



Benzylopenicillin breakpoints: *S. pneumoniae* and viridans group streptococci

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Malmö, 27 May 2025

Why did we start the revision?

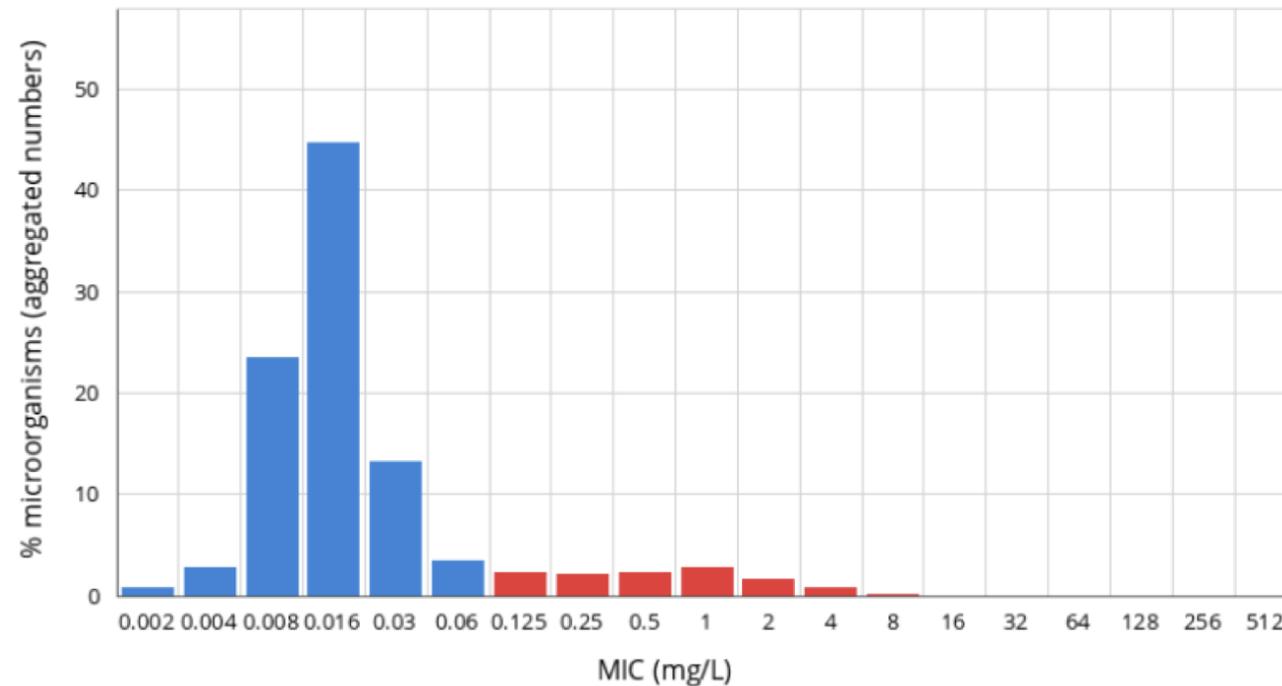
Penicillins	Standard dosage	High dosage	Uncomplicated UTI	Special situations
Benzylicillin	0.6 g (1 MU) x 4 iv	1.2 g (2 MU) x 4-6 iv		<p>Meningitis caused by <i>S. pneumoniae</i>: For a dose of 2.4 g (4 MU) x 6 iv, isolates with MIC ≤0.06 mg/L are susceptible.</p> <p>Pneumonia caused by <i>S. pneumoniae</i>: breakpoints are related to dosage: For a dose of 1.2 g (2 MU) x 4 iv, isolates with MIC ≤ 0.5 mg/L are susceptible. For a dose of 2.4 (4 MU) g x 4 iv or 1.2 g (2 MU) x 6 iv, isolates with MIC ≤1 mg/L are susceptible. For a dose of 2.4 g (4 MU) x 6 iv, isolates with MIC ≤2 mg/L are susceptible.</p>

- You could use whatever breakpoint you wanted in the previous version...
- The breakpoints required laboratories to frequently perform MIC-testing
- Gradient diffusion tests for benzylpenicillin against *S. pneumoniae* tend to undercall the MIC as measured in reference broth microdilution.
- If the MIC of a clinical isolate is determined and used for patient management decisions, the intrinsic variation (+/- one 2-fold dilution) in the MIC measurement did not allow the granular approach to dosing presented above
- Additionally
 - Comparison of surveillance data for penicillin-resistance was very difficult due to the various cut-offs used as R-breakpoint
 - Clinical data were not robust at higher MIC-values – poor quality of the data
- Could we make a simple system that did not require routine MIC-testing?

MIC distribution

Benzylpenicillin / *Streptococcus pneumoniae* International MIC distribution - Reference database 2024-01-15 **Based on aggregated distributions**

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

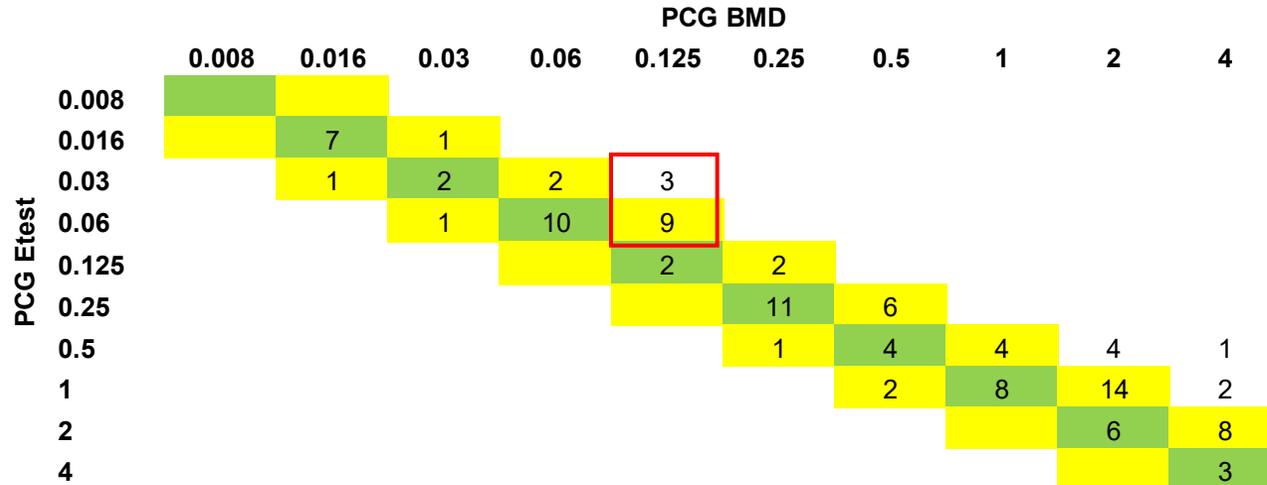


MIC
Epidemiological cut-off (ECOFF): 0.06 mg/L
Wildtype (WT) organisms: ≤ 0.06 mg/L

Confidence interval: 0.016 - 0.06
15161 observations (31 data sources)

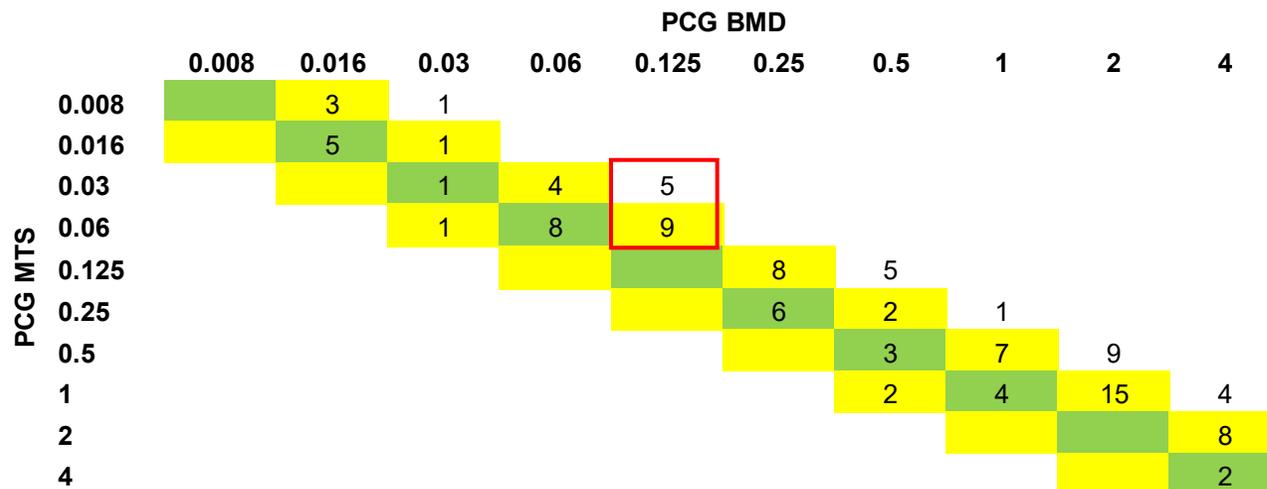
Evaluation of benzylpenicillin gradient tests

Etest



Essential agreement	91%
Bias	-45%

MTS



Essential agreement	78%
Bias	-69%

Conclusions benzylpenicillin gradient tests

- Etest and MTS systematically underestimate benzylpenicillin MICs for *S. pneumoniae*.
- A panel of 10 *S. pneumoniae* with varying beta-lactam susceptibility is available from CCUG for validation of MIC determination of benzylpenicillin in *S. pneumoniae*. Reference MICs are available on the EUCAST website, https://www.eucast.org/ast_of_bacteria/strains_with_defined_susceptibility/.

Pharmacokinetics and dynamics

The current EUCAST rationale document for benzylpenicillin (v1.0) reports the following PD target values:

- 25-35% $fT > MIC$ for stasis
- 35-45% $fT > MIC$ for cidal activity
- 40% from clinical data

Monte Carlo simulation of target attainment

A simulation was carried out in Pmetrics. The following assumptions were made:

-1 compartment model

-CL 24L/h, V 26L, 25% CV on each parameter, fraction unbound 55% (fixed) (based on Visser et al. 1993)

Dosage	0.6 g x 4	1.2 g x 4	1.2 g x 6	2.4 g x 6	3 g x 3	3 g x 4	3 g x 6
$f\%T > MIC$	40	40	40	40	40	40	40
0.06	97.1	98.3	100	100	99.3	99.1	100
0.125	93.3	97.1	100	100	98.3	98.8	100
0.25	81.9	93.0	100	100	97.0	97.6	100
0.5	61.0	81.9	99.8	100	93.7	94.5	100
1	26.8	61.0	99.5	99.8	84.9	86.1	99.9
2	6.6	26.8	95.0	99.5	65.6	68.4	99.8
4	0.9	6.6	49.6	95.0	32.8	38.8	97.9
8	0.1	0.1	8.1	49.6	8.6	10.5	72.0

The PTA analysis suggest the following PK-PD cut-off values:

- $S \leq 0.06 \text{ mg/L}$, with 0.6 x 4 as the lowest dose, assuming 40% $fT > MIC$
- $R > 1 \text{ mg/L}$ if 1.2g x 6 is considered

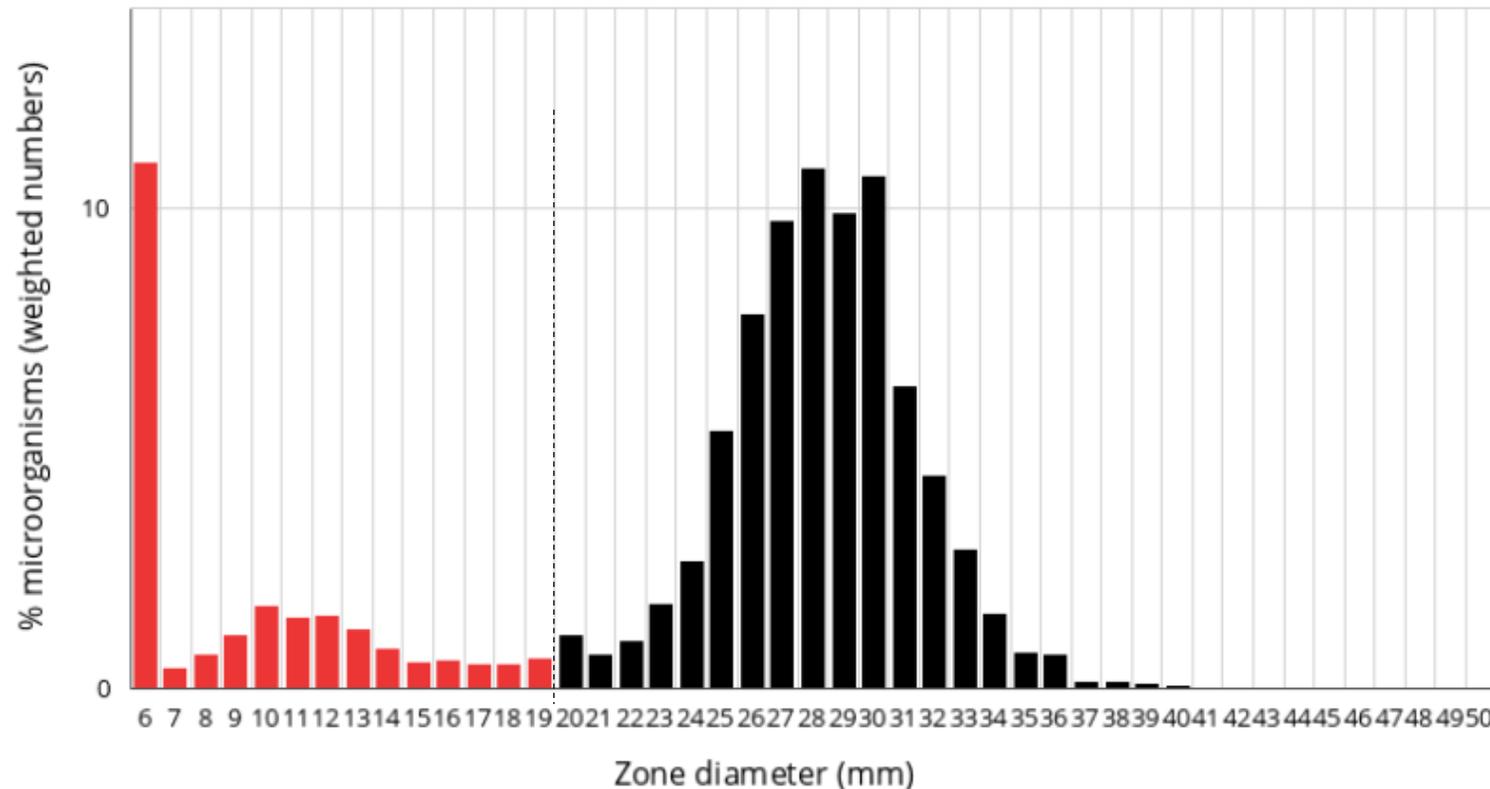
Conclusions

- The proposed breakpoints were
 - $S \leq 0.06$ mg/L (dosing minimum 0.6 g x 4)
 - $R > 1$ (dosing for the I-group 1.2 g x 6)
- But what about the consequences for AST?

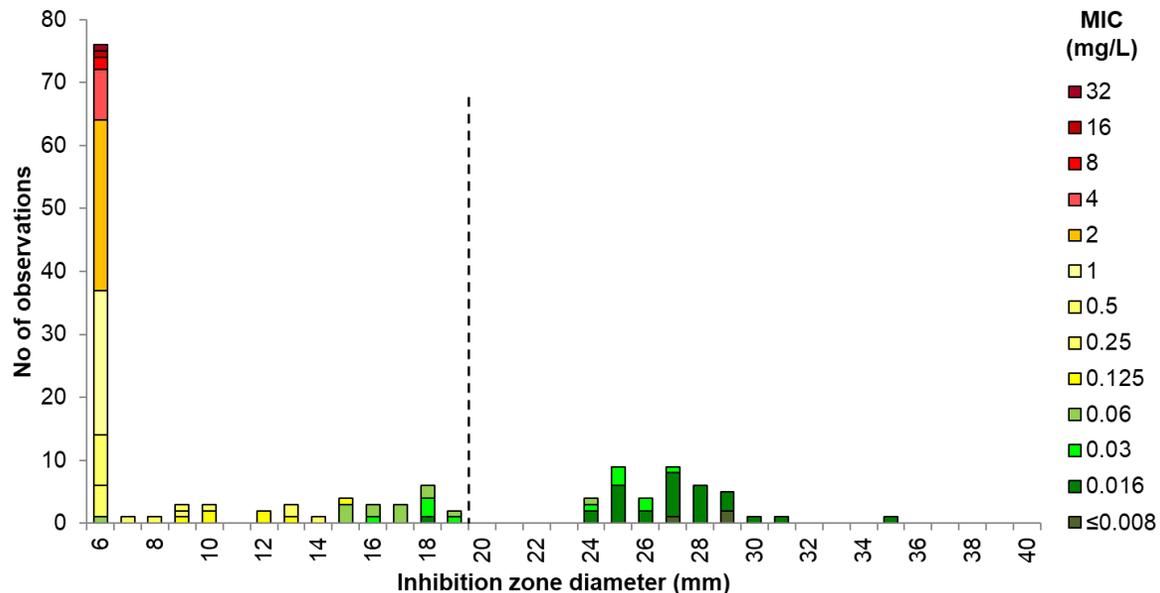
Antimicrobial susceptibility
testing of *S. pneumoniae* and
benzylpenicillin

Screening for beta-lactam resistance in *S. pneumoniae*

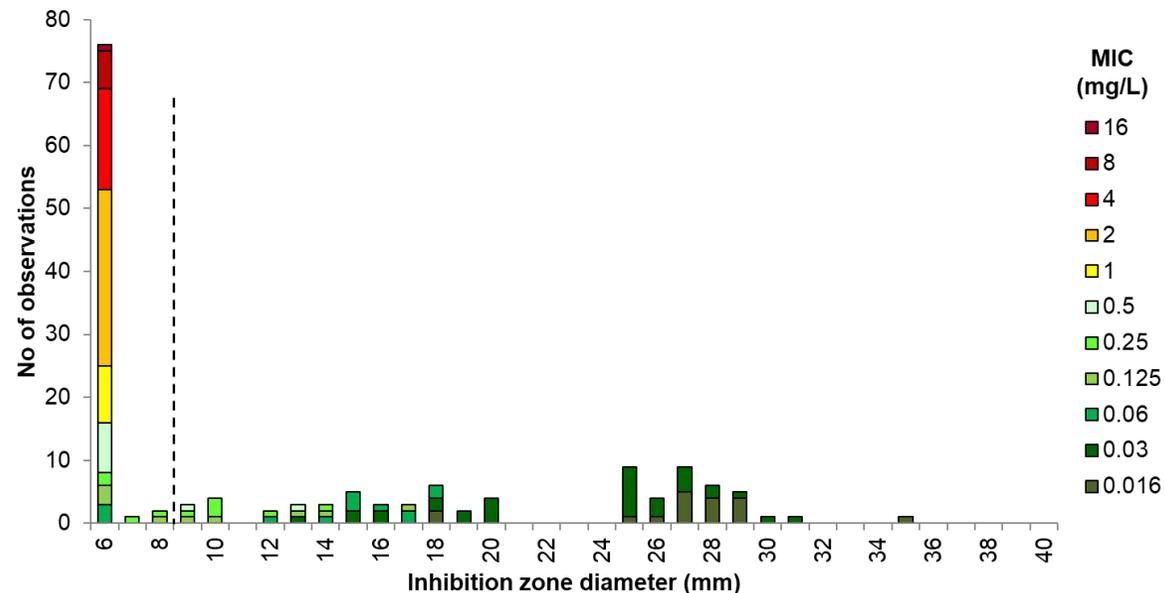
- Oxacillin 1 μg differentiates between wild-type and non-wild type for beta-lactam agents



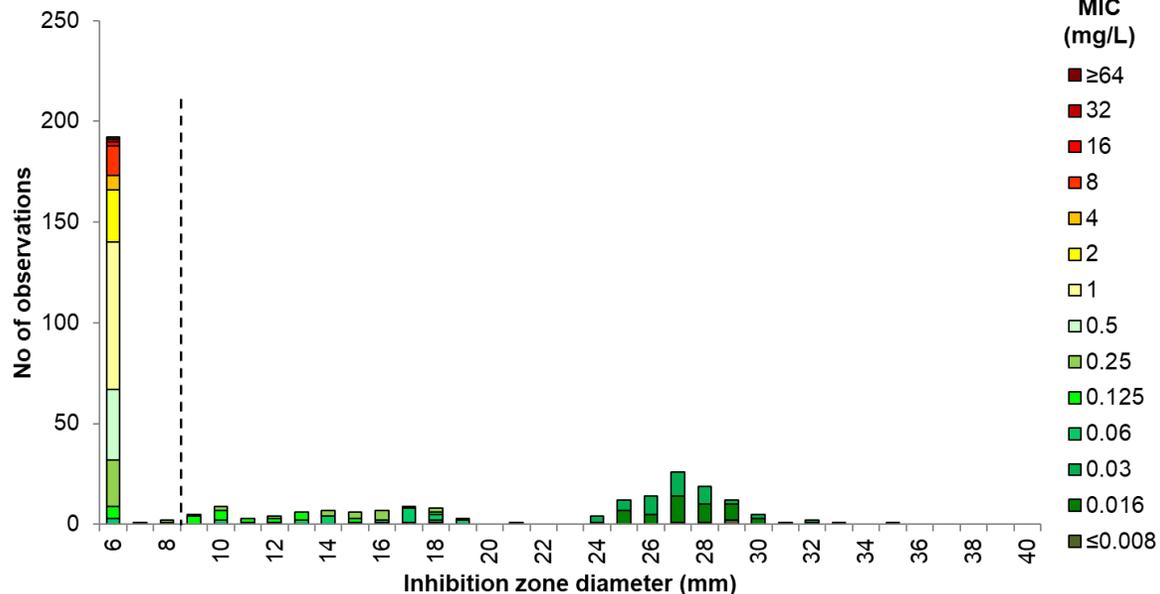
Oxacillin 1 µg vs. Benzylpenicillin MIC
S. pneumoniae, 148 isolates



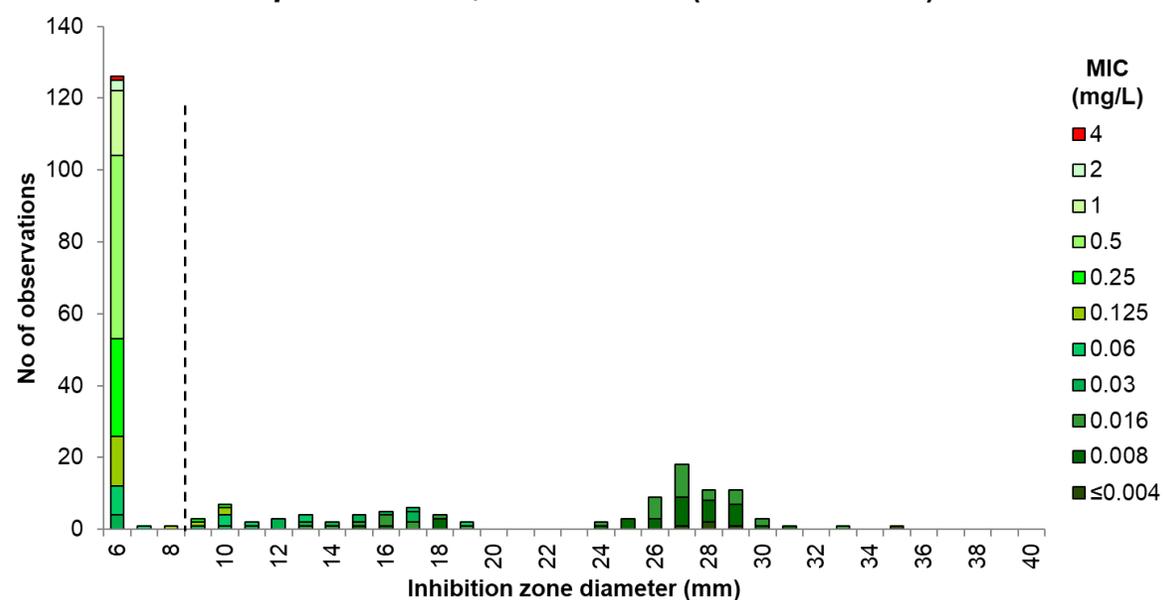
Oxacillin 1 µg vs. Ampicillin MIC
S. pneumoniae, 153 isolates



Oxacillin 1 µg vs. Cefotaxime MIC
S. pneumoniae, 151 isolates (360 correlates)



Oxacillin 1 µg vs. Meropenem MIC
S. pneumoniae, 130 isolates (230 correlates)



**Oxacillin 1 µg zone diameter <20 mm
(or benzylpenicillin MIC >0.06 mg/L)**

Mechanism: beta-lactam resistance detected

Report resistant (R) to benzylpenicillin in endocarditis and meningitis and to phenoxymethylpenicillin (all indications).

For benzylpenicillin in indications other than endocarditis and meningitis,
read and interpret the benzylpenicillin disk:
If zone ≥14 mm, report benzylpenicillin “susceptible, increased exposure” (I),
If zone <14 mm, report benzylpenicillin resistant (R).

For other beta-lactam agents, see below.

Question 1

S. pneumoniae in the amount $>1,000,000$ cfu/mL is found in a sputum culture. The oxacillin disk is 15 mm. Which of the following statements are true?

- 1) You can report cefotaxime based on the oxacillin disk
- 2) You need MIC-testing to be able to report benzylpenicillin
- 3) You can report benzylpenicillin based on the PCG 1U disk
- 4) You should not use gradient test to report benzylpenicillin

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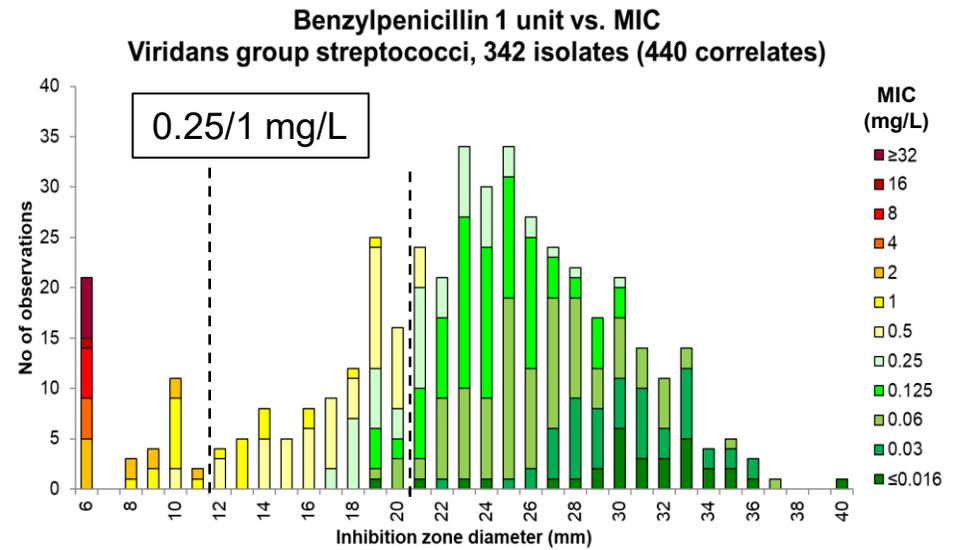
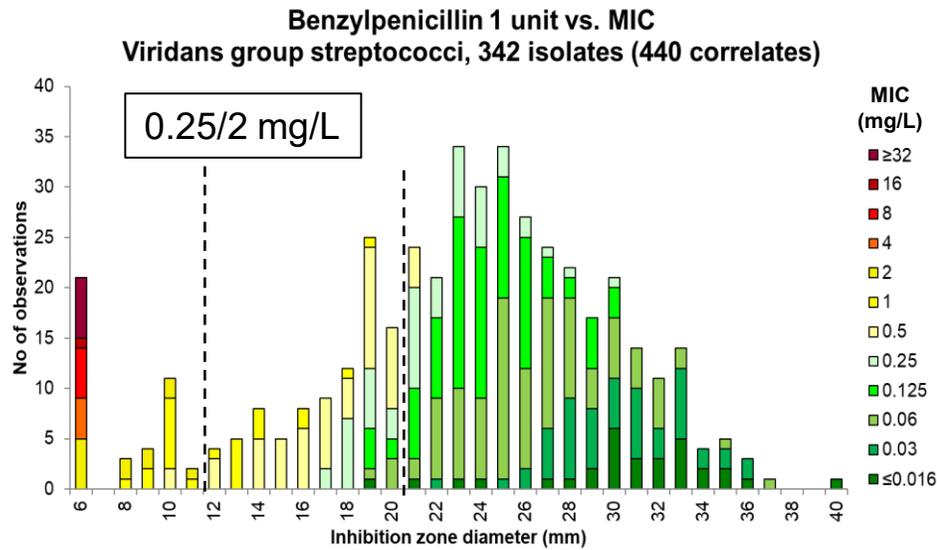
Viridans group streptococci and PCG

Viridans group streptococci Expert Rules and Expected Phenotypes

Guidance documents

EUCAST Clinical Breakpoint Tables v. 15.0, valid from 2025-01-01
For abbreviations and explanations of breakpoints, see the Notes sheet

Penicillins	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	
Benzylpenicillin (screen only)	0.25 ¹	0.25 ¹		1 unit	21 ^A	21 ^A		<p>Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.</p> <p>1/A. Benzylpenicillin (MIC or disk diffusion) can be used to screen for beta-lactam resistance in viridans group streptococci. Isolates categorised as screen negative can be reported susceptible to beta-lactam agents for which clinical breakpoints are listed (including those with "Note"). Isolates categorised as screen positive should be tested for susceptibility to individual agents or reported resistant.</p> <p>2/B. For information on how to use breakpoints in brackets, see https://www.eucast.org/eucastguidancedocuments/.</p> <p>3. The addition of a beta-lactamase inhibitor does not add clinical benefit.</p> <p>4/C. For benzylpenicillin screen negative isolates, susceptibility can be inferred from benzylpenicillin or ampicillin. For benzylpenicillin screen positive isolates, susceptibility is inferred from ampicillin.</p> <p>D. Susceptibility can be inferred from the benzylpenicillin screen test or from "Ampicillin iv (endocarditis)".</p>
Benzylpenicillin (indications other than endocarditis)	0.25	1		1 unit	21	12		
Benzylpenicillin (endocarditis)	0.25	0.25			21	21		
Benzylpenicillin (endocarditis, in combination with other antimicrobial treatment)	(1) ²	(1) ²			(12) ^B	(12) ^B		
Ampicillin (indications other than endocarditis)	0.5	2		2	21	15		
Ampicillin iv (endocarditis)	0.5	0.5		2	21	21		



No changes in disk breakpoints

Guidance in endocarditis

- If the zone diameter is ≥ 21 mm, the isolate can be regarded susceptible
- In some places there is tradition for using benzylpenicillin in combination therapy up to MICs of 1 mg/L (≥ 12 - < 21 mm) - the old I-group
 - These are bracketed breakpoints and should not be reported with SIR-categorisation – only presence and absence of acquired resistance and possibility of using in combination therapy (bracketed I-group)
 - There is some evidence that combination therapy may be of value, and the recommendation is consistent with the European guidelines

Question 2

A clinician is requesting you to conduct MIC-testing on a viridans group streptococcus growing in a blood culture from a patient with vegetations on the aortic valve according to echocardiography. Which of the following is true?

- MIC-testing is reasonable in endocarditis – it is important to be able to select the agent with lowest MIC in a severe infection
- MIC-testing is not needed according to endocarditis guidelines
- MIC is not absolutely required, but it is still understandable that the clinician wants a more robust result than just disk diffusion

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