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EUCAST zone diameter breakpoints for ceftazidime-avibactam

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Background: Ceftazidime-avibactam is a combination of ceftazidime and a novel non-β-lactam β-lactamase inhibitor, avibactam, with activity against a number of β-lactamases, including ESBLs and some carbapenemases. The EUCAST disk mass for ceftazidime-avibactam is set to 10-4 µg (10 µg ceftazidime and 4 µg avibactam) and quality control criteria were presented at ECCMID 2015 (P1295). The objective of this study was to establish zone diameter breakpoints for the ceftazidime-avibactam 10-4 µg disk corresponding to the EUCAST clinical MIC breakpoints for Enterobacteriaceae and *Pseudomonas aeruginosa* (Susceptible ≤8, Resistant >8 mg/L).

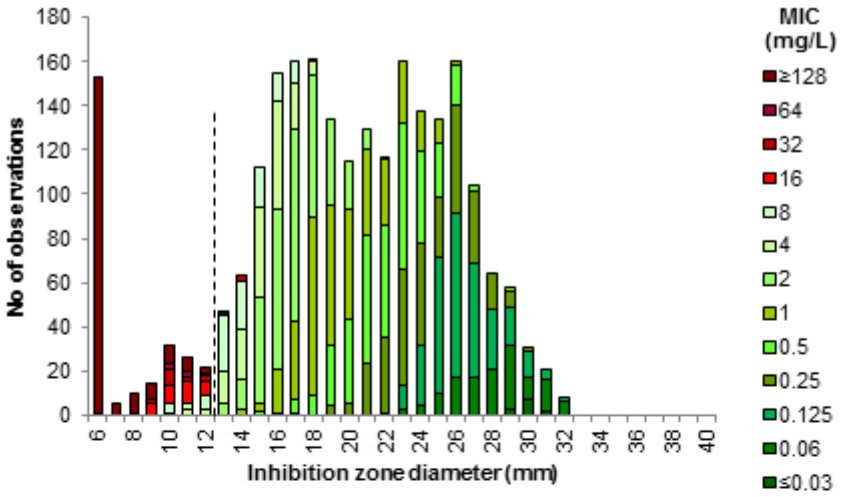
Material/methods: Zone diameter breakpoints for ceftazidime-avibactam were established according to EUCAST SOP 9.0 (www.eucast.org). Antimicrobial susceptibility testing was performed at two laboratories for Enterobacteriaceae (n=304, of which 130 were *Escherichia coli*) and *P. aeruginosa* (n=105). The isolates were of different geographical origin and intentionally biased towards β-lactam resistance. MIC determination was performed with broth microdilution (BMD) according to the ISO standard 20776-1 using custom Sensititre plates (TREK Diagnostics/Thermo Fisher Scientific) with a fixed concentration of avibactam (4 mg/L). Disk diffusion was performed according to EUCAST methodology with ceftazidime-avibactam 10-4 µg disks (BD, Mast and Oxoid/Thermo Fisher Scientific) on in-house prepared Mueller-Hinton agar plates (BBL/BD and Oxoid). Both for BMD and disk diffusion, piperacillin-tazobactam, ceftazidime and meropenem were used as control agents. *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853 and *Klebsiella pneumoniae* ATCC 700603 were used for quality control (QC). Inter-laboratory variation was examined at five additional laboratories by disk diffusion testing of local clinical isolates of *E. coli* and *P. aeruginosa* using local Mueller-Hinton media.

Results: All ceftazidime-avibactam inhibition zones were within QC ranges, with 55/89 zones on target ± 1 mm. All MICs were on the QC target values. Based on the MIC-zone diameter correlations,

zone diameter breakpoints for Enterobacteriaceae (S≥13, R<13 mm) and *P. aeruginosa* (S≥17, R<17 mm, equal to ceftazidime breakpoints) were proposed to minimize the number of isolates reported as false susceptible (Figure 1). The MIC-zone diameter correlations for Enterobacteriaceae were excellent, despite the high number of β-lactam resistance mechanisms represented. For *P. aeruginosa*, inhibition zones for isolates with ceftazidime-avibactam MICs of 4, 8 and 16 mg/L overlapped, and these results were unrelated to testing site, disk and media manufacturer. Overall, differences between disks and media from different manufacturers were small. The proposed breakpoints were supported by data from the additional laboratories.

Conclusions: The proposed zone diameter breakpoints for ceftazidime-avibactam 10-4 µg vs. Enterobacteriaceae and *P. aeruginosa* were accepted by EUCAST and will be included in the EUCAST Breakpoint Tables v. 7.0, January 2017. The zone diameter breakpoints were set to minimize the number of isolates reported as false susceptible but may have a slight increase in reporting false-resistant *P. aeruginosa*.

a)



b)

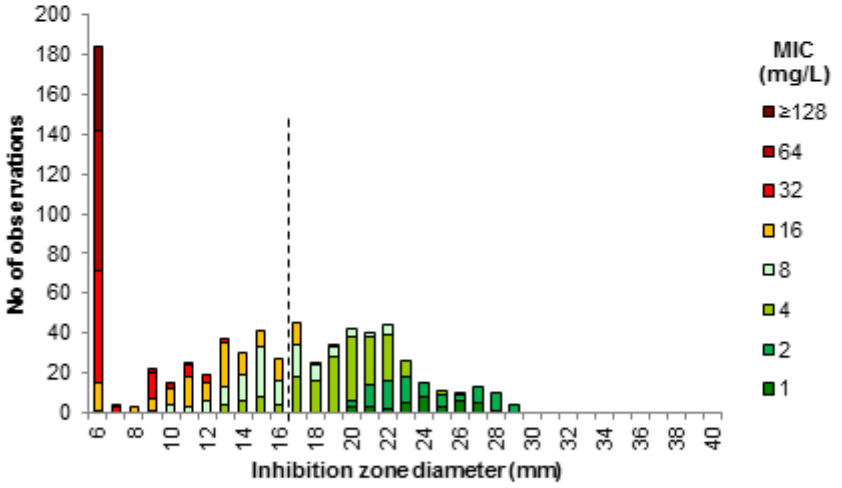


Figure 1. Inhibition zone diameter distributions for ceftazidime-avibactam 10-4 µg with corresponding MIC values as coloured bars.
EUCAST zone diameter breakpoints are shown as dotted lines.

a) Enterobacteriaceae (304 isolates, 2333 correlates)
b) *Pseudomonas aeruginosa* (105 isolates, 726 correlates)