a consistent finding in patients with severe CDI, and if it contributes to infection outcome, then several potential therapies could be studied. Intravenous immunoglobulin has been shown to contain low levels of antibodies to *C. difficile* toxins and has been used empirically as adjunctive treatment for severe CDI. Some reports suggest benefit, whereas others do not [9]. However, a potentially improved passive immunotherapy might be hyperimmunoglobulin for TcdA and TcdB, but this preparation has not yet been developed. Intravenous administration of specific monoclonal antibodies against TcdA and TcdB to patients with CDI significantly decreases recurrences when given in addition to standard antibiotic treatment [10]. This treatment is being developed for patients with recurrent CDI but might potentially also be effective in patients with severe CDI. Finally, a toxoid vaccine is being developed for CDI that may prevent CDI or, theoretically, decrease the severity of disease if CDI occurs [11]. The report by Steele and colleagues [5] provides an impetus for further studies on the mechanism and treatment of severe CDI in humans.

**Notes**

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