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**Recommended Citation**
Gonzalez, Mark D.; Wallace, Meghan A.; Hink, Tiffany; Dubberke, Erik R.; and Burnham, Carey-Ann D., "Ceftolozane-tazobactam activity against phylogenetically diverse Clostridium difficile strains."  
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Ceftolozane-Tazobactam Activity against Phylogenetically Diverse *Clostridium difficile* Strains

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Ceftolozane-tazobactam (C/T) is approved for the treatment of complicated intra-abdominal and urinary tract infections and has varied activity against anaerobic bacteria. Here, we evaluate the activity of C/T against a phylogenetically diverse collection of *Clostridium difficile* isolates and report uniformly high MICs (≥256 µg/ml) to C/T.

In December of 2014, ceftolozane-tazobactam received U.S. Food and Drug Administration (FDA) approval for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI) (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427534.htm). Ceftolozane-tazobactam is a novel β-lactam/β-lactamase inhibitor combination with activity against *Pseudomonas aeruginosa*, extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*, and members of the *Streptococcus anginosus* group (1). The activity of ceftolozane-tazobactam against anaerobic bacteria is varied. For example, the MIC<sub>50</sub> of 244 *Bacteroides fragilis* isolates, 86 *Bacteroides thetaiotaomicron* isolates, and 12 *Fusobacterium* species isolates was 4 µg/ml, 32 µg/ml, and 0.25 µg/ml, respectively (2).

*Clostridium difficile* infection (CDI) is well documented as a potential adverse consequence of antimicrobial therapy with a cephalosporin (3–5). The incidence and severity of CDI have increased in recent years, resulting in significant morbidity, mortality, and cost to the health care system (6, 7). *C. difficile* is classified as one of only three urgent, or highest priority, multidrug-resistant microbial threats by the Centers for Disease Control and Prevention (http://www.cdc.gov/drugresistance/threat-report-2013/).

To date, limited clinical data regarding ceftolozane-tazobactam therapy exist, and the risk of CDI following therapy with this specific agent is relatively understudied. In two of the clinical trials that evaluated ceftolozane-tazobactam treatment of cIAI (8) and cUTI (9), 3 cases of CDI were documented (<1% incidence).

In light of the varied antianerobic activity of ceftolozane-tazobactam, an assessment of the antimicrobial resistance profile for ceftolozane-tazobactam with *C. difficile* could be important for understanding the potential risk of developing CDI during therapy with this agent. A recent study by Snydman et al. (2) evaluated different strain types (10–12). Unfortunately, no *C. difficile* strain typing data were available as part of the Snydman et al. study (2), and thus it was unknown if this profile was generalizable to different *C. difficile* strain types.

The objective of our study was to evaluate the antimicrobial activity of ceftolozane-tazobactam against a diverse collection of *C. difficile* strain types. The isolates investigated were recovered from fecal specimens or rectal swab specimens from patients at Barnes-Jewish Hospital from January 2010 to July 2012. Specimens were collected as part of other ongoing studies to assess *C. difficile* diagnostic assays, *C. difficile* infection, or asymptomatic colonization (3, 10, 13, 14). *C. difficile* isolates were recovered in culture (15) and ribotyped (16), as previously described. All isolates were recovered from frozen stocks and were subcultured twice on preduced 5% sheep blood agar (Hardy Diagnostics, Santa Maria, CA) in an anaerobic environment prior to testing. The identity of each *C. difficile* isolate was confirmed by matrix-assisted laser desorption ionization—time of flight mass spectrometry (MALDI-TOF MS) using the Vitek MS (IVD version 2.3.3; bioMérieux, Durham, NC) (17). Ceftolozane-tazobactam susceptibility testing was performed using a gradient diffusion method (Etest; bioMérieux, Durham, NC), according to the manufacturer’s recommendations. In brief, a McFarland standard suspension of each isolate was prepared in 0.9% saline and plated as a lawn onto brucella blood agar with hemic and vitamin K (Hardy Diagnostics), and ceftolozane-tazobactam Etest strips were applied. The plates were incubated under anaerobic conditions and read at 24 and 72 h of incubation. During each day of analysis, the quality control strain *B. fragilis* ATCC 25285 (acceptable quality control [QC] range, 0.12 to 1 µg/ml) was tested.

Eighty-one *C. difficile* isolates were tested, representing 15 different ribotypes (Table 1). Of note, our test set included 26 *C. difficile* ribotype 027 (NAP1/BI/ST-1) strains and 3 *C. difficile* ri-
bototype 078 isolates. These strain types are currently among the most common ribotypes in North America and parts of Europe (18, 19); the toxigenic status of each ribotype was determined by phenotypic (i.e., toxin enzyme immunoassays) and/or genotypic methods (3, 10, 13, 14).

Cefolozane-tazobactam demonstrated no activity against any of the isolates investigated. All isolates tested (n = 81) had ceftolozane-tazobactam MICs of ≥256 μg/ml at both the 24- and 72-h incubation time points. This phenotype appears to be distinct from that of other Clostridium species (2).

A potential limitation of this study is that all of the isolates investigated were recovered at a single medical center. However, this limitation is mitigated by the careful characterization of the isolates, which demonstrated that a phylogenetically diverse population of strains was tested, and this is a strength of this investigation. The impact of ceftolozane-tazobactam on the gastrointestinal microbiota is unknown at this time. Similar to other cephalosporins that are documented to be risk factors for developing CDI (3–5), ceftolozane-tazobactam is predominantly eliminated by renal clearance (17). The concentration of this agent in the stool or the gastrointestinal tract is not known at this time.

In conclusion, we have demonstrated that C. difficile appears to be uniformly resistant to cefolozane-tazobactam. Additional clinical data are needed to appreciate the impact of this agent on both the intestinal microbiota and the relative risk of developing CDI during therapy.

ACKNOWLEDGMENT

The Etest strips used in this investigation were provided by Cubist.

REFERENCES


TABLE 1 Ribotypes and toxigenic statuses of evaluated C. difficile isolates (n = 81)