# Antimicrobial Activity of Ceftazidime-Avibactam and Comparator Agents Tested against *Enterobacteriaceae* and *Pseudomonas aeruginosa* from United States Medical Centers Stratified by Infection Type (2015–2016)

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## INTRODUCTION

- Ceftazidime-avibactam is approved by the United States Food and Drug Administration (US FDA) and by the European Medicine Agency (EMA) to treat complicated intra-abdominal infection (cIAI) in combination with metronidazole, as well as complicated urinary tract infections, including pyelonephritis
- Ceftazidime-avibactam is also approved to treat hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP) in Europe and has been studied in pediatric patients (NCT01893346)
- As part of the International Network for Optimal Resistance Monitoring (INFORM) surveillance program, we evaluated and compared the *in vitro* activities of ceftazidime-avibactam and comparators against *Enterobacteriaceae* and *Pseudomonas aeruginosa* from various infection types

## MATERIALS AND METHODS

**Bacterial isolates**

- 19,249 *Enterobacteriaceae* and 4,191 *Pseudomonas aeruginosa* isolates were collected from 85 medical centers among 37 states from all 9 US census divisions in 2015–2016 as part of the INFORM program
- These isolates were collected from patients with bloodstream (BSI; 3,434 isolates; 14.7%), pneumonia (6,439; 27.5%), skin and skin structure (SSSI; 4,134; 17.6%), intra-abdominal (IAI; 951; 4.1%), urinary tract (UTI; 7,873; 33.6%), and other infection types combined (609; 2.6%)
- Only isolates determined to be significant by local criteria as the reported probable cause of infection were included in the program

**Resistant subsets**

- Carbapenem-resistant *Enterobacteriaceae* (CRE) isolates were defined as displaying imipenem, meropenem, and/or doripenem MIC values at ≥4 µg/mL (CLSI, 2017)
  - Imipenem was not applied to *Proteus mirabilis* and indole-positive *Proteeae* due to the intrinsically elevated MIC values
- MDR, extensively drug-resistant (XDR), and pan-drug-resistant (PDR) *Enterobacteriaceae* strains were classified according to recommended guidelines (Magiorakos et al., 2012) — see poster #1232 for antimicrobial classes and drug representatives used in the analysis
- Classifications were based on the following recommended parameters:
  - MDR = nonsusceptible (NS; CLSI breakpoints) to at least 3 antimicrobial classes
  - XDR = susceptible (S) to 2 or fewer antimicrobial classes
  - PDR = NS to all antimicrobial classes

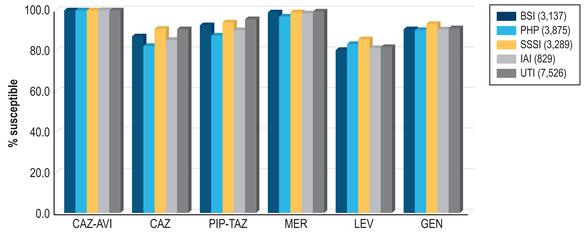
**Susceptibility testing**

- Broth microdilution test method was conducted according to CLSI, and ceftazidime-avibactam was tested with avibactam at fixed concentration of 4 µg/mL
- CLSI susceptibility interpretive criteria were applied for comparator agents, and the US FDA breakpoint criteria were applied for ceftazidime-avibactam (susceptible at ≤8 µg/mL and resistant at ≥16 µg/mL when testing *Enterobacteriaceae* and *P. aeruginosa*)

## RESULTS

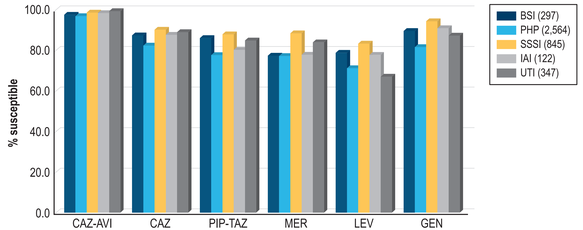
- Ceftazidime-avibactam was active against 99.9% to 100.0% of *Enterobacteriaceae* and 97.0% (pneumonia) to 99.4% (UTI) of *P. aeruginosa* isolates (Figures 1 and 2)
- Susceptibility rates were consistently lower among *Enterobacteriaceae* from pneumonia compared to other infection types for β-lactams such as ceftazidime (82.3% vs. 87.1%–90.8%), piperacillin-tazobactam (87.5% vs. 90.2%–95.6%), and meropenem (96.8% vs. 98.4%–99.4%; Figure 1)
- *Enterobacteriaceae* susceptibility to gentamicin was slightly higher among isolates from SSSI compared to other infection types (Figure 1), whereas susceptibility to levofloxacin and colistin were lowest among BSI (Figure 1) and SSSI isolates, respectively (data not shown)
- Among *P. aeruginosa*, susceptibility rates for ceftazidime, piperacillin-tazobactam, and gentamicin were lowest among isolates from pneumonia (Figure 2)
- *P. aeruginosa* susceptibility to meropenem was similar among isolates from bloodstream infection, pneumonia, and intra-abdominal infection (77.3%–77.9%), and susceptibility to levofloxacin was markedly lower among UTI isolates (67.1%) compared to other infection types (71.3%-83.3%; Figure 2)
- The occurrence of MDR, XDR, and CRE phenotypes were markedly higher among isolates from patients with pneumonia compared to other infection types (Figure 3)
- The frequency of *P. aeruginosa* isolates with MDR and XDR phenotypes, as well as nonsusceptible to ceftazidime, meropenem, and piperacillin-tazobactam, were also highest among isolates from patients with pneumonia compared to other infection types (Figure 4)
- The best overall coverage against *Enterobacteriaceae* and *P. aeruginosa* isolates combined was shown by ceftazidime-avibactam (99.9% and 97.6%, respectively); whereas meropenem was very active against *Enterobacteriaceae* (98.6%) but showed limited activity against *P. aeruginosa* (80.2% susceptible; Figure 5)
- Only ceftazidime-avibactam and colistin exhibited good activity against MDR *Enterobacteriaceae* (99.4% susceptible to ceftazidime-avibactam) and MDR *P. aeruginosa* (89.3% susceptible to ceftazidime-avibactam; Figure 6)
- Ceftazidime-avibactam was also the most active compound against the subset of XDR *Enterobacteriaceae* and *P. aeruginosa* isolates combined (Figure 7)

**Figure 1. Antimicrobial activity of ceftazidime-avibactam and comparator agents tested against *Enterobacteriaceae* isolates from US hospitals stratified by infection type**



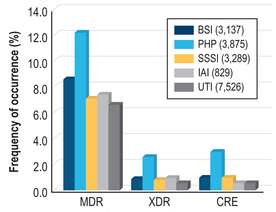

Abbreviations: BSI, bloodstream infection; PHP, pneumonia in hospitalized patient; SSSI, skin and skin structure infection; IAI, intra-abdominal infection; UTI, urinary tract infection; CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; PIP-TAZ, piperacillin-tazobactam; MER, meropenem; LEV, levofloxacin; GEN, gentamicin

**Figure 2. Antimicrobial activity of ceftazidime-avibactam and comparator agents tested against *P. aeruginosa* isolates from US hospitals stratified by infection type**



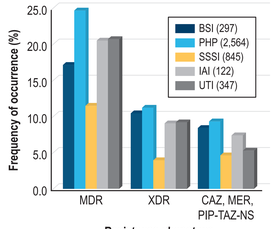

Abbreviations: BSI, bloodstream infection; PHP, pneumonia in hospitalized patients; SSSI, skin and skin structure infection; IAI, intra-abdominal infection; UTI, urinary tract infection; CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; PIP-TAZ, piperacillin-tazobactam; MER, meropenem; LEV, levofloxacin; GEN, gentamicin

**Figure 3. Frequency of occurrence of MDR, XDR, and CRE among *Enterobacteriaceae* isolates from US hospitals stratified by infection type**




Abbreviations: BSI, bloodstream infection; PHP, pneumonia in hospitalized patient; SSSI, skin and skin structure infection; IAI, intra-abdominal infection; UTI, urinary tract infection; MDR, multidrug-resistant; XDR, extensively drug-resistant; and CRE, carbapenem-resistant

**Figure 4. Frequency of occurrence of MDR, XDR, and isolates nonsusceptible to ceftazidime, meropenem, and piperacillin-tazobactam among *P. aeruginosa* isolates from US hospitals stratified by infection type**




Abbreviations: BSI, bloodstream infection; PHP, pneumonia in hospitalized patient; SSSI, skin and skin structure infection; IAI, intra-abdominal infection; UTI, urinary tract infection; MDR, multidrug-resistant; XDR, extensively drug-resistant; CAZ, ceftazidime; MER, meropenem; PIP-TAZ, piperacillin-tazobactam; NS, nonsusceptible

**Figure 5. Comparative coverage (susceptibility rates) of ceftazidime-avibactam and key comparator agents when tested against *Enterobacteriaceae* and *P. aeruginosa* isolates from US hospitals (2015–2016)**

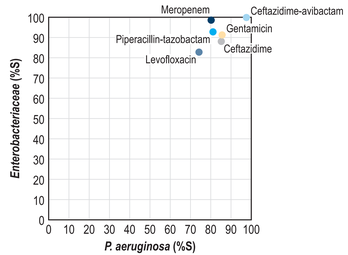



**Figure 6. Comparative coverage (susceptibility rates) of ceftazidime-avibactam and key comparator agents when tested against MDR isolates of *Enterobacteriaceae* and *P. aeruginosa* from US hospitals (2015–2016)**

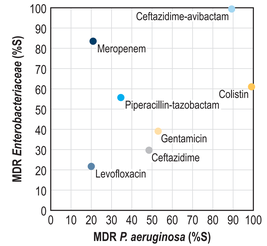
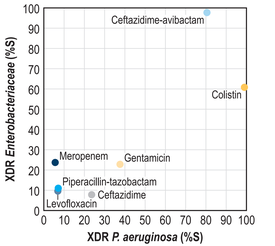



**Figure 7. Comparative coverage (susceptibility rates) of ceftazidime-avibactam and key comparator agents when tested against XDR isolates of *Enterobacteriaceae* and *P. aeruginosa* from US hospitals (2015–2016)**




## CONCLUSIONS

- Antimicrobial susceptibility rates were generally lower among *Enterobacteriaceae* and *P. aeruginosa* isolates from patients with pneumonia compared to other infections
- Ceftazidime-avibactam was highly active against a large collection of contemporary *Enterobacteriaceae* and *P. aeruginosa* isolates from US hospitals (2015–2016), including MDR and XDR organisms, regardless of the infection type
- Ceftazidime-avibactam represents a potential valuable option for empiric antimicrobial therapy in US hospitals with elevated rates of MDR or XDR *Enterobacteriaceae* and *P. aeruginosa* isolates

## ACKNOWLEDGEMENTS

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