Impact of Cefepime Susceptible-Dose-Dependent MIC for *Enterobacteriaceae* on Reporting and Prescribing

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The CLSI cefepime breakpoints were revised to include a susceptible-dose-dependent (SDD) category for *Enterobacteriaceae*, with the intention that higher cefepime doses be used for these isolates. In this study, 1.6% of *Enterobacteriaceae* isolates were reported as SDD, with *Escherichia coli* the most common SDD organism. Cefepime was prescribed in three cases (4.8%); the majority of SDD isolates were treated with a carbapenem. *Enterobacteriaceae* with cefepime SDD MICs were not commonly treated with cefepime at our institution.

Cefepime is a broad-spectrum, fourth-generation cephalosporin commonly used to treat serious infections caused by Gram-negative bacteria (1). For organisms with high MICs, optimal pharmacodynamic targets (time > MIC) may not be achieved (1, 2). Given studies demonstrating cefepime treatment failure of *Enterobacteriaceae* with elevated MICs, the Clinical Laboratory and Standards Institute (CLSI) adopted a susceptible-dose-dependent (SDD) category in 2014 for cefepime MIC values of 4 and 8 µg/ml (3, 4). The SDD category indicates that cefepime is a treatment option if higher doses are used, specifically 1 g every 8 h or 2 g every 12 h for an MIC of 4 µg/ml or 2 g every 8 h for an MIC of 8 µg/ml. The study objective was to characterize SDD *Enterobacteriaceae* isolates and describe antimicrobials used to treat the associated infections.

A report of inpatients (≥18 years old) who had cultures positive for *Enterobacteriaceae* and cefepime MICs in the SDD range at a tertiary hospital in Rochester, MN, from 1 April 2014 through 6 March 2015 was reviewed. The total number *Enterobacteriaceae* isolated over the study period was also obtained. Repeat isolates are not routinely tested for susceptibility and thus were excluded. MIC testing was performed by agar dilution. A total of 3,796 *Enterobacteriaceae* isolates underwent cefepime susceptibility testing during the study period: 1,297 *Escherichia coli*, 410 *Klebsiella pneumoniae*, 270 *Enterobacter cloacae* complex, 77 *Serratia marcescens*, and 127 *Klebsiella oxytoca*, and the remainder were *Enterobacter aerogenes* and *Providencia*, *Proteus*, *Morganella*, and *Citrobacter* species that had no reported SDD isolates. There were 62 unique *Enterobacteriaceae* isolates reported as cefepime SDD, including 34 (55%) *E. coli*, 15 (24%) *K. pneumoniae*, 9 (15%) *E. cloacae* complex, 2 (3%) *S. marcescens*, and 2 (3%) *K. oxytoca*. The overall cefepime SDD isolate rate was low (1.6%) and represented a minority of the total isolates for each species: 2.7% of *E. coli*, 3.6% of *K. pneumoniae*, 3.3% of *E. cloacae* complex, 2.6% of *S. marcescens*, and 1.6% of *K. oxytoca*. The majority of SDD isolates were from urine (28, 45%), followed by respiratory (11, 17%), blood (8, 13%), abdominal (8, 13%), soft tissue (6, 9.6%), and bone/joint (1, 1.5%) sources. The same number of samples were from medical (22, 35%) and intensive care (22, 35%) units, with 11 from surgical units (18%) and 7 from the emergency department (11%).

The cefepime MIC was 4 µg/ml for 27 (43%) and 8 µg/ml for 35 (57%) isolates. Susceptibility to sulfamethoxazole-trimethoprim, ciprofloxacin, and gentamicin was 32%, 37%, and 50%, respectively. Susceptibility to piperacillin-tazobactam and ertapenem was 75% and 90%, respectively. All SDD isolates were

susceptible to meropenem. Conversely, only 2 were susceptible to ceftriaxone (3.2%).

The majority of SDD *Enterobacteriaceae* (50, 80%) were treated as infections. Infectious disease consultation was obtained for more than half (37, 60%) of the cases. Definitive therapy with cefepime was prescribed in 3 cases (6%). Most of the patients were prescribed a carbapenem, i.e., ertapenem (14, 28%), meropenem (6, 12%), or imipenem (2, 4%). Eleven patients received a fluoroquinolone, either ciprofloxacin (8, 16%) or levofloxacin (3, 6%). Amoxicillin-clavulanate was given to 3 patients and fosfomycin to 2 patients. Concomitant antimicrobials were used for a separate infectious indication in 14 cases. Reported resistance to third-generation cephalosporin may have been an influence in the predominant selection of carbapenems.

The three cases receiving cefepime were all under infectious disease physician supervision. A neutropenic patient with normal renal function was treated with cefepime 2 g every 12 h in the setting of *E. cloacae* complex urine culture positivity (cefepime MIC, 4 µg/ml). A liver transplant candidate undergoing intermittent hemodialysis was transitioned from meropenem to cefepime 0.5 g daily for *E. coli* (cefepime MIC, 4 µg/ml) peritonitis. The cefepime dose was increased to 1 g daily when cefepime susceptibilities were reported, and this was continued to complete a 2-week course of therapy posttransplant. In the third case, a patient with a complex medical history, including spinal cord injury, renal transplant, and recurrent urinary tract infections, was treated with 2 g of cefepime every 24 h for *E. coli* (cefepime MIC, 8 µg/ml) urinary tract infection. His creatinine clearance was estimated to be 20 to 25 ml/min. Repeat culture showed persistence of *E. coli* with an increased cefepime MIC of ≥16 µg/ml; treatment was changed to ertapenem. Cefepime treatment of an SDD isolate was considered successful in the first two cases, and the third case was considered a failure.

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In this small study, the overall incidence of SDD was low (1.6%) and represented a small percentage of the total isolates for each species. *E. coli* and *K. pneumoniae* were the most common cefepime SDD organisms. Carbapenems were used as definitive therapy in the majority of infections caused by SDD *Enterobacteriaceae*, while cefepime use was low. This study reports findings similar to those by Hamada et al. (5), where 1% of *Enterobacteriaceae* isolates fell into the SDD range. Cefepime dosing was in alignment with CLSI guidelines intended for SDD isolates in the few cases in which it was utilized. *Enterobacter* and *Citrobacter* were the most common SDD species in the study by Hamada et al. (5), suggesting a possible local influence. Given the limitations of local prescribing habits and resistance patterns, exploration across other centers may yield further insight into how providers are selecting and dosing antimicrobials for organisms in the reported SDD category.

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