Penicillin resistant *Streptococcus dysgalactiae*: is it possible?

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Penicillins	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Kommentarer
	S ≤	R >	ATU		S ≥	R <	ATU	
								Betalaktamer som er angitt med "Note" kan besvares ut fra benzylpenicillin unntatt for fenoksymetylpenicillin og isoxazolylpenicilliner for streptokokker gruppe B. Benzylpenicillin 1 unit kan benyttes som screeningmiddel for å oppdage lavgradig betalaktamresistens (sone <23 mm for gruppe A, C og G og sone <19 mm for gruppe B). Resistens mot betalaktamantibiotika hos streptokokker gruppe A, C og G er sjelden eller ikke beskrevet. Gjenta arts- og resistensbestemmelse og send isolatet til referanselaboratoriet.
Benzylpenicillin (indications other than meningitis)	0.25	0.25		**1 unit**	18	18		
Benzylpenicillin (meningitis), *S. agalactiae* (group B streptococci)	0.125	0.125		**1 unit**	19	19		

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Penicillins[1]	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Benzylpenicillin[2], Streptococcus groups A, C and G	0.03	0.03		**1 unit**	23	23	
Benzylpenicillin[2], *S. agalactiae* (group B streptococci)	0.125	0.125		**1 unit**	18	18	

1/A. The susceptibility of streptococcus groups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility ~~(indications other than meningitis)~~ with the exception of phenoxymethylpenicillin and isoxazolylpenicillins for streptococcus group B, where there is insufficient evidence for clinical efficacy.
2. Resistant isolates are rare or not yet reported. The identification and antimicrobial susceptibility test result on any such isolate must be confirmed and the isolate sent to a reference laboratory.
3. The addition of a beta-lactamase inhibitor does not add clinical benefit.

EUCAST Breakpoint table 15.0 (2025)

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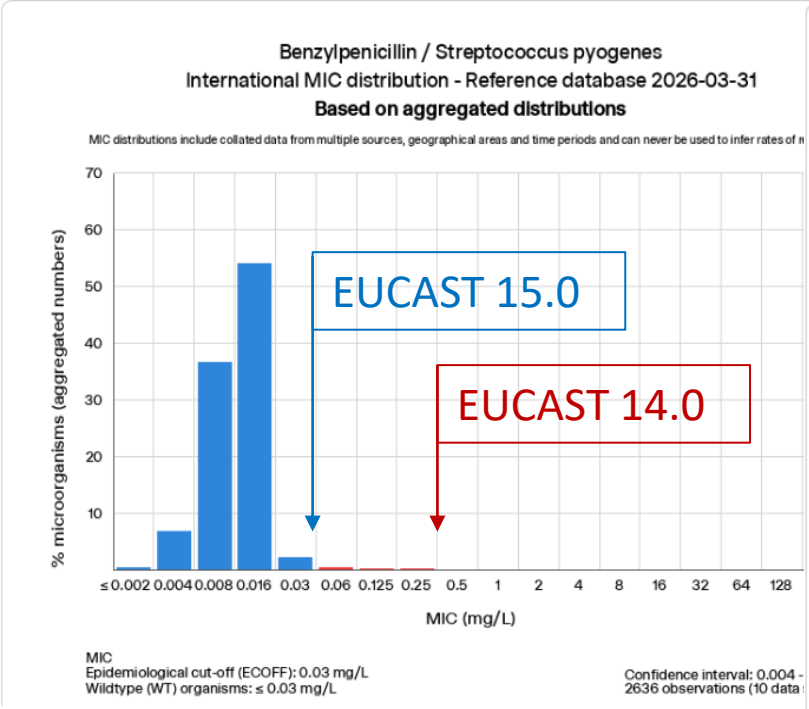

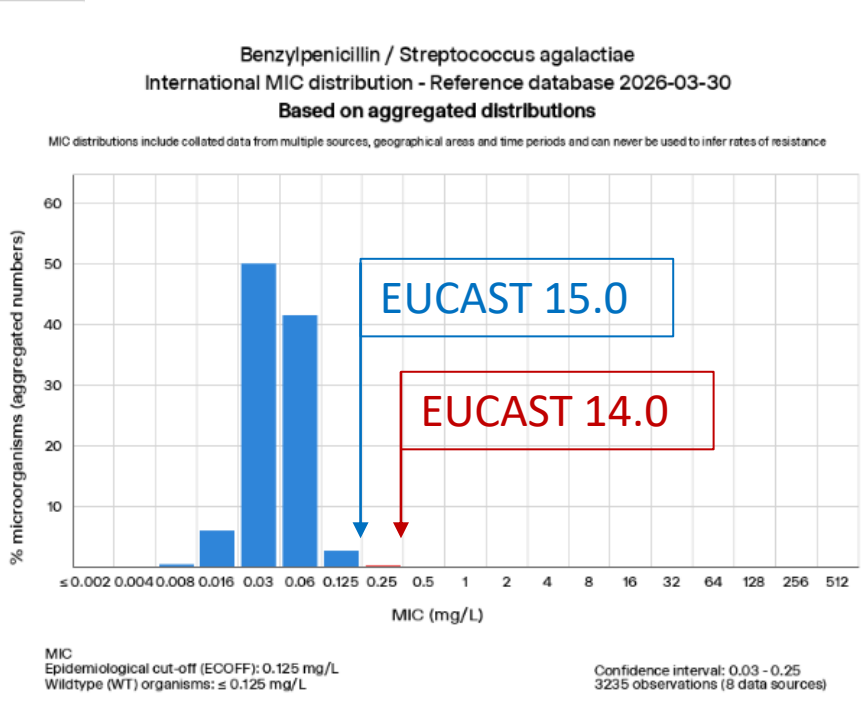

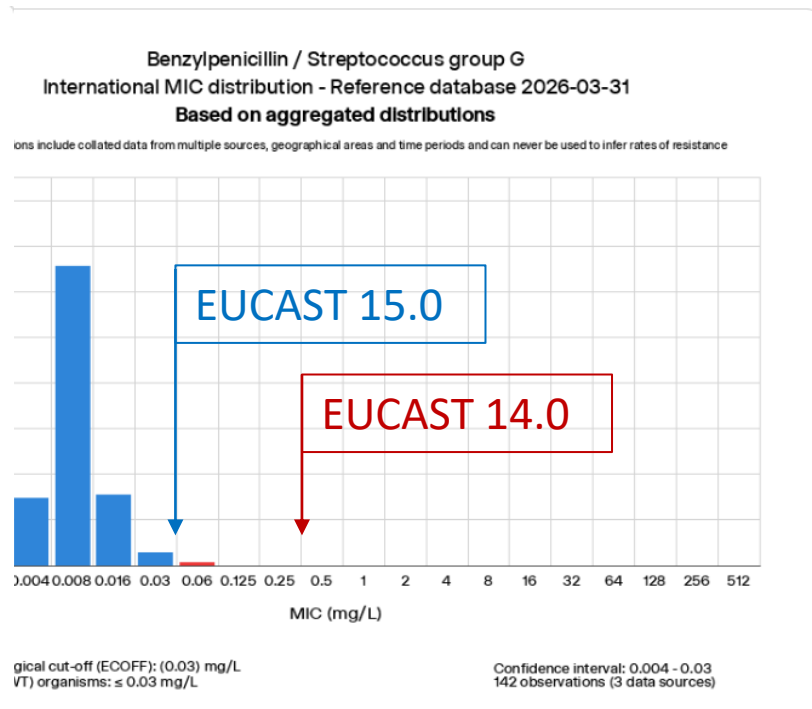

For all β-hemolytic streptococci

- 14.0 breakpoints are clearly higher than the ECOFF
- 15.0 breakpoints are placed on the ECOFF

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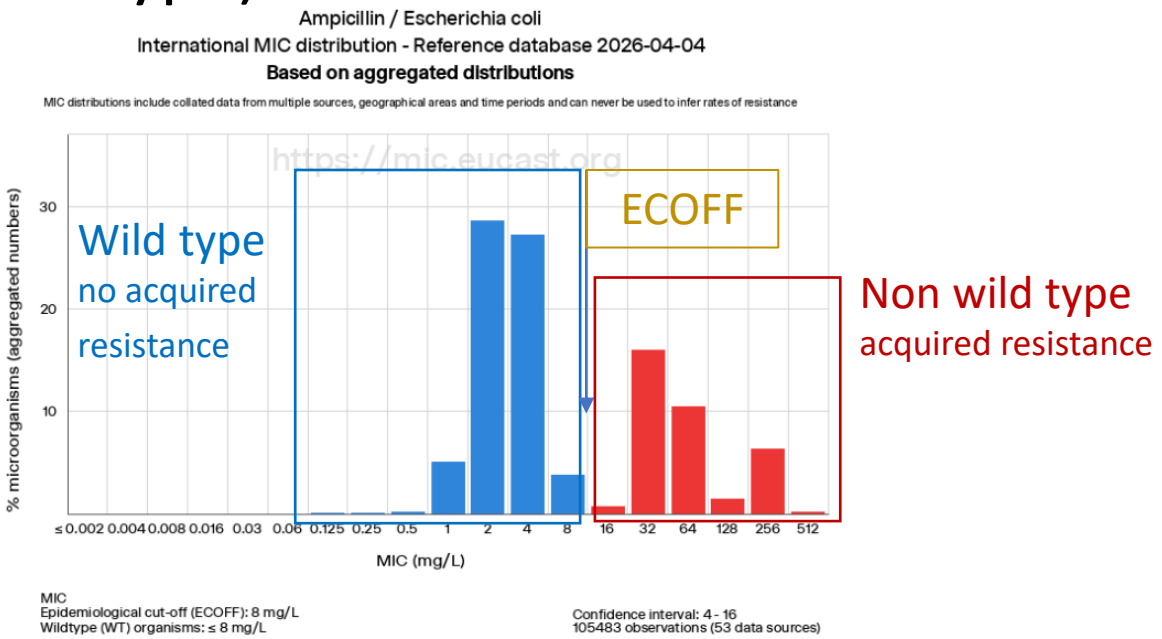
Why is it important to place the BP close to the ECOFF?

- Epidemiological Cut Off (ECOFF) distinguish microorganisms without (wild type) and with phenotypically detectable acquired resistance mechanisms (non-wild type)



- Setting the breakpoints at the ECOFF, ensures that the resistant population is detected and appropriately reported as resistant

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Description and characterization of a penicillin-resistant *Streptococcus dysgalactiae* subsp. *equisimilis* clone isolated from blood in three epidemiologically linked patients

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- 4 penicillin R *S. dysgalactiae* strains isolated between 2010 and 2012 from blood culture samples (3 patients)

Table 1. Characteristics of three patients with invasive PR-SDSE

Case-year	Gender	Primary ward speciality	Clinical condition (presumable origin of infection)
1-2010	male	vascular surgery	aortic aneurysm and limb amputation (complicated leg ulcers)
2-2010 and 2-2012	female	dermatology	dyskeratosis follicularis (complicated leg ulcers)
3-2012	female	internal medicine	cancer of the cervix, radiotherapy-related skin condition, COPD and recurrent urinary tract infections

- WGS analysis: comparaison of the 4 penicillin resistant strains with 40 penicillin susceptible strains

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Table 2. Characteristics of the 4 PR-SDSE compared with 40 penicillin-susceptible isolates (36 blood culture isolates and 4 published genome sequence isolates)

	Case-year			
	1-2010	2-2010	2-2012	3-2012
MLST	novel	novel	novel	novel
Allele profile[a]	18-2-3-4-2-7-3	18-2-3-4-2-7-3	18-2-3-4-2-7-3	18-2-3-4-2-7-3
Mutations in PBP2x (337–549[b])	**T341P**[e], Y392N, **Q555E**	**T341P**, Y392N, **Q555E**	**T341P**, A373V, Y392N, **Q555E**	**T341P**, A373V, Y392N, **Q555E**
Mutations in PBP1a (370–557)	L411F, T487I, A489V	L411F, T487I, A489V	L411F, T487I, A489V	L411F, T487I, A489V
Mutations in PBP1b (337–782)	S662L	S662L	S662L	S662L
Mutations in PBP2a (264–678)	none	none	none	none
Mutations in PBP2b (386–617)	outside the domain	outside the domain	outside the domain	outside the domain
Penicillin MIC[c]: Etest/BMD (SIR[d])	0.5/0.5 (R)	0.5/0.5 (R)	2/0.5 (R)	2/0.5 (R)
Oxacillin MIC: Etest	8	8	8	8
Cefuroxime MIC	≤0.5	≤0.5	≤0.5	≤0.5
Ceftriaxone MIC	0.25	0.25	≤0.125	0.25
Cefotaxime MIC	≤0.125	≤0.125	≤0.125	≤0.125
Cefepime MIC	≤0.5	≤0.5	≤0.5	≤0.5
Meropenem MIC	≤0.25	≤0.25	≤0.25	≤0.25
Levofloxacin MIC (SIR)	2 (I)	2 (I)	2 (I)	1 (S)
Linezolid MIC (SIR)	2 (S)	1 (S)	1 (S)	1 (S)
Vancomycin MIC (SIR)	≤0.5 (S)	≤0.5 (S)	≤0.5 (S)	≤0.5 (S)
Co-trimoxazole MIC (SIR)	≤0.5 (S)	≤0.5 (S)	≤0.5 (S)	≤0.5 (S)
Daptomycin MIC (SIR)	0.125 (S)	0.125 (S)	0.125 (S)	≤0.06 (S)
Erythromycin MIC (SIR)	≤0.25 (S)	≤0.25 (S)	>2 (R)	>2 (R)
Clindamycin MIC (SIR)	≤0.125 (S)	≤0.125 (S)	>1 (constitutive R)	>1 (inductible R)
Tetracycline MIC (SIR)	≤1 (S)	≤1 (S)	≤1 (S)	≤1 (S)
Resistance genes detected with ResFinder 2.1	none	none	*erm*(A)	*erm*(A) and *erm*(B)

- Clonal transmission with a link to dermatology department
- PBP mutations: PBP2x, PBP1a ja PBP1b

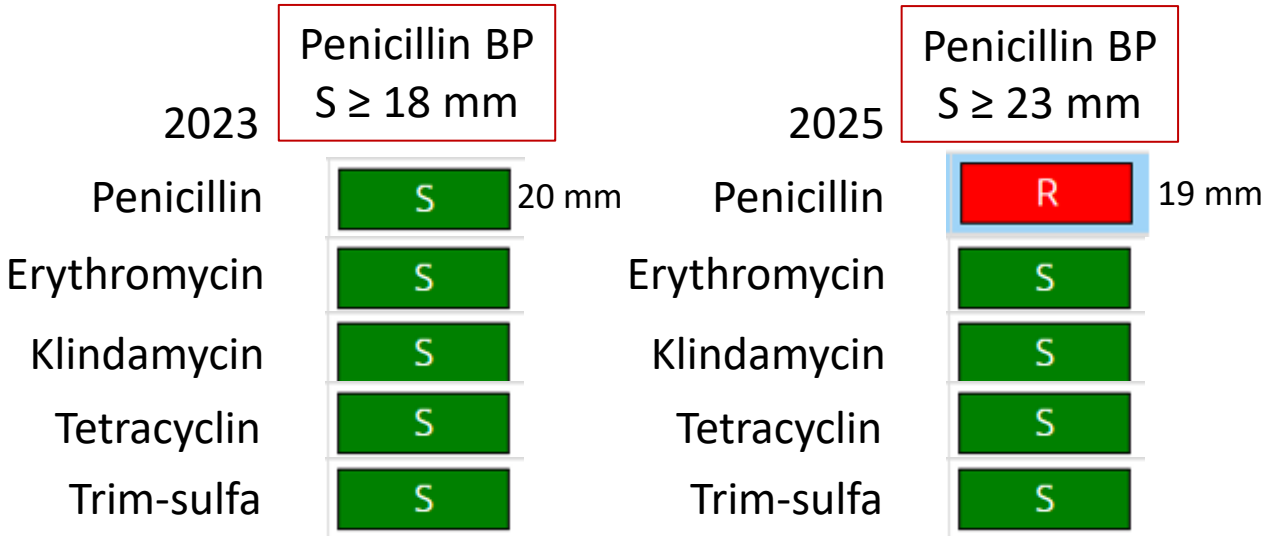
Penicillin **B**inding **P**rotein (PBP)

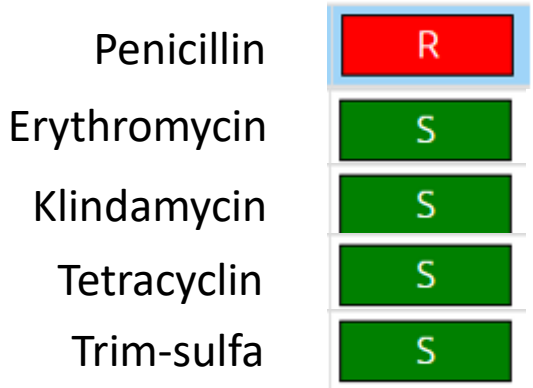
- PBP are a group of enzymes (mainly transpeptidases) that build the cell wall (peptidoglycan)
- β-lactam antibiotics (penicillins, cephalosporins, carbapenems) bind to PBPs and inhibit their enzymatic function, leading to cell wall disruption and bacterial death
- Different species express different PBPs, and each β-lactam targets PBPs with varying affinity
- The most important PBPs for β-hemolytic streptococci are PBP2x, PBP1a, and PBP2b and they are are highly conserved
- Resistance: changes in the structure of PBP can impair antibiotic binding
  - MRSA: S. aureus acquires the mecA gene, it can produce PBP2a, which has a very low affinity for β-lactams
  - *S. pneumoniae*: genetic recombination (horizontal gene transfer e.g from viridans group streptococci) creating mosaic PBP genes, cumulative effect of multiple PBP alteration
  - β-hemolytic streptococci: single nucleotid mutation leading to amino acid substitution changing β-lactam affinity to PBP

Case 1

Case 2

Both patient visited the same dermatology polyclinic





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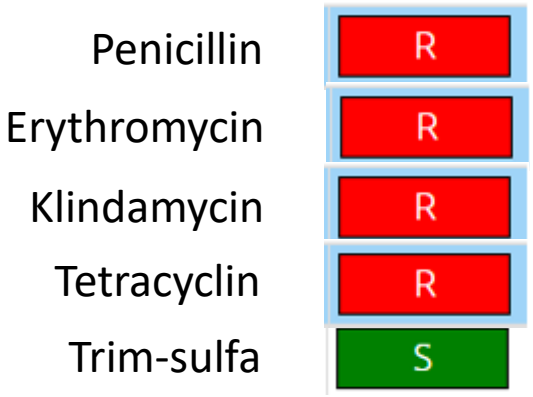
Case 3


Penicillin
R
Erythromycin
R
Klindamycin
R
Tetracyclin
R
Trim-sulfa
S

Confirmation tests

- QC checked: no abnomalies were noticed
- DD was redone with a different penicillin disk lot
- Strains were sent for confirmation and MIC to Tykslab (Turku) and to EDL (Växjö)

Penicillin DD	Own results mm (S/R)	EDL: BBL MH mm (S/R)	EDL: Bio-Rad MH mm (S/R)	EDL: Oxoid MH mm (S/R)
Strain 1	19 (R)	19 (R)	20 (R)	19 (R)
Strain 2	17 (R)	16 (R)	18 (R)	17 (R)
Strain 3	20 (R)	22 (R)	22 (R)	22 (R)

Breakpoints
S ≥ 23 mm
R < 23 mm

Penicillin MIC BMD	Tykslab MIC (S/R)	EDL MIC (S/R)
Strain 1	0,25 (R)	0,25 (R)
Strain 2	0,5 (R)	0,25 (R)
Strain 3	0,125 (R)	0,06 (R)

Breakpoints
S ≤ 0,03
R > 0,03

What about the others β-lactams?

1/A. The susceptibility of streptococcus groups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility (indications other than meningitis)

1/A. The susceptibility of streptococcus groups A, B, C and G to cephalosporins is inferred from the benzylpenicillin susceptibility.

EUCAST

- How do you report other b-lactams if benzylpenicillin is R ?
- For other β-lactams than benzylpenicillin, there is no MIC distribution available in the EUCAST database
- Use the EUCAST document ”When there are no breakpoints in breakpoint table”

MIC (EDL)	Strain 1	Strain 2	Strain 3	Cut-off
Ampicillin	0,12	0,5	0,12	0,5
Amoxicillin	0,12	0,25	0,06	0,5
Amox-clav	0,12	0,25	0,06	0,5
Cefuroxime	0,12	0,12	0,25	-
Cefotaxime	0,06	0,06	0,12	0,5
Ceftriaxone	0,06	0,12	0,25	0,5
Meropenem	0,06	0,06	0,03	2

Emm typing and WGS results

- The strains were sent to our reference laboratory (THL) for emm-typing and WGS (interpretation from SSI)
- The strains were all different though strain 1 and 2 were close
- All strains harbored PBP mutations within the transpeptidase domains, located in or near the active site

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Summary

- Yes, it is possible to isolate penicillin resistant *S. dysgalactiae* strain
- However, resistance to penicillin among beta-hemolytic streptococci is rare
- The new EUCAST breakpoints allows us to find such strains
- Disk diffusion method gives reliable results but since resistance if rare, DD results should be confirmed
- Be in contact with your reference laboratory and with your infection prevention and control team

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