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Introduction

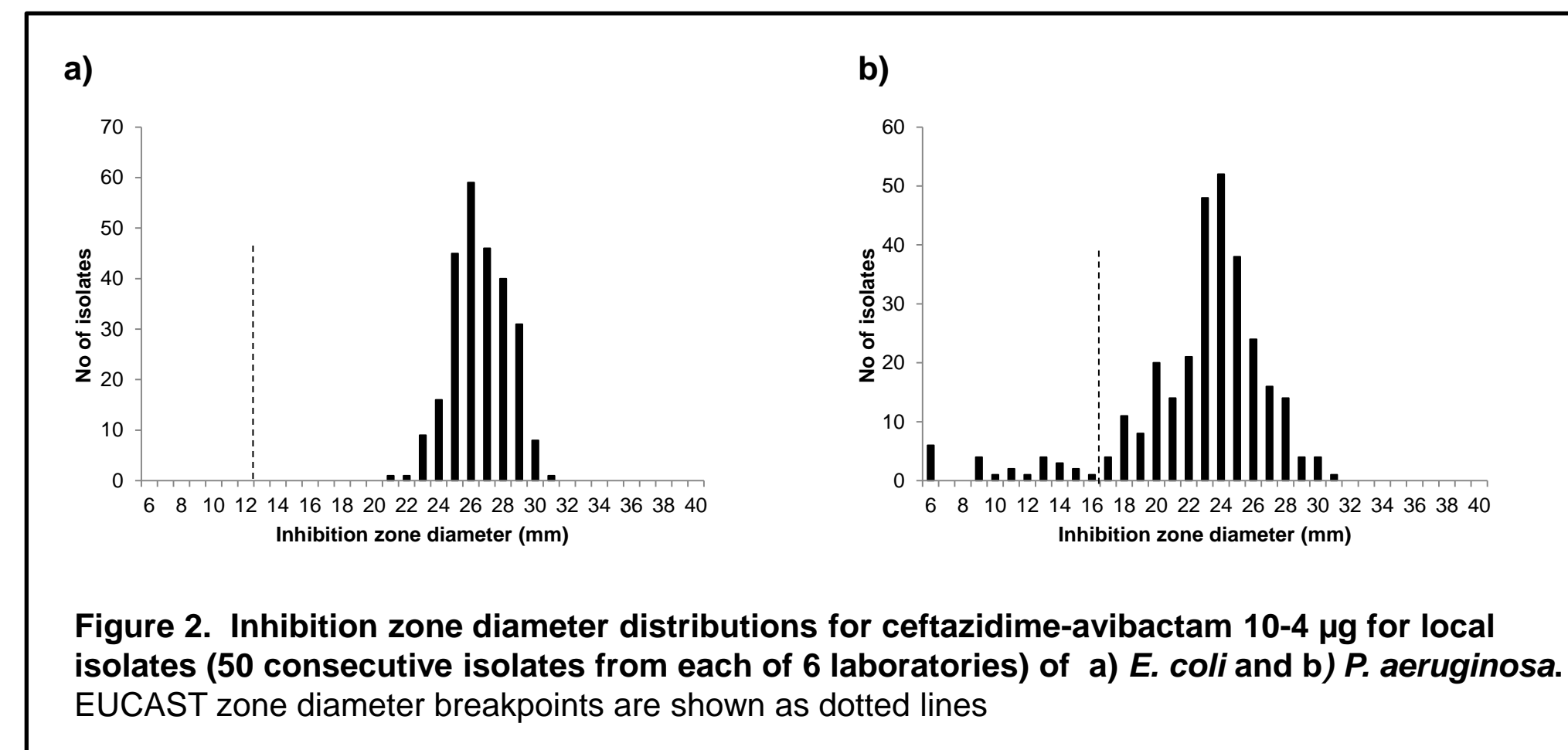
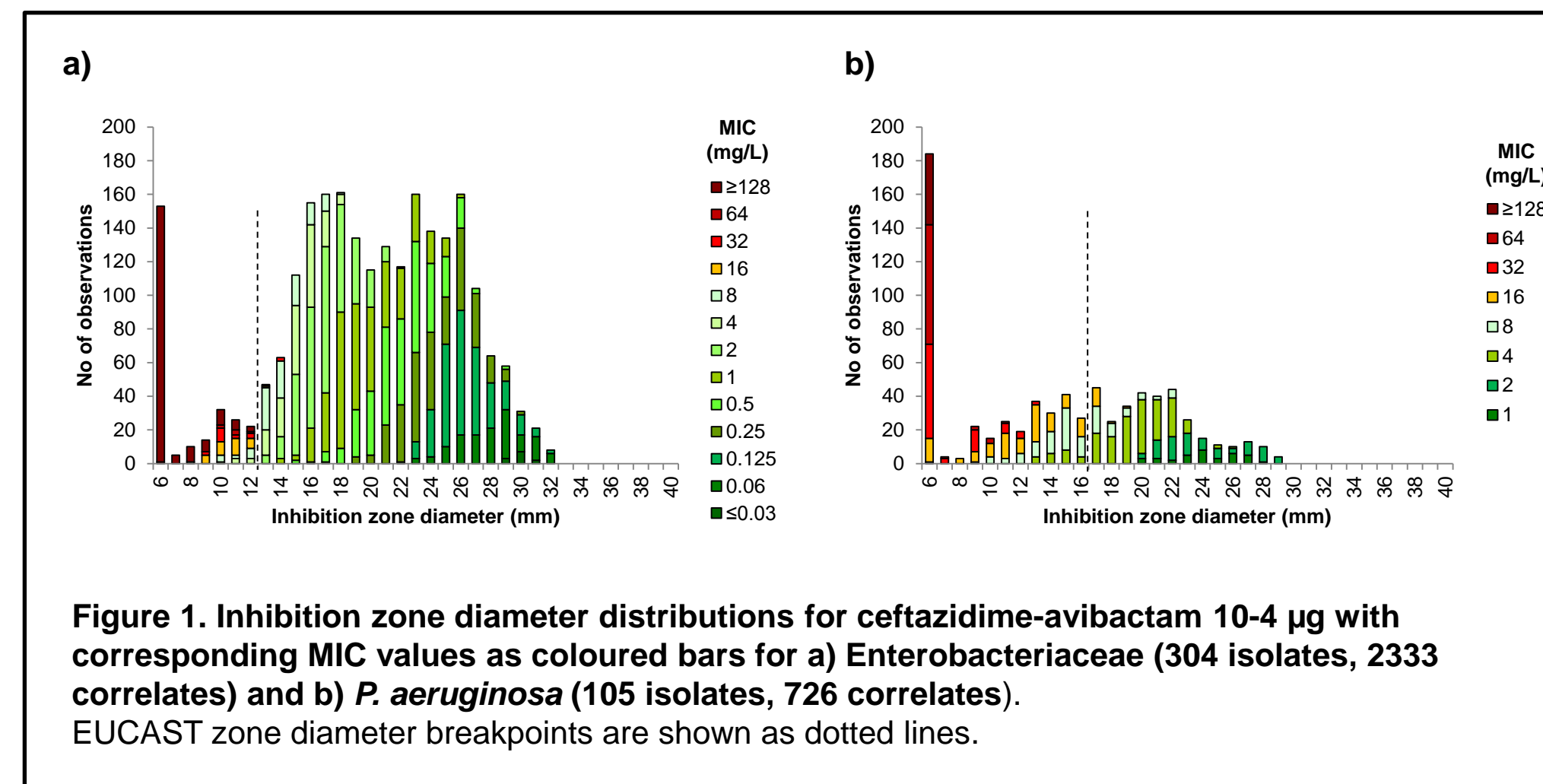
Ceftazidime-avibactam is a combination of ceftazidime and a novel non- β -lactam β -lactamase inhibitor, avibactam, with activity against a number of β -lactamases, including ESBLs and some carbapenemases. EUCAST breakpoints for Enterobacteriaceae and *Pseudomonas aeruginosa* were set to susceptible ≤ 8 and resistant >8 mg/L. The EUCAST disk mass for ceftazidime-avibactam is set to 10-4 μ g and quality control (QC) criteria were presented at ECCMID 2015 [1].

Objective

The objective of this study was to establish zone diameter breakpoints for ceftazidime-avibactam corresponding to the EUCAST clinical MIC breakpoints for Enterobacteriaceae and *P. aeruginosa*.

Methods

Zone diameter breakpoints for ceftazidime-avibactam were established according to EUCAST SOP 9.0 [2]. 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 (Thermo Scientific) with a fixed concentration of avibactam (4 mg/L). Disk diffusion was performed according to EUCAST methodology with ceftazidime-avibactam 10-4 μ g disks (BD, Mast and Oxoid/Thermo Fisher Scientific) on in-house prepared Mueller-Hinton agar plates (BBL/BD and Oxoid). *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853 and *Klebsiella pneumoniae* ATCC 700603 were used for QC. Inter-laboratory variation was examined at six additional laboratories by disk diffusion testing of local clinical isolates of *E. coli* and *P. aeruginosa* using local Mueller-Hinton media.



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Results

For ceftazidime-avibactam, all inhibition zones were within QC ranges, with 55/89 zones on target ± 1 mm, and all MICs were on the QC target values.

Based on the MIC-zone diameter correlations, zone diameter breakpoints for Enterobacteriaceae ($S \geq 13$, $R < 13$ mm) and *P. aeruginosa* ($S \geq 17$, $R < 17$ mm, equaling breakpoints for ceftazidime 10 μ g) were set to minimize the number of isolates reported as false susceptible (Figure 1).

Despite the high number of isolates with β -lactam resistance mechanisms included, the false susceptible rates (calculated on the total number of resistant results) were 1.6 and 4.0% for Enterobacteriaceae and *P. aeruginosa*, respectively. For *P. aeruginosa*, inhibition zones for isolates with ceftazidime-avibactam MICs of 4, 8 and 16 mg/L overlapped, resulting in an increase in reporting isolates as false resistant. These results were unrelated to testing site, disk and media manufacturer.

Overall, differences between disks and media from different manufacturers were small. Data from testing of local consecutive clinical isolates at six additional laboratories supported the proposed breakpoints (Figure 2).

Conclusions

The proposed zone diameter breakpoints for ceftazidime-avibactam 10-4 μ g vs. Enterobacteriaceae and *P. aeruginosa* were accepted by EUCAST and published in the EUCAST Breakpoint Tables v. 7.0, January 2017 [3].

References

- Matuschek *et al.* EUCAST quality control criteria for the ceftazidime-avibactam 10-4 μ g disk. Poster 1295, ECCMID, Copenhagen, 2015.
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