

P0157 Disk content assessment and proposed breakpoint interpretive criteria for cefepime in combination with AAI101

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Background: AAI101 is a novel extended-spectrum β -lactamase inhibitor active against a broad array of β -lactamases, including ESBLs. The combination of AAI101 with cefepime is in Phase II clinical trials. A disk content study was conducted to identify appropriate cefepime and AAI101 masses supporting CLSI recommendations for zone diameter susceptibility testing.

Materials/methods: Disk contents were selected and recommended cefepime-AAI101 breakpoint interpretive criteria were generated according to CLSI guidelines M02-A12, M07-A10, M23-A4, and M100-S27. A panel of 576 recent, geographically diverse Enterobacteriaceae representing diverse species and a wide range of cefepime-AAI101 MIC values was surveyed, with cefepime, meropenem, and piperacillin-tazobactam as controls. Four cefepime-AAI101 concentrations (30/30, 30/20, 30/15, 30/10 μg) were examined initially (Tier 1), from which two were chosen for second-round testing (Tier 2). Error-rate bounded analyses compared MIC values for cefepime-AAI101 (fixed AAI101 concentrations of 4 and 8 $\mu\text{g}/\text{mL}$) to inhibition zone diameters for disks containing cefepime-AAI101. From these data, disk diffusion breakpoint interpretive criteria were proposed.

Results: Proposed CLSI disk diffusion breakpoints of ≥ 25 mm (S) and ≤ 19 mm (R) were calculated for cefepime-AAI101 30/20 μg disks against cefepime-AAI101 (fixed AAI101 concentrations of 4 and 8 $\mu\text{g}/\text{mL}$ [Figure]) and cefepime-AAI101 30/10 μg disks against cefepime-AAI101 (fixed 4 $\mu\text{g}/\text{mL}$). A high minor error rate (68.8%; $<40\%$ allowed [$+1$ to -1]) was observed for cefepime-AAI101 30/10 μg disks versus cefepime-AAI101 (fixed 8 $\mu\text{g}/\text{mL}$).

Conclusions: Resistance development in Enterobacteriaceae to existing β -lactam/ β -lactamase inhibitor combinations due to ESBL production requires new treatment options. AAI101 is a novel β -lactamase inhibitor with potent activity against ESBLs. Proposed CLSI interpretive criteria for cefepime-AAI101 30/20 μg disks compared to cefepime-AAI101 MICs (determined with AAI101 fixed at concentrations of 4 and 8 $\mu\text{g}/\text{mL}$) met CLSI criteria for

- susceptible isolates in the inhibition zone range of 15-35 mm;
- adequate discrimination between targeted susceptible and resistant populations;
- acceptable very major, major, and minor error rates;
- reproducibility using a minimum number of replicates ($n = 2$); and

- a cefepime disk concentration that conforms to the concentration accepted for “cefepime-only” disks by CLSI.

Proposed disk breakpoints based on the error-rate bounded method, of cefepime-AAI101 (fixed 8 µg/mL) MIC versus cefepime-AAI101 30/20 µg disks (CLSI cefepime breakpoints for *Enterobacteriaceae* applied)

Cefepime-AAI101 (fixed 8 µg/mL)	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40		
≥5 >128																																		
≥4 128																																		
≥3 64																																		
≥2 32																																		
≥1 16																																		
1 8																																		
1 4																																		
1-1 2																																		
1-2 1																																		
1-3 0.5																																		
1-4 0.25																																		
1-5 0.12																																		
1-6 0.06																																		
1-7 0.03																																		
1-8 0.015																																		
1-9 0.008																																		

* = *K. pneumoniae* (#965823; OXA-48, SHV-28, CTX-M-15); * = *Enterobacter cloacae* species complex (#952344; ACT-17); * = *S. marcescens* (#937712); * = *K. pneumoniae* (#942544; KPC-2, SHV-28, CTX-M-15, OXA-1/30); * = *E. coli* (#978205; KPC-3, TEM-1)

Calculated disk breakpoints of ≥25 mm (S) and ≤ 19 mm (R)

MIC range	Number	Very major (%)	Major (%)	Minor (%)
≥1-2	8	0	N/A	0
1-1 to 1-1	16	0	0	4 (25.0)
≤1-2	1,012	N/A	0	5 (0.49)
Total	1,036	0	0	7 (0.68)