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Determination of a tentative epidemiological cut-off value (tECOFF) for dalbavancin and *Enterococcus faecium*

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Background

Dalbavancin is a semi-synthetic lipoglycopeptide antibiotic that shows potent activity against gram-positive bacteria including staphylococci, streptococci and supposedly *vanB*-positive enterococci (1). Although extensive data are available on the in vitro activity of dalbavancin for *E. faecalis*, comprehensive data on *E. faecium* are generally scarce due to the global dissemination of *vanA*-positive and glycopeptide-resistant VRE (2). In Central Europe, however, a continuing shift from *vanA*-type vancomycin-resistance to *vanB*-type resistance has been observed from 2006 onwards. Therefore, dalbavancin may become a possible treatment option. We aimed to investigate the in vitro activity of dalbavancin against different *van* genotypes, with particular focus on *vanB*-type *E. faecium*, in order to find a dalbavancin tentative ECOFF for *E. faecium*.

Methods

Susceptibility testing for 25 *van*-negative, 50 *vanA*-positive and 101 *vanB*-positive clinical *E. faecium* isolates was performed using broth microdilution (BMD) as a reference method. All isolates were from bloodstream infections from patients in Germany, isolated between January 2018 and December 2019. In addition, dalbavancin MICs were determined by MIC gradient strips (Liofilchem, Rosetti degli Abruzzi, Italy) using the standard and the macromethod. All isolates were routinely genome-sequenced and revealed 16 MLST and 74 cgMLST types (not shown in details). The *van* genotypes were deduced from NGS data. ECOFFs were determined by the use of ECOFFinder and a threshold of 99% (https://eucast.org/mic_distributions_and_ecoffs/). Reference isolates were *S. aureus* ATCC29213 and *E. faecalis* ATCC29212. We compared our aggregated MIC data with the CLSI breakpoint S ≤0,25 mg/L provided for *E. faecalis*.

Results

For *vanB* type *E. faecium* isolates, dalbavancin MICs were similar to those of vancomycin-susceptible isolates reaching values not higher than 0.125 mg/L (**Table 1, Figure 1**). ECOFFs for *van*-negative and *vanB*-positive isolates were 0.5 mg/l and 0.25 mg/L respectively (BMD). In contrast, *E. faecium* possessing *vanA* predominantly showed dalbavancin MICs >8 mg/L, therefore preventing the determination of an ECOFF. Results from gradient strip tests were in the range of BMD results (+/- dilution step; not shown). Calculations of ECOFF values for *vanB*-positive and *van*-negative isolates would be 0.25 mg/L, which is the tentative ECOFF for dalbavancin and *E. faecium*.

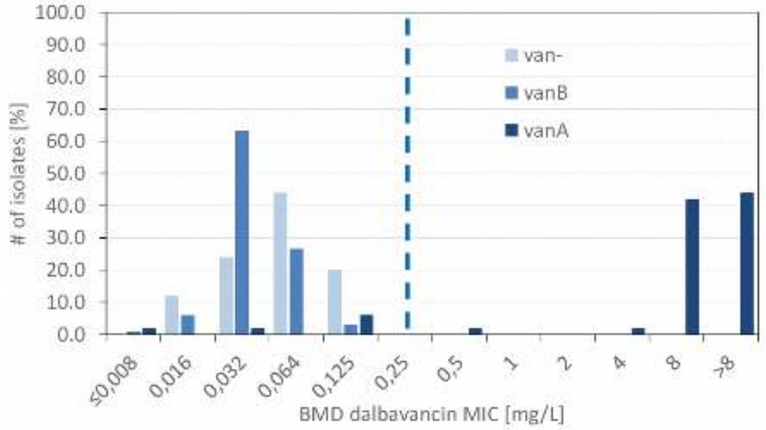

Figure 1. Distribution of dalbavancin MICs determined by broth microdilution.
MICs were obtained for 25 vancomycin-susceptible, 50 *vanA*-positive and 101 *vanB*-positive *E. faecium* isolates. The number of isolates with corresponding MICs is given in %. MIC breakpoint for dalbavancin for *E. faecalis* according to CLSI is indicated by the vertical dashed line, which is equivalent with the suggested tECOFF for *E. faecium*.

Table 1. Distribution of dalbavancin MICs for *E. faecium* isolates (n= 176). Gradient strip MICs were extrapolated to the next double dilution value equivalent to values for broth microdilution (BMD).

genotype / method	n	MIC (mg/l)												MIC_{50} mg/l	MIC_{90} mg/l	tECOFF	CLSI * % S
		≤0,08	0,016	0,032	0,064	0,125	0,25	0,5	1	2	4	8	>8				
vanA, BMD	50	1		1		3		1			1	21	22	8	>8	-	10
vanA, strip	50			1	1	1	1	1					45	>8	>8	-	8
vanB, BMD	101	1	6	64	27	3								0,032	0,064	0,125	100
vanB, strip	101	6	45	44	6									0,016	0,032	0,064	100
van-, BMD	25		3	6	11	5								0,064	0,125	0,125	100
van-, strip	25		6	11	7		1							0,032	0,064	0,25	100

Legend: BMD, broth microdilution; strip, gradient strip test.

* we applied the susceptibility breakpoint for vancomycin-susceptible *E. faecalis* as provided CLSI.

ᵃ MIC gradient strip values of 16, 32 and >32 mg/L were downsized to >8 mg/L (maximum measurable value by BMD)

Conclusion

We determined dalbavancin MICs for the largest well-characterized strain collection of clinical *E. faecium* isolates (16 MLST and 74 cgMLST types), comprising both vancomycin-susceptible and vancomycin-resistant isolates of the *vanA*- and *vanB*-types. Dalbavancin MICs were determined using broth microdilution as a reference method and subsequently confirmed via MIC gradient test strips. Results are reliable and consistent across different methodologies. Overall, we could show that dalbavancin reveals strong *in vitro* activity against vancomycin-susceptible *E. faecium* and *vanB*-type VRE. We suggest a tentative ECOFF of 0,25 mg/L for *E. faecium*.

References

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2. Sader HS, Mendes RE, Pfaller MA, Flamm RK. Antimicrobial activity of dalbavancin tested against Gram-positive organisms isolated from patients with infective endocarditis in US and European medical centres. J Antimicrob Chemother. 2019;74(5):1306-10.2.

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