Clostridium difficile Infection: Same Incidence and Worse Prognosis?

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(See the article by Gravel et al. on pages 568–76)

Gravel et al. [1] must be congratulated for their article in this issue of *Clinical Infectious Diseases* that reports incidence of *Clostridium difficile* infection (CDI) in Canada. During a 6-month period, the authors performed a prospective surveillance of adult patients in 29 hospitals and compared the data with those obtained from the same institutions 10 years before. Gravel et al. conclude that the figures are “remarkably similar” [1, p.568 and p.572]; however, “the attributable mortality increased almost 4-fold” [1, p.568]. I will try to summarize several points for discussion that, in my opinion, this article prompts.

**The evolution of CDI and the need for a consensus in the way of reporting incidence rates.** The incidence and severity of CDI seem to be increasing in several institutions and different countries [2–8]; however, the changes in alert and diagnostic awareness of this disease must be borne in mind before interpreting the rates. We are lacking a uniform definition of the disease; most reports do not include pediatric cases, and the impact of community-acquired CDI is not yet determined [9, 10]. In my opinion, during recent years, physicians enormously increased their awareness of CDI, and the expertise of laboratory personnel and availability of laboratory diagnosis of toxigenic *C. difficile* have much improved.

CDI rates in the literature are frequently reported as episodes per 100 or 1000 admissions; per 1000, 10,000, or 100,000 days of hospital stay; or per 100,000 inhabitants. A plea for uniformity is appropriate.

**CDI-related mortality and economic burden.** In their series, Gravel et al. [1] report an overall and attributable mortality of patients with CDI of 16.3% and 5.7%, respectively. They indicate that the attribution of death to CDI was “assessed by the hospital epidemiologist or a designated physician” [1, p. 570], and death was evaluated at 30 days after diagnosis. Again, results should be interpreted with caution. There are obvious methodological difficulties of attributing or not attributing the death of a patient to CDI, because many variables can be confounding.

The mortality related to CDI episodes may also depend on the virulence of the predominant strain. For example, the overall mortality at 30 days during the Quebec outbreak was 23.0%, compared with 7.0% for the matched control subjects, and cumulative attributable mortality was 16.7% [11]. In the United States, reported mortality rates involving CDI increased from 5.7 per million population in 1999 to 23.7 per million population in 2004. Those increased rates were also related to the presence of the hypervirulent strain [12]. On the contrary, in our institution in Madrid, with no hypervirulent strains, the overall mortality of CDI was 14.4%, but we were able to directly attribute death to CDI for only 1 patient [5]. Bishara et al. [13] and Song et al. [4] were also unable to attribute an increased mortality directly to CDI.

There is no question that CDI is an independent predictor of increased length of hospital stay and total cost for both patients and hospitals [11, 14]. In a recent study, the mean CDI-related incremental length of stay was 2.95 days, and the mean incremental cost per patient $13,675 [15].

**The benchmark for CDI diagnosis.** An important discussion topic that the article by Gravel et al. [1] prompts is the current benchmark for the laboratory confirmation of CDI.

The authors state clearly their diagnostic criteria for CDI, and I fully agree with them. Nevertheless, in the article, the authors have not clarified how CDI was searched for routinely in the different institutions. For instance, it is possible that...
cultures of fecal samples were not performed systematically for patients with diarrheic stools after a negative direct assay result or that the presence of *C. difficile* was only searched for when requested by the clinicians rather than a policy of systematically testing all unformed stool samples that arrived in the microbiology laboratory for any reason. The “gold standard” routine, in my opinion, must include the performance of toxin immunnoassays and systematic culture for the isolation of *C. difficile* in all diarrheic stools that are sent to the microbiology laboratory, both from inpatients and outpatients. Detection of toxin in *C. difficile* isolates obtained in stool samples with a direct negative test, the so-called toxigenic culture or “second look” cytotoxicity, increases the rate of positive results by ≥15% [16–18]. In comparison with the sensitivity of toxigenic culture and PCR techniques, the sensitivities of the toxin immunnoassays are unacceptably low [19].

**Treatment with metronidazole versus vancomycin.** The study by Gravel et al. [1] also provides interesting results with regard to the treatment of CDI. “Among the 1430 patients with CDI, 1215 (85%) were prescribed metronidazole, 230 (16%) received vancomycin, and 51 (4%) also received probiotics” [1, p. 571]. The high rate of metronidazole choice probably suggests that a significant number of the institutions involved did not have a high proportion of CDI episodes caused by the hypervirulent strains and that many of the cases were, in fact, mild. Zar et al. [20] compared metronidazole and vancomycin results in patients stratified by their level of infection severity. Among the patients with mild CDI, treatment with metronidazole or vancomycin resulted in clinical cure in 90% and 98% of patients, respectively. But among the patients with severe disease, treatment with metronidazole or vancomycin resulted in clinical cure in 76% and 97% of patients, respectively. The reasons for treatment failure with metronidazole are not yet clear and may be attributable to a slower and less consistent microbiological response than that with orally administered vancomycin treatment [21]. At present, antimicrobial resistance to metronidazole is very low. Resistance to metronidazole is heterogeneous and can be missed if it is not determined in fresh isolates [22, 23]. Preliminary data in our hospital suggest that metronidazole-heteroresistant strains, when treated with metronidazole, may be associated with a higher rate of clinical failure [5].

Gravel et al. [1] appropriately caution that a wrong interpretation of their results could show a worse prognosis with vancomycin use. They properly link the higher use of vancomycin with areas that have more-severe cases and probably a higher proportion of hypervirulent strains.

The use of probiotics as an adjunctive therapy to antibiotics remains controversial and is not recommended at the present time [24]. Probiotics like *Saccharomyces boulardii* may not only be inefficient but may also be associated with catheter colonization and catheter-related fungemia in patients receiving critical care involving intravascular catheters [25].

**The issue of complications.** Finally, complications or severe outcome occurred in 22% of the patients reported by Gravel et al. [1]. Severe outcome was significantly associated with advanced age, hospital admission from nursing homes, liver disease, and vancomycin treatment. Present indications recommend repeating the initial treatment in the first recurrent episode and treating the second and successive recurrences with vancomycin [26]. Higher doses of vancomycin, sequentially tapered, or pulsed-dosing regimens may result in a significantly higher cure rate for CDI.

In complicated situations, intravenous immunoglobulins may be effective for severe, refractory, or recurrent CDI that failed to respond to conventional treatment [27–29].

The proper role of rifaximin, nitazoxamide, binding agents, whey protein concentrates, fecal transplants, and vaccines has yet to be defined [30–34].

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**References**


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