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In Vitro Activity of a Novel Extended-Spectrum β-Lactamase Inhibitor, AAI101, in Combination with Cefepime, against *Enterobacteriaceae* Isolates Collected during 2016

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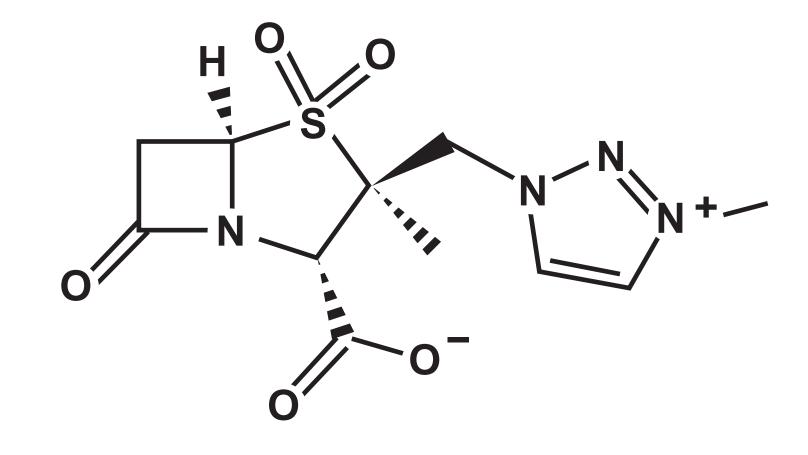
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Introduction

- Resistance development to existing β -lactam therapies due to the spread of extended-spectrum β -lactamases (ESBLs) among *Enterobacteriaceae* has created the need for new treatment options
- AAI101 is a novel extended-spectrum β-lactamase inhibitor (Figure 1) highly active against ESBLs and a broad array of other β-lactamases
- The combination of cefepime/AAI101 recently has completed a Phase 2 clinical trial in complicated urinary tract infections and Phase 3 is planned to be initiated in 2018
- Cefepime/AAI101 was granted Qualified Infectious Disease Product and Fast Track designations by the United States Food and Drug Administration
- A collection of 572 recent *Enterobacteriaceae* clinical isolates were tested for susceptibility to cefepime/AAI101, cefepime, meropenem, and piperacillin-tazobactam
- The isolates were obtained mostly from year 2016, primarily collected from North America and Europe, and included challenge strains

Figure 1. Chemical structure of AAI101



Materials and Methods

- A collection of 572 *Enterobacteriaceae* was obtained from US (74.0%), European (25.0%), and Latin American (1.0%) medical centers, with 91.1% of organisms isolated during 2016
- The panel included 16.8% (96/572) cefepime-nonsusceptible and 5.4% (31/572) carbapenem-resistant isolates with diverse resistance mechanisms
- Organisms were identified by matrix-assisted laser desorption ionization time-of-flight mass spectrometry or next-generation sequencing
- Susceptibility testing was performed using CLSI reference broth microdilution methodology; CLSI interpretive criteria were applied

- Isolates were tested for susceptibility to cefepime/AAI101, cefepime, meropenem, and piperacillin-tazobactam
- Fixed AAI101 concentrations of 4 μg/mL and 8 μg/mL, in combination with cefepime, were chosen for broth microdilution susceptibility testing based on prior microbiological and pharmacokinetic/pharmacodynamic studies
- For comparative purposes, CLSI breakpoint interpretive criteria for cefepime were applied to cefepime/AAI101 combinations

Results

- Against the complete collection of 572 Enterobacteriaceae, which included cefepime-nonsusceptible and carbapenem-resistant isolates, AAI101 restored the activity of cefepime to the susceptible interpretive category against 95.1%-97.0% of the isolates with an MIC₉₀ value of 0.5 μg/mL (fixed AAI101 concentrations of 4 μg/mL or 8 μg/mL; Table 1 and Figure 2)
- MIC₉₀ values for cefepime-only and piperacillin-tazobactam were in the resistant interpretive category with values of 16 μg/mL and 128 μg/mL, respectively
- Cefepime/AAI101 activity was comparable to that of meropenem: 97.0% of isolates were inhibited at or below the cefepime susceptible breakpoint of 2 μg/mL, and 94.2% of the isolates inhibited at or below the meropenem susceptible breakpoint of 1 μg/mL, respectively
- Against cefepime-resistant, carbapenem-susceptible isolates of Enterobacteriaceae (n=40), AAI101 restored the activity of cefepime to the susceptible interpretive category against 97.5% of the isolates with an MIC₉₀ value of 1 μg/mL (fixed AAI101 concentration of 8 μg/mL; Table 2 and Figure 3)
- MIC₉₀ values for piperacillin-tazobactam and meropenem were >128 μg/mL and 0.5 μg/mL, respectively (Table 2 and Figure 4)
- Against carbapenem-resistant isolates of *Enterobacteriaceae* (n=31), cefepime/AAI101 (fixed AAI101 concentration of 8 μg/mL), piperacillin-tazobactam, and meropenem showed 51.6%, 3.2% and 0% susceptible isolates
- Against *K. pneumoniae* (n=135) and *E. coli* (n=121), cefepime-only MIC₉₀ values were in the resistant category (MIC₉₀ values >128 μg/mL and 32 μg/mL, respectively). AAI101 at fixed concentrations of 4 μg/mL or 8 μg/mL restored cefepime MIC₉₀ values to the susceptible-dose-dependent and susceptible interpretive categories (Table 2)
- Piperacillin-tazobactam MIC₉₀ values (>128 μg/mL and 64 μg/mL, respectively) were in the resistant category for *K. pneumoniae* and intermediate interpretive category for *E. coli*
- Meropenem MIC₉₀ value (>8 μg/mL) was in the resistant category for *K. pneumoniae* with 80% susceptible isolates
- with 60% susceptible isolates

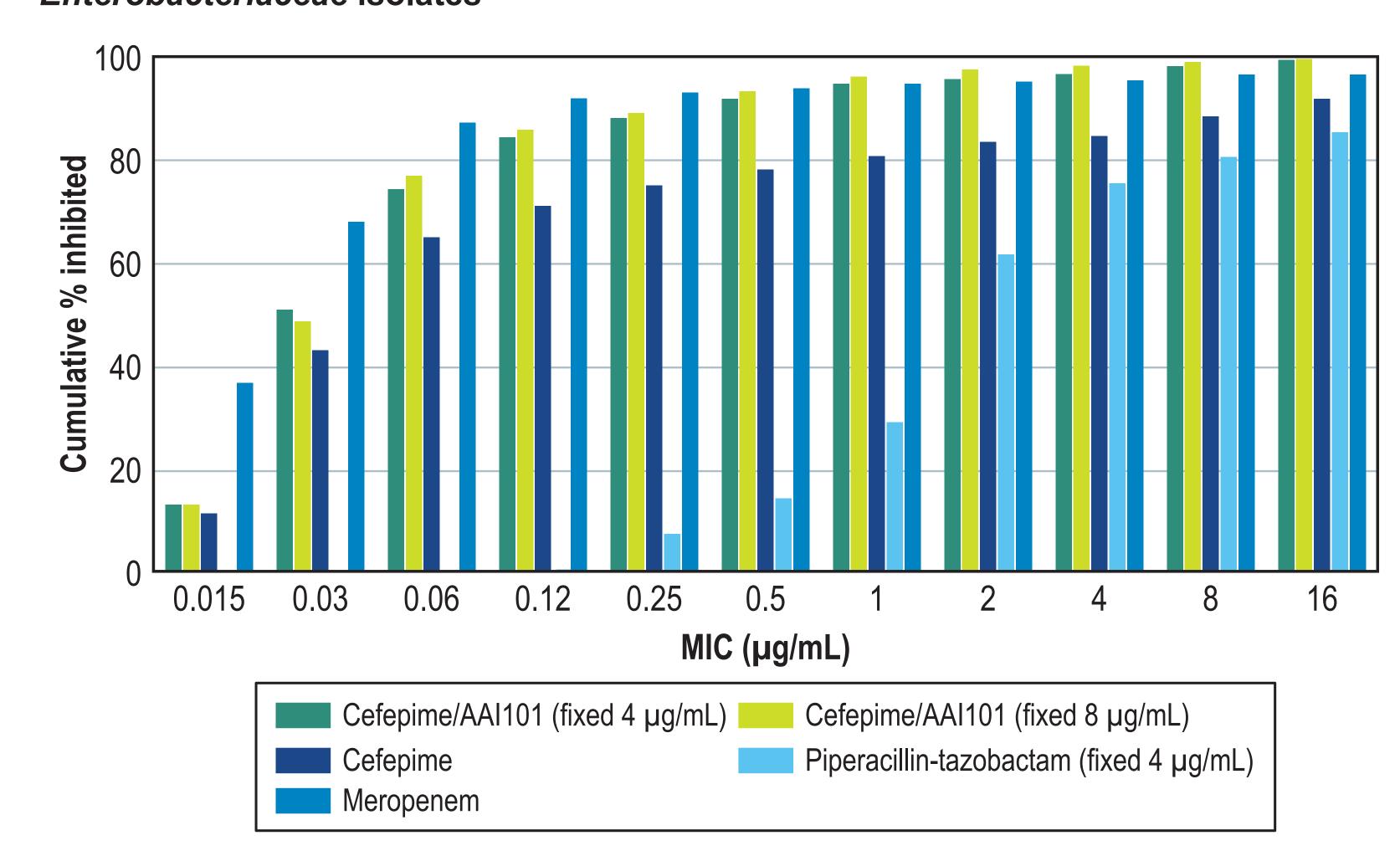
Table 1 Cumulative percent inhibition results for cefepime/AAI101 (fixed AAI101 concentrations of 4 μg/mL and 8 μg/mL) and comparators against 572 recent *Enterobacteriaceae* isolates

	No. of isolates at MIC (μg/mL; cumulative %)																		
Organism group (no. tested)/antimicrobials	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	> ^a	MIC ₅₀	MIC ₉₀
Enterobacteriaceae (572) ^b																			
Cefepime/AAI101 (fixed AAI101 concentration of 4 µg/mL)	0 0.0	6 1.0	67 12.8	216 50.5	133 73.8	58 83.9	21 87.6	21 91.3°	17 94.2	5 95.1	6 96.1	8 97.6	7 98.8	4 99.5	0 99.5	1 99.7	2 100.0	0.03	0.5
Cefepime/AAI101 (fixed AAI101 concentration of 8 µg/mL)	0 0.0	1 0.2	72 12.8	203 48.3	161 76.4	51 85.3	19 88.6	24 92.8	16 95.6	8 97.0	4 97.7	4 98.4	3 99.0	4 99.7	0 99.7	2 100.0		0.06	0.5
Cefepime	0 0.0	2 0.3	62 11.1	180 42.7	125 64.5	35 70.6	23 74.6	17 77.6	15 80.2	16 83.0	6 84.1	22 87.9	19 91.3	19 94.6	5 95.5	4 96.2	22 100.0	0.06	16
Meropenem	0 0.0	6 1.0	202 36.4	178 67.5	110 86.7	27 91.4	6 92.5	5 93.3	5 94.2	2 94.6	2 94.9	6 96.0					23 100.0	0.03	0.12
Piperacillin-tazobactam					0 0.0	2 0.3	39 7.2	39 14.0	85 28.8	185 61.2	79 75.0	29 80.1	27 84.8	8 86.2	16 89.0	15 91.6	48 100.0	2	128

aMIC value is greater than the highest concentration tested.

bComprised of 21 Citrobacter freundii spp. complex, 21 Citrobacter koseri, 28 Enterobacter aerogenes, 77 Enterobacter aerogenes, 77 Enterobacter aerogenes, 77 Enterobacter aerogenes, 77 Enterobacter aerogenes, 80 Enterobacter aerogenes, 81 Enterobacter aerogenes, 82 Enterobacter aerogenes, 83 Enterobacter aerogenes, 84 Enterobacter aerogenes, 85 Enterobacter aerogenes, 85 Enterobacter aerogenes, 85 Enterobacter aerogenes, 85 Enterobacter aerogenes, 86 Enterobacter aerogenes, 86 Enterobacter aerogenes, 87 Enterobacter aer

Figure 2 Cumulative percent inhibition results for cefepime/AAI101 (fixed AAI101 concentrations of 4 µg/mL and 8 µg/mL) and comparators against 572 recent *Enterobacteriaceae* isolates



- Against Enterobacter spp. cefepime-only MIC₉₀ values were in the susceptible interpretive category for E. aerogenes and in the susceptible-dose-dependent category for E. cloacae. AAI101 reduced cefepime MIC₉₀ values by ≥2 log₂ dilutions and restored cefepime MIC₉₀ values to the susceptible interpretive category for both species (Table 2)
- Piperacillin-tazobactam MIC₉₀ values were in the intermediate interpretive category for *E. aerogenes* and resistant interpretive category for *E. cloacae* spp. complex isolates
 Meropenem MIC₉₀ values were in the susceptible interpretive category for both species
- Against Citrobacter spp., K. oxytoca, M. morganii, Proteus spp., Providencia spp., and S. marcescens, MIC₉₀ values for cefepime-only, cefepime/AAI101, piperacillin-
- AAI101 reduced cefepime MIC₉₀ values by 4 log₂ dilutions for *Proteus* spp.
 Reductions of 1 to 2 log₂ dilutions by AAI101 were observed for *K. oxytoca*,
 Providencia spp., and *S. marcescens*

tazobactam, and meropenem were in the susceptible categories (Table 2)

Conclusions

- AAI101, a novel β-lactamase inhibitor with potent activity against ESBLs and a variety of other β-lactamases, restored the activity of cefepime against a panel of recent
- Enterobacteriaceae collected primarily in 2016 from US and European medical centers

 Activity of AAI101, when combined with cefepime, was most prominent against

 K. pneumoniae and E. coli, followed by E. cloacae and Proteus spp.
- Cefepime/AAI101 was as effective as meropenem and outperformed cefepime and piperacillin-tazobactam against this collection of isolates
- Against Citrobacter spp., K. oxytoca, M. morganii, Providencia spp., and S. marcescens, cefepime-only demonstrated potent activity
- Cefepime/AAI101 warrants further clinical investigation to evaluate its potential as a therapeutic option for difficult-to-treat gram-negative pathogens
- Cefepime/AAI101 may be a carbapenem-sparing option for settings with increasing resistance to piperacillin-tazobactam

Figure 3 Cumulative percent inhibition results for cefepime/AAI101 (fixed AAI101 concentrations of 4 µg/mL and 8 µg/mL) and comparators against 40 cefepimeresistant, carbapenem-susceptible *Enterobacteriaceae* isolates

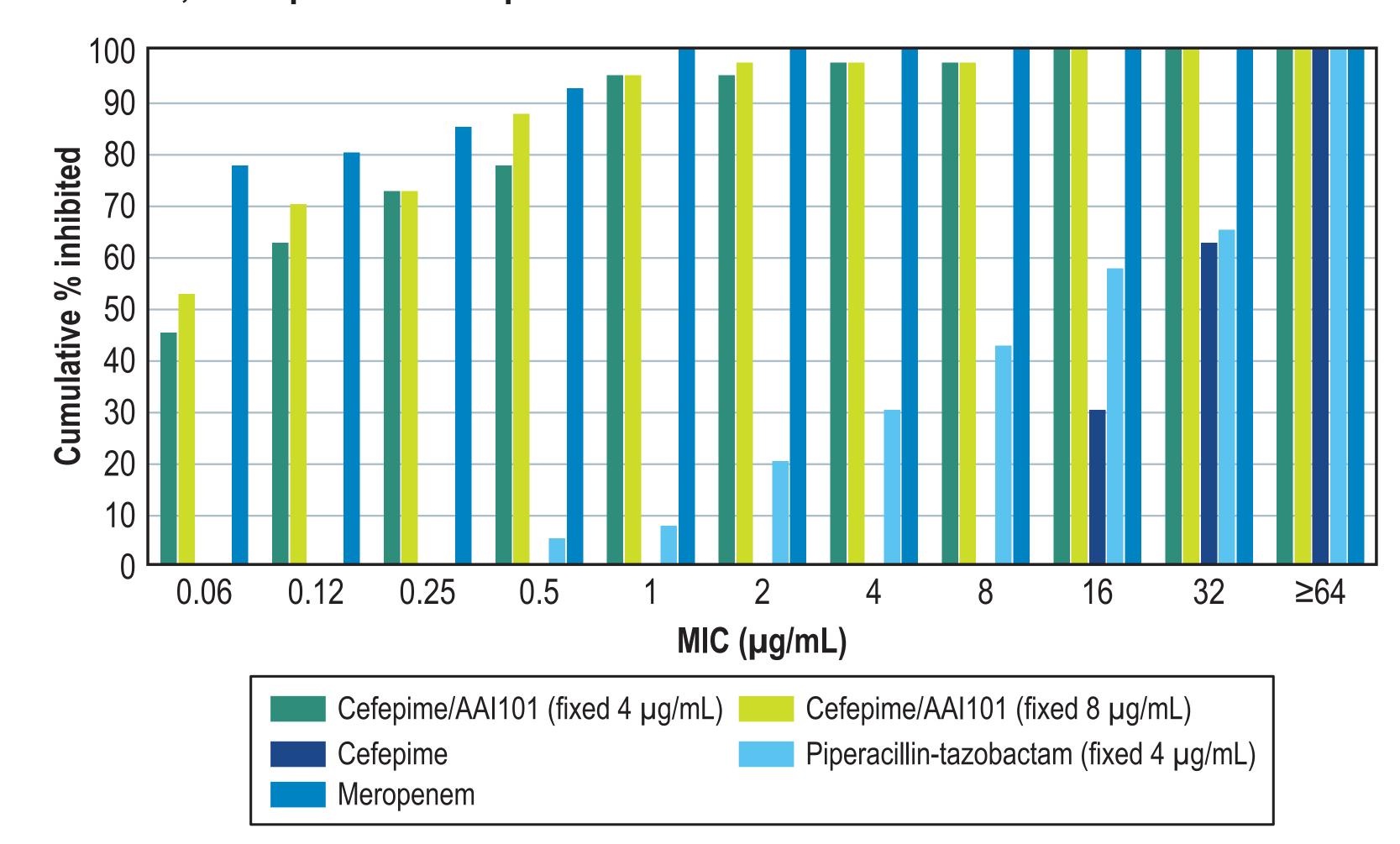
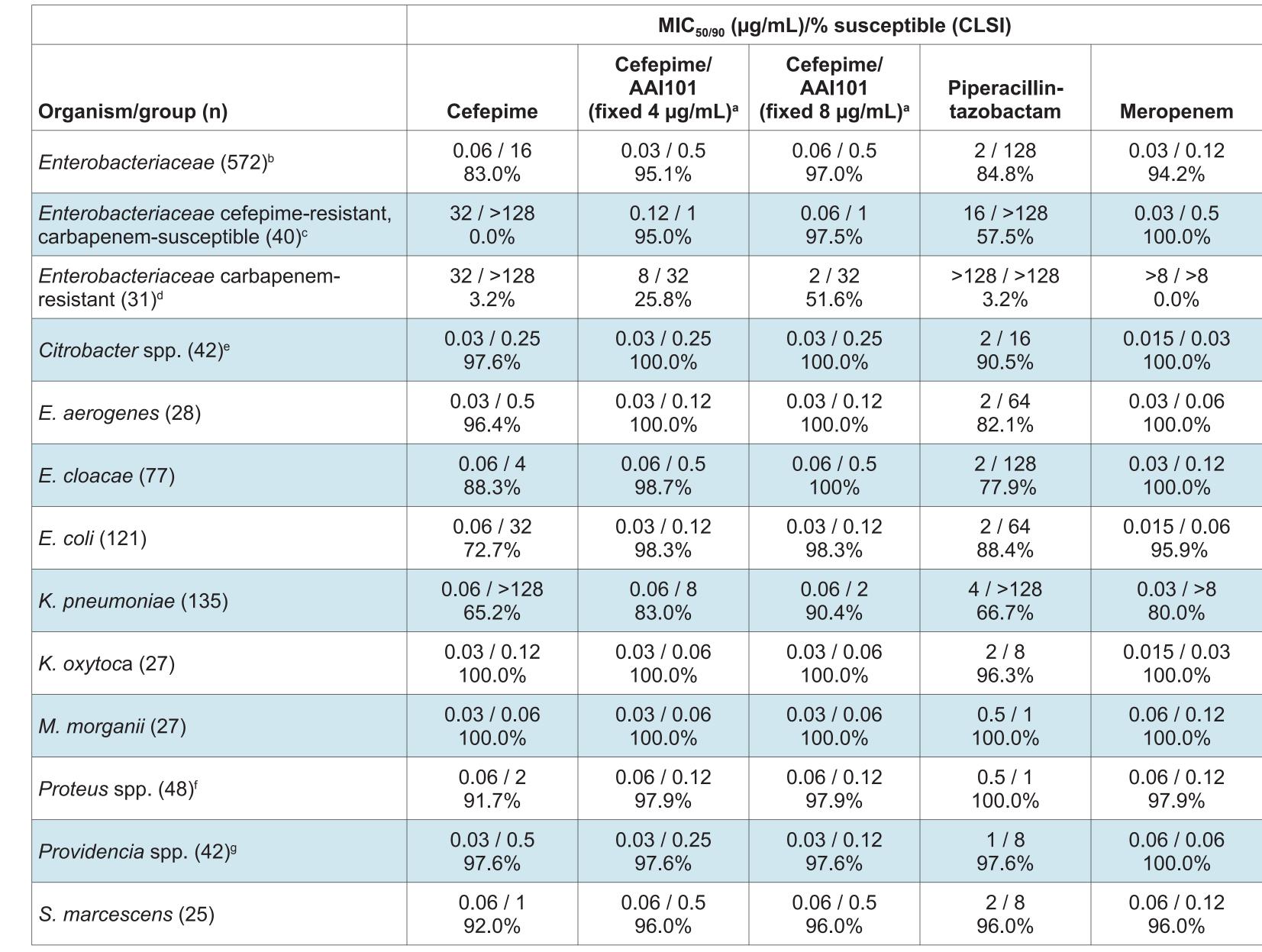


Table 2 Antimicrobial activity of cefepime/AAI101 and comparators against 572 recent *Enterobacteriaceae* isolates



^aCefepime breakpoint interpretive criteria were applied to cefepime/AAI101 combinations for comparison purposes only.

^b Comprised of 21 *Citrobacter freundii* species complex, 21 *C. koseri*, 28 *Enterobacter aerogenes*, 77 *E. cloacae* species complex, 121 *Escherichia coli*, 27 *Klebsiella oxytoca*, 135 *K. pneumoniae*, 27 *Morganella morganii*, 27 *Proteus mirabilis*, 21 *P. vulgaris* group, 21 *Providencia rettgeri*, 21 *P. stuartii*, and 25 *Serratia marcescens* isolates. The cefepime- and carbapenem-resistant isolates represent subsets of the 572 *Enterobacteriaceae* surveyed.

^cComprised of 1 *E. aerogenes*, 6 *E. cloacae* spp. complex, 16 *E. coli*, 14 *K. pneumoniae*, 2 *P. mirabilis*, and 1 *P. stuartii* isolates.

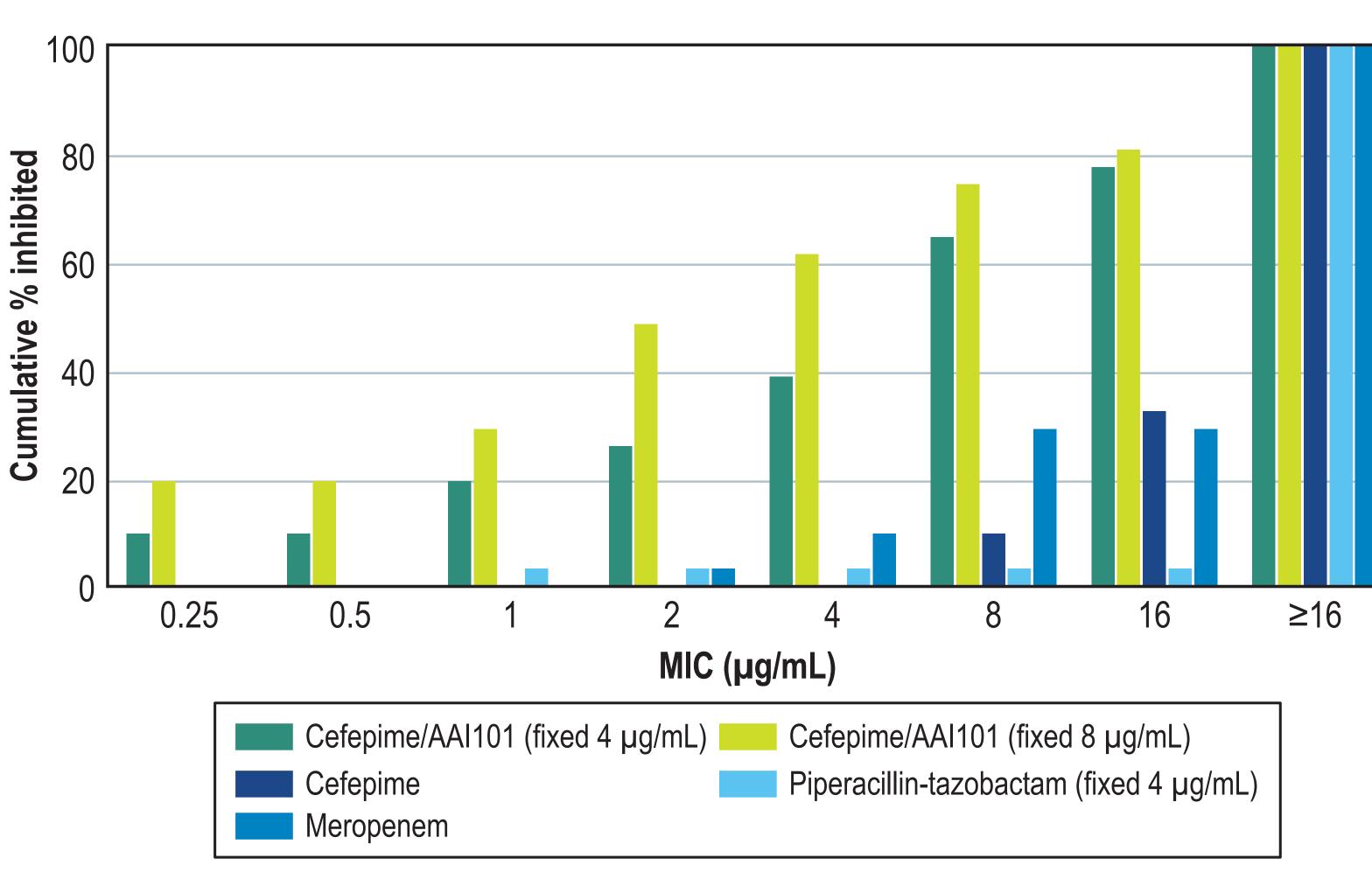
^dComprised of 4 *E. coli*, 26 *K. pneumoniae*, and 1 *P. mirabilis* isolates.

^eComprised of 21 *C. koseri* and 21 *C. freundii* species complex isolates.

^fComprised of 27 *P. mirabilis* and 21 *P. vulgaris* group isolates.

Comprised of 21 *P. rettgeri* and 21 *P. stuartii* isolates.

Figure 4 Cumulative percent inhibition results for cefepime/AAI101 (fixed AAI101 concentrations of 4 µg/mL and 8 µg/mL) and comparators against 31 carbapenem-resistant *Enterobacteriaceae* isolates



Acknowledgements

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