Intravenous Tigecycline Facilitates Cure of Severe *Clostridium difficile* Infection (CDI) After Failure of Standard Therapy: A Case Report and Literature Review of Tigecycline Use in CDI

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Standard treatment for severe *Clostridium difficile* infection (CDI) is oral vancomycin with metronidazole. After failure of this standard regimen, treatment becomes challenging. A young woman treated for septic shock developed CDI. Standard treatment failed and she was ineligible for fecal transplant. Addition of tigecycline to her regimen resulted in cure.

   Keywords.   *Clostridium difficile*; severe *Clostridium difficile*; tigecycline.

Clostridium difficile infection (CDI) is recognized as one of the most common causes of hospital-acquired infection in the United States [1]. The cost expenditure for management in the United States is estimated to be approximately $1.5 billion annually [1]. In severe CDI cases, treatment options are limited for patients who fail standard therapy. Fecal microbiota transplant (FMT) may be an effective treatment option, but it has been used primarily for recurrent CDI cases [2]. Critically ill patients who are receiving other antibiotics for ongoing serious infections might not be favorable candidates to receive FMT, because the concomitant antibiotics may impair the important bacteria in the transplant flora. We present a case of severe CDI in a critically ill patient who was receiving meropenem and thus was ineligible for fecal transplant. For this patient the addition of tigecycline to her regimen of oral vancomycin and intravenous (IV) metronidazole led to cure.

CASE PRESENTATION

A 38-year-old female with prior history of nephrolithiasis and urinary tract infections (UTIs) presented with 2 days of left flank pain and dysuria. She had received nitrofurantoin for UTI 1 month ago, but microbiologic data were not available for confirmation. On admission, vital signs were stable and physical examination was positive for left costovertebral angle tenderness. Urinalysis showed pyuria and hematuria. Computed tomography (CT) of the abdomen and pelvis demonstrated left hydronephrosis and ureteral nephrolithiasis (2 stones of 0.7 cm in the distal ureter). She was taken emergently for left ureteral stent placement, and preoperative ampicillin and gentamicin were administered.

Postoperatively, she went into septic shock requiring emergent intubation and pressor therapy. Blood cultures were obtained, and empiric treatment with vancomycin and piperacillin-tazobactam was initiated. Blood cultures as well as urine cultures yielded extended-spectrum β-lactamase-containing (ESBL) *Escherichia coli*. After 2 days of empiric therapy, definitive treatment with IV meropenem was started.

On day 3 of hospitalization, she developed new-onset diarrhea with fever of 40°C and rising white blood cell count (WBC) of 32 000/mm^3. Repeat CT of the abdomen ruled out renal abscess. Transesophageal echocardiogram was negative for vegetation. Stool for *C difficile* polymerase chain reaction (PCR) was positive; treatment with metronidazole 500 mg IV Q8 hours and oral vancomycin 500 mg Q6 hours was initiated. By day 5 of CDI treatment, she still passed 1 liter of liquid stool/24 hours and had WBC 57 000/mm^3. Other treatment options including vancomycin rectal enema and oral fidaxomicin were eliminated due to high stool output, causing uncertainty in achieving effective therapy. Fecal transplant was precluded, because treatment with meropenem was crucial for sepsis management. On day 6 of CDI treatment, tigecycline therapy was added to her current regimen with a 100 mg IV loading dose followed by 50 mg Q12 hours. Marked reduction in stool output was seen on the next day to 400 mL/24 hours followed by 175 mL/24 hours on day 10 of CDI treatment. By day 10 of combination therapy including tigecycline, diarrhea and leukocytosis had resolved and metronidazole was discontinued. Tigecycline treatment was completed and discontinued after 14 days of treatment, and vancomycin was tapered over the following week. After the completion of CDI treatment, stool for *C difficile* PCR and enzyme immunoassay for toxins A and B were sent for episodic loose stools, but all were negative. The patient had good outcome with successful recovery.

DISCUSSION

Clostridium difficile is a fastidious Gram-positive anaerobic bacterium present in vegetative form in the environment. It accounts for 10%–20% of cases of nosocomial antibiotic-associated diarrhea.

Over the last few years, treatment options for CDI have broadened and are no longer limited to metronidazole and oral vancomycin, although both of them still remain as standard therapy for initial episodes of CDI. Fidaxomicin is superior to vancomycin in preventing recurrence within 28 days of completion of therapy, but it is very expensive [3].

Fecal microbiota transplant is increasingly becoming an accepted treatment option in recurrent CDI cases. Its role in management of severe-complicated CDI is promising but still limited to case studies. A major barrier for the use of FMT is the need for discontinuation of critical concomitant antibiotic treatment. A requirement for continuing antibiotic treatment for serious infection, such as the sepsis in our patient, would have negated the beneficial effect of the transplanted intestinal microflora and thus limited the applicability of FMT.

Overall, only limited data are available on the treatment of severe refractory CDI after failure of standard therapy. Most of the treatment available for CDI is oral therapy. A major drawback of oral therapy is that gut motility is often impaired in critically ill patients. In this type of situation, intracolonic delivery has been recommended, although it is questionable whether an enema can deliver vancomycin to the transverse colon and the ascending colon especially during diarrhea. Alternative therapies include probiotics, IV immunoglobulins, toxoid vaccine, anion-binding resins, and antibiotics such as teicoplanin, rifaximin, and nitazoxanide. However, these alternatives are for refractory CDI and not well studied [4].

Tigecycline is the first glycylcycline antibiotic, a derivative of minocycline. It has broad-spectrum activity against Gram-positive organisms including methicillin-resistant *Staphylococcus aureus*, vancomycin-intermediate or resistant enterococci, Gram-negative organisms such as *Enterobacteriaceae* including ESBL-containing strains, and anaerobic bacteria such as *Bacteroides fragilis* [5]. It is approved by the US Food and Drug Administration for the treatment of complicated skin/skin-structure infections, community-acquired pneumonia, and intra-abdominal infections.

Multiple case reports and case series have reported the use of tigecycline for severe and refractory cases of CDI with successful outcome. A recently published in vitro analysis by Aldape et al [6] demonstrated that tigecycline stimulated increased cytotoxin- and sporulation-related gene expression in both nucleosome assembly protein 1 (NAP1) and non-NAP1 *C difficile* strains, but the inhibition of protein synthesis by tigecycline blocked their production. In their study, this resulted in reducing toxin A and B production and prevention of sporulation. Tigecycline has good activity against *C difficile* with minimum inhibitory concentrations ranging from 0.06 to 1.0 mg/L [7]. Tigecycline also achieves higher fecal concentration in formed stools compared with metronidazole [8].

Herpers et al [9] reported the use of tigecycline in 4 patients for severe refractory CDI. Tigecycline was used after failure of standard therapy in 3 of the 4 patients: in combination with vancomycin in 1 patient and as monotherapy followed by vancomycin taper in 2 patients. The fourth patient received tigecycline as a first-line therapy followed by vancomycin taper. Surgery was deferred in 3 of the 4 patients after successful outcome with tigecycline. No relapses were seen at the 3-month follow-up. Lu et al [10] reported a case of 55-year-old woman with severe refractory CDI. Diarrhea resolved after initiating 2-week combination therapy of IV tigecycline and oral metronidazole. She received maintenance therapy with vancomycin for 8 weeks without relapses during the 6-month follow-up. Cheong and Gottlieb [11] reported a successful treatment outcome in an 83-year-old woman with CDI. After failure of treatment with metronidazole and vancomycin taper for recurrent CDI, tigecycline was initiated and diarrhea improved within 1 week of treatment onset. Lao et al [12] reported a case of immunocompromised patient with severe complicated CDI who failed vancomycin treatment. He was initiated on IV tigecycline and oral rifaximin with vancomycin. Resolution of diarrhea was seen within 4 days of treatment without relapse of CDI at 1-month follow-up. Similar successful treatment outcome with tigecycline in combination with rifaximin was reported by El-Herte et al [13], with a patient with severe refractory recurrent CDI.

A few case reports have shown no benefits of tigecycline in the treatment of CDI. Kopterides et al [14] reported a case of a 70-year-old male who received combination therapy with tigecycline, metronidazole, and vancomycin for severe CDI without resolution. The course was complicated by development of multidrug-resistant Gram-negative bacteremia. A retrospective study by Thomas et al [15] compared similarly ill patients who received standard therapy with tigecycline (n = 18) against standard therapy without tigecycline (n = 26) for severe CDI. No difference in treatment outcomes including overall survival, colectomy rates, and relapse rates were observed between the 2 groups.

CONCLUSIONS

Tigecycline has shown good in vitro activity against *C difficile*, with a potential to reduce disease progression and transmission in patients. It is readily available in IV formulation for severe refractory CDI cases when oral therapy might not be a suitable option. Although most of the data on the use of tigecycline are in retrospective case reports and small studies, it requires further larger trial studies for support. Efficacy as monotherapy is still not established, and hence monotherapy is not advised. Based on our case report and review of the literature, we

conclude that the use of tigecycline in combination with standard therapy is a promising treatment option for CDI when FMT cannot be used.

Acknowledgments

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