Intravenous Tigecycline as Adjunctive or Alternative Therapy for Severe Refractory *Clostridium difficile* Infection

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*Clostridium difficile* infection (CDI) has become more refractory to standard therapy. We describe 4 patients with severe refractory CDI who were successfully treated with tigecycline. Symptoms improved within 1 week. No relapses were observed. This favorable outcome suggests that tigecycline might be a useful alternative for treating severe refractory CDI.

*Clostridium difficile* infection (CDI) has become an increasing health care problem. The incidence of CDI is increasing rapidly, and outbreaks have been described throughout North America and Europe [1]. With the emergence of hypervirulent strains of CDI, patients have presented with more-severe diarrhea and are more likely to relapse [1, 2]. Moreover, infections with these hypervirulent strains were more refractory to standard therapy, especially to metronidazole [3].

Oral vancomycin is now advocated as the therapy of choice for severe CDI [4]. Vancomycin administered intravenously does not reach therapeutic levels in the colonic lumen. Metronidazole, administered either orally or intravenously, only reaches low therapeutic levels in the colon. Therefore, even a slightly elevated minimal inhibitory concentration (MIC) of *C. difficile* for metronidazole may lead to therapy failure [3]. No clear guidelines exist on how to treat severe CDI that is refractory to treatment with vancomycin and metronidazole. Alternative therapies include probiotics, fecal bacteriotherapy, intravenous immunoglobulins, vaccination, anion-binding resins, and antibiotics such as teicoplanin, rifaximin, tiamcinum, ramosplanin, and nitazoxanide [5]. However, these alternatives have been described for treatment of a relapse of disease rather than for treatment of refractory disease. Furthermore, most are not generally available.

Recently, *C. difficile* was reported to have low MIC values for tigecycline [6, 7]. Here, we describe 4 patients with severe refractory CDI who were successfully treated with intravenous tigecycline. The demographic and clinical characteristics of these 4 patients with severe refractory CDI are shown in table 1.

**Case reports.** Case 1 occurred in a 59-year-old man who was admitted to the intensive care unit after cardiothoracic surgery. At day 14 of hospitalization, treatment with cefuroxime and gentamicin was started for a catheter-related bloodstream infection. Soon after, he developed CDI, as diagnosed by use of a toxin enzyme immunoassay and a culture that were both positive for *C. difficile*. The treatment with cefuroxime and gentamicin was discontinued, and treatment with metronidazole (500 mg administered intravenously 3 times per day) was started on day 16. After 5 days of treatment, the patient had not responded, and the treatment with metronidazole was replaced by treatment with vancomycin (500 mg administered orally 4 times per day). The patient’s condition deteriorated further, and 500 mg of metronidazole 3 times per day was again administered intravenously in addition to 500 mg of vancomycin administered orally 4 times per day (day 26). The patient’s condition was complicated by bloody diarrhea with hypovolemia. At day 30, the patient developed septic shock. Cefuroxime (for 5 days) and gentamicin (for 2 days) were administered in addition to vancomycin and metronidazole. CDI remained refractory, and the following severity marker peak values were recorded: leukocyte count, 22 g/L; creatinine level, 275% above baseline; lactate level, 3.7 mmol/L. The patient also experienced hypoalbuminemia. Gastric emptying was minimal, and there was uncertainty about whether vancomycin had reached the colon. Colectomy was considered but not performed, because a colonoscopy revealed pseudomembranes but no ischemia. Because of the failure of standard therapy and the severity of CDI, tigecycline was started on day 58 (standard dosage, 50 mg administered intravenously 2 times per day after a loading dose of 100 mg). Treatment with vancomycin was continued, but treatment with metronidazole was stopped. Fe...
Table 1. Demographic and clinical characteristics of 4 patients with severe refractory *Clostridium difficile* infection who were treated with tigecycline.

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age, years</th>
<th>Symptoms</th>
<th>Method of diagnosis&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Duration of previous standard therapy&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Duration of tigecycline therapy&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Date of relief of symptoms after start of tigecycline therapy</th>
<th>Date of negative toxin EIA result after start of tigecycline therapy</th>
<th>Relapse within 3 months?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>60</td>
<td>Diarrhea &gt;8 times per day; temperature &gt;38.5°C; hypovolemic shock; pseudomembranes; bloody stools</td>
<td>Toxin EIA (day 16); culture positive for ribotype 159</td>
<td>Mtz (days 16–20); Vm (days 21–25); Vm and Mtz (days 26–57)</td>
<td>3 weeks, in combination with Vm (days 58–78)</td>
<td>Day 3</td>
<td>Day 3</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>36</td>
<td>Ileus; temperature &gt;38.5°C; hypovolemic shock; pseudomembranes</td>
<td>Toxin EIA (day 22); culture</td>
<td>Vm (day 22–26); Vm and Mtz (days 27–35)</td>
<td>15 days (days 36–50)</td>
<td>Day 5</td>
<td>Day 5</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>36</td>
<td>Diarrhea &gt;8 times per day; temperature &gt;38.5°C; hypovolemic shock</td>
<td>Toxin EIA (day 36); culture positive for ribotype 078</td>
<td>No standard therapy</td>
<td>7 days (days 36–42), followed by 4 weeks of Vm (days 43–70)</td>
<td>Day 5</td>
<td>Day 13</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>82</td>
<td>Diarrhea &gt;8 times per day; temperature &gt;38.5°C; hypovolemic shock; pseudomembranes; bloody stools</td>
<td>Toxin EIA (day 6); culture positive for ribotype 087</td>
<td>Mtz (days 6–16); Vm (days 17–27)</td>
<td>24 days (days 28–51), then 2 courses of pulse therapy&lt;sup&gt;b&lt;/sup&gt; (days 59–65 and 73–79)</td>
<td>Day 7</td>
<td>Day 4</td>
<td>No</td>
</tr>
</tbody>
</table>

**NOTE.** EIA, enzyme immunoassay; Mtz, metronidazole; Vm, vancomycin.

<sup>a</sup> The day (after hospital admission) on which the toxin EIA result was positive or the day (after hospital admission) on which therapy was started is given in parentheses.

<sup>b</sup> After 24 days, 2 additional weeks of treatment were interspersed with 1 treatment-free week.
ver subsided, and watery stools were less frequent within 3 days. Stools became semifomed after 1 week. The patient was dismissed from the intensive care unit after 2 weeks of therapy. Treatment with tigecycline and vancomycin was continued for a total of 3 weeks. There was no relapse of CDI during 3 months of follow-up.

Case 2 occurred in a 36-year-old woman who developed an ileus with septic shock and respiratory insufficiency 13 days after undergoing an ovariectomy. Treatment with meropenem was started. At day 15, adhesiolysis and a partial resection of the ileum were performed, and the patient was admitted to the intensive care unit. At day 21, a second adhesiolysis and an ileoceleal resection were performed. Histology of the resected segment revealed pseudomembranes. CDI was confirmed by a toxin enzyme immunoassay result that was positive for *C. difficile*. Treatment with meropenem was stopped, and treatment with vancomycin (250 mg administered orally 4 times per day) was started on day 22. Metronidazole (500 mg administered intravenously 3 times per day) was added 5 days later. At day 36, the patient was transferred to a university hospital as a result of developing a severe refractory CDI with hypovolemic shock (with a leukocyte count of 22 g/L, a creatinine level that was 225% above baseline, and a lactate level of 5.6 mmol/L). The treatment with vancomycin and metronidazole was stopped, and treatment with intravenous ticagycline was started. After 5 days of treatment, the patient’s clinical signs improved, and the results of subsequent toxin enzyme immunoassays were negative. Treatment with ticagycline was continued for 15 days in total. No relapses were observed.

Case 3 occurred in a 36-year-old male lung transplant recipient with a history of cystic fibrosis who was admitted to the intensive care unit because of acute respiratory distress syndrome and septic shock. He was treated with meropenem, ciprofloxacin, and voriconazole for 2 weeks. After a short period of recovery, he experienced a second episode of sepsis and was treated with piperacillin-tazobactam, starting on day 22. At day 36, he developed severe diarrhea. CDI was diagnosed by use of an enzyme immunoassay and culture that were both positive for *C. difficile*. The strain was typed as polymerase chain reaction (PCR) ribotype 078. CDI was considered too severe for metronidazole therapy; the patient had a leukocyte count of 6 g/L, a creatinine level that was >50% above baseline, and a lactate level of 2.8 mmol/L. Furthermore, the patient continued to require broad-spectrum antibiotic coverage for sepsis. Therefore, treatment with piperacillin-tazobactam was stopped, and, taking the successful outcome of case 2 into account, ticagycline was started as initial therapy instead of vancomycin (day 36). After 5 days, the patient’s stools became more solid, and systemic signs of infection subsided. After 7 days, treatment with ticagycline was stopped. Culture results were negative, but the enzyme immunoassay results remained positive. Treatment was continued with oral vancomycin for 4 weeks. The last enzyme immunoassay result that was positive for *C. difficile* was found 6 days after initiation of treatment with vancomycin. There was no relapse of CDI.

Case 4 occurred in an 82-year-old woman who underwent a relaparotomy and was treated with cefuroxime and metronidazole because of bleeding and infection after a cholecystectomy. Four weeks later, she was readmitted to the hospital because of profuse diarrhea and dehydration (day 1). CDI was diagnosed, and treatment with intravenous metronidazole was started (day 6). Her clinical condition worsened when she developed a hypovolemic shock. Her CDI was now classified as severe (with a leukocyte count of 20 g/L, a creatinine level that was 225% above baseline, a lactate level of 2.7 mmol/L, and hypoalbuminemia), and intravenous metronidazole was replaced by oral vancomycin (day 17). The patient’s clinical condition further deteriorated with the development of bloody diarrhea and refractory shock. A colectomy was considered but was deemed too risky. After 11 days, vancomycin was switched to ticagycline. Within 1 week, the patient became stable, her stools were semifomed, and *C. difficile* toxin test results were negative. After 24 days, 2 additional weeks of treatment with ticagycline were interspersed with 1 treatment-free week. No relapse was observed.

Discussion. This case series of 4 patients describes the successful treatment of severe refractory CDI with intravenous ticagycline. All of the patients had ≥4 of the following severity markers recently reviewed: leukocytosis, elevated creatinine level, elevated lactate level, hypoalbuminemia, fever, and signs of severe colitis [3]. Previous standard therapy had failed for 3 of the 4 patients, whereas 1 patient was treated primarily with ticagycline. In all cases, the symptoms of CDI subsided within 1 week after initiation of treatment with ticagycline. In 3 of the 4 patients, a colectomy was considered. After initiation of ticagycline therapy, all patients recovered quickly, and surgery was no longer indicated.

For 1 of the 4 patients, vancomycin therapy was continued after the initiation of ticagycline therapy, because ticagycline therapy was considered experimental. Although it is unclear whether the observed outcome was attributable to ticagycline therapy alone or to the combination of therapies (i.e., to both ticagycline and vancomycin), the unsuccessful outcome of standard therapy and the successful outcome of ticagycline mono-therapy for the other 3 patients suggests the former.

Use of vancomycin is considered standard therapy for severe CDI, because the fecal concentrations acquired by the oral route are often several hundred-fold higher than the highest MIC measured for *C. difficile* [4], and because the decreased effectiveness of metronidazole has been described elsewhere [3, 4]. However, with the emergence of the NAP1/BI/027 strain of *C. difficile*, Pépin et al. [8] reported that vancomycin lost its su-
periority to metronidazole, probably because of the strain's hyperproduction of toxins. A major drawback of oral vancomycin therapy is that gut motility is often impaired in critically ill patients. In this type of situation, then, intracolic delivery has been recommended, although it is questionable whether an enema can deliver vancomycin to the transverse colon and the ascending colon [9].

Standard therapy for CDI became less effective as hypervirulent strains of *C. difficile* became more prevalent (i.e., as cases of CDI became more severe) [1]. It is interesting to note that 1 of the strains that was isolated in our study belonged to PCR ribotype 078. This emerging strain has recently been associated with increased severity of CDI, probably because it has virulence factors that are similar to those of ribotype 027 [2].

Besides vancomycin and metronidazole, no effective agents are readily available yet for the treatment of severe refractory CDI. We sought a feasible alternative in the form of intravenous tigecycline therapy.

Tigecycline is a broad-spectrum, intravenous antimicrobial approved for the treatment of complicated skin and soft-tissue infections and complicated intra-abdominal infections [10]. Reported MIC<sub>90</sub> values for *C. difficile* are low, ranging from 0.06 to 0.25 μg/mL [6, 7]. The fecal concentrations of tigecycline in formed stools (median value, 5.6 μg/mL; range, 3.0–14.1 μg/mL) are significantly higher than those of metronidazole or hydroxymetronidazole (median value 0 μg/mL; range, 0–10.2 μg/mL) [11, 12]. We did not measure tigecycline levels in our patients. However, as with metronidazole, fecal concentrations of tigecycline are likely to be higher during inflammation than in formed stools [11]. Despite its inhibition of gut microflora, tigecycline did not induce proliferation or cytotoxin production of *C. difficile* in a gut model [6]. The intravenous administration of tigecycline is more favorable than the oral administration of vancomycin for critically ill patients.

In summary, 4 patients with severe CDI were successfully treated with tigecycline. Previous standard therapy had failed in 3 patients, whereas 1 patient was treated primarily with tigecycline. *C. difficile* was reported to have low MIC values for tigecycline, and fecal levels are well above the MIC, even in formed stools. The favorable outcomes suggest that use of tigecycline is a feasible alternative to use of other antimicrobials for treating severe refractory CDI.

Acknowledgments

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References