Round table: Q&A from the participants

Moderators: Karianne Wiger Gammelsrud and Erika Matuschek

Panel: Barbara Holzknecht

NordicAST workshop 12-13 May 2026

Today´s agenda:

- Trim-sulfa vs. trimethoprim
- *Corynebacterium* vs dalbavancin and daptomycin
- Routine linezolid AST for all clinical *Enterococcus* isolates?
- *S. aureus* NCTC 12493 vs FOX 30
- «When there are no breakpoints» vs anaerobes vs. iv/po administration

<u>Not time:</u>

- Interpretation of cefixime/ceftibuten from cefadroxil?
- ESBL-A vs cefixime and ceftibuten AST

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Is there some new recommendations regarding testing of trimethoprim-sulfamethoxazole when trimethoprim is R?

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Trim-sulfa vs trimethoprim

- No EUCAST recommendations
- Personal views?
  - Let’s look at some background data

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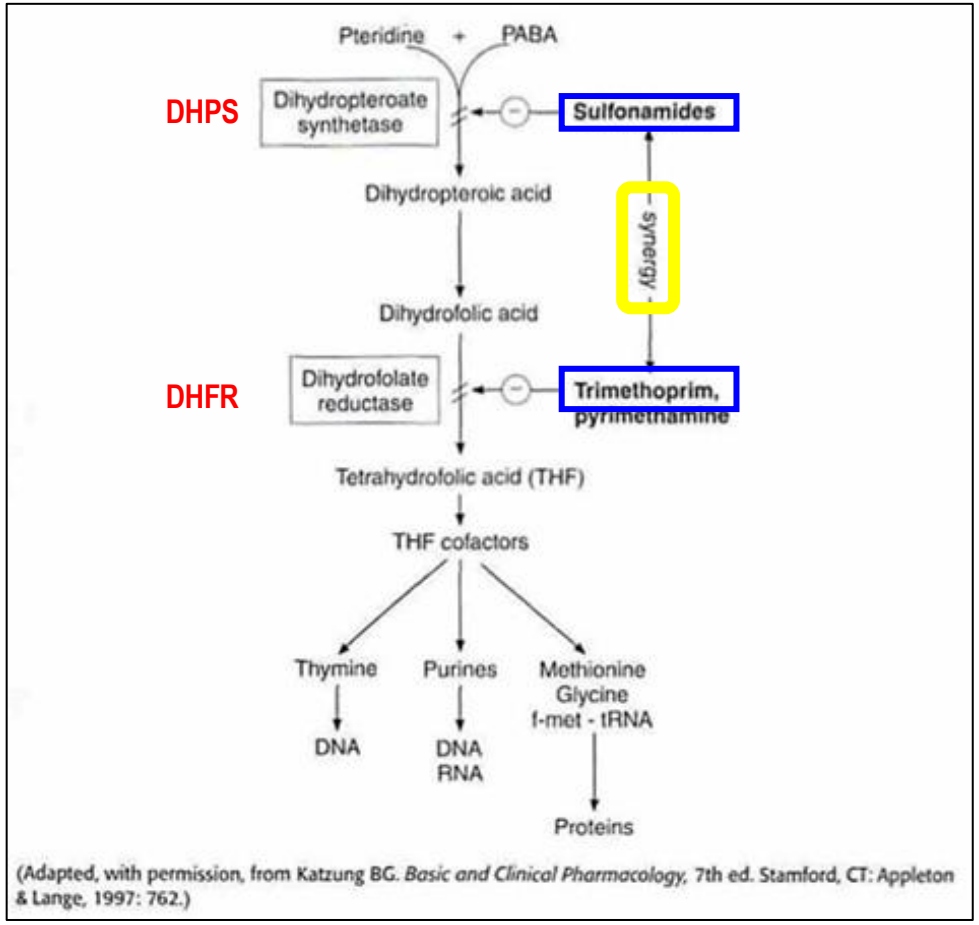
What is the mechanism of action?

- **Folate inhibition**:
  - Essential for bacterial DNA, RNA, proteins
- Each alone:
  - Bacteriostatic, limited systemic effect
- Combined:
  - Bactericidal, good systemic effect
  ⇒ given that both substances are active!



(Adapted, with permission, from Katzung BG. *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT: Appleton & Lange, 1997: 762.)

https://step1.medbullets.com/microbiology/104144/sulfonamides

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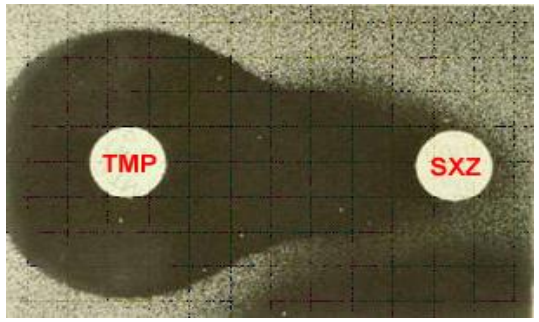
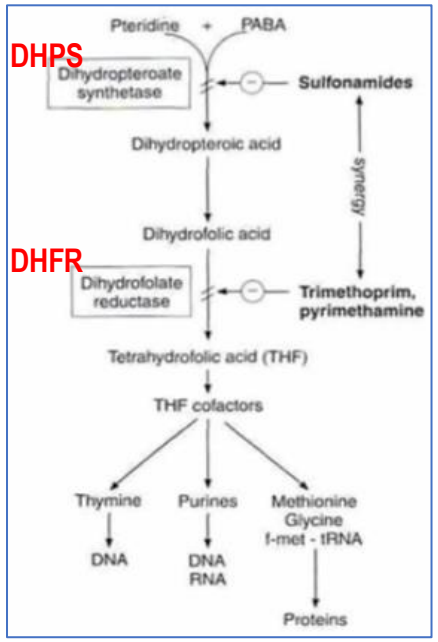
Trimethoprim-sulfamethoxazole resistance mechanisms





Mechanisms of resistance	Genes affected	Molecular effect	MIC (mg/L) (*) SMX	TMP	TMP+SMX
—	—	Inhibition DHPS and DHFR	32–128 **(S)**	0,25–1 **(S)**	≤ 2/38 **(S)**
SMX	Mutaciones *folP* (cromosómico)	Modified DHPS	512–1024 **(R)**	0,25–1 **(S)**	2/38–4/76 **(R)**
	sul1, sul2, sul3 (plasmídico)	Alternative DHPS	≥1024 **(R)**	0,25–1 **(S)**	2/38–4/76 **(R)**
	Hiperproducción de PABA	Competence with SMX	≥ 512 **(R)**	0,25–1 **(S)**	≤ 0,5/9,5–4/76 **(S–R)**
TMP	Mutaciones *folA* (cromosómico)	Modified DHFR	32–128 **(S)**	4–8 **(R)**	≤ 0,5/9,5–4/76 **(S–R)**
	dfrA y variantes (plasmídico)	Alternative DHFR	32–128 **(S)**	32–128 (R)	2/38–4/76 (R)
SMX+TMP	*sul* + *dfrA*	Normal folate syntesis	≥ 1024 **(R)**	≥ 64 **(R)**	≥ 8/152 **(R)**

Sulfa R

Trim. R

SMX: sulfametoxazol, TMP: trimethoprim; SMX+TMP: co-trimoxazol; *EUCAST breakpoint interpretation.
TMP (only in uUTI for *E. coli* and *Klebsiella* spp., except *K. aerogenes*): Susceptible ≤ 2mg/L, Resistant >2 mg/L;
TMP +SXT (except *Serratia* spp.): ≤0.5 mg/L, susceptible >0.5 mg/L. For *S. marcescens*: ≤0.001 mg/L, sensible >0.5 mg/L.
No existen punto de corte a SMX (ECOFF ≤64 mg/L)

Then RL. Mechanisms of resistance to trimethoprim, the sulfonamides, and trimethoprim-sulfamethoxazole. Rev Infect Dis. 1982; 4:261-9
Huovinen P. Increases in rates of resistance to trimethoprim. Clin Infect Dis. 1997 Jan;24 Suppl 1:S63-6

Slide borrowed from Rafael Cantón; EUCAST: What's new in susceptibility testing, ESCMID Global, Munich 2026

So, how should we go about: trim-sulfa S vs trimethoprim R?

- Resistance towards trimethoprim, sulfa, trim-sulfa together and alone is a complex matter
- Not able to test sulfa alone – so we will always miss if sulfa is R
- Many uncertainties and lack of clinical data
  - e.g: bp for trimethoprim is lacking for several species
- If both substances are tested with result trim-sulfa S vs trimethoprim R, prehaps be careful to report trim-sulfa S if serious systemic infection
  - Does not occur too often (?)
  - No need to always test both substances routinely

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Will EUCAST set breakpoints for dalbavancin and daptomycin for *Corynebacterium* spp.?

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Corynebacterium: Dalbavancin and daptomycin

- No MICs in the EUCAST database
- Few publications, mainly with MIC_{50} and MIC_{90} only
- EUCAST Guidance document ”When there are no breakpoints”.
  - Perform an MIC test
  - MIC values above which therapy with the agent should be discouraged:
    - Dalbavancin: 0.125 mg/L
    - Daptomycin: 1 mg/L

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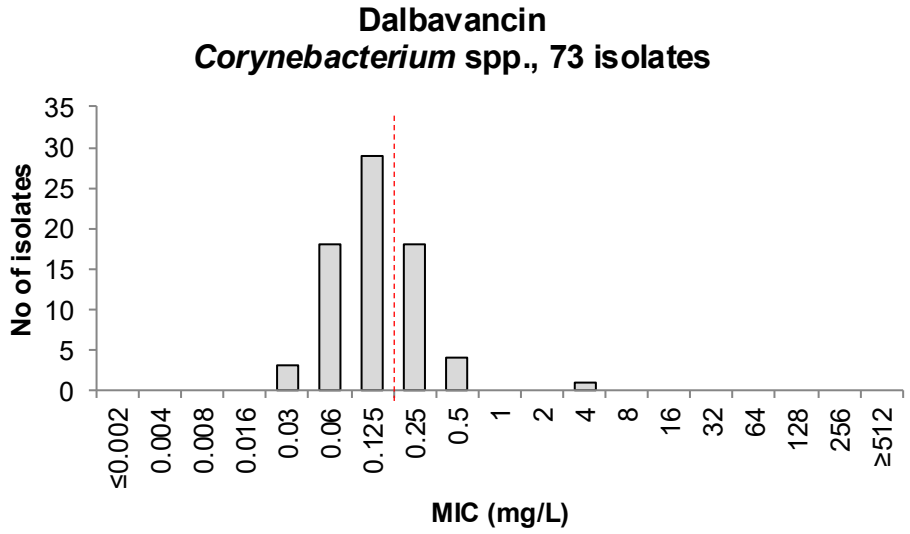
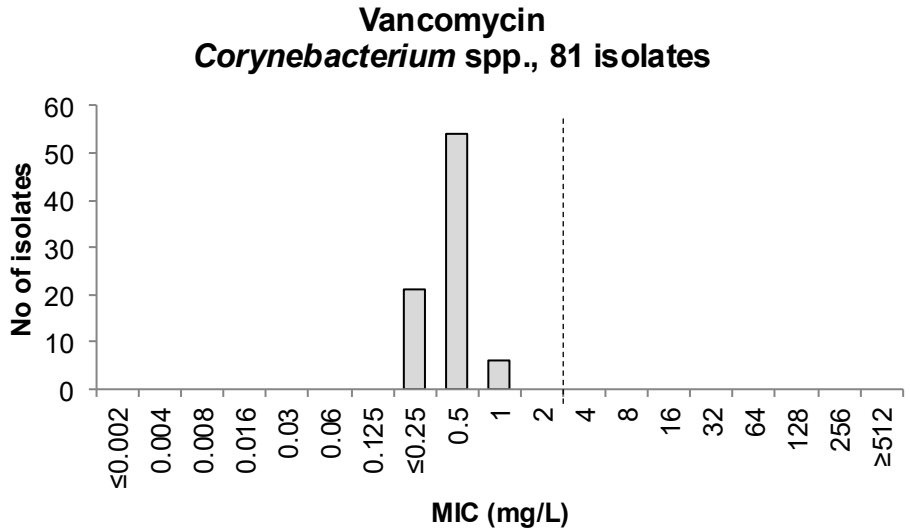
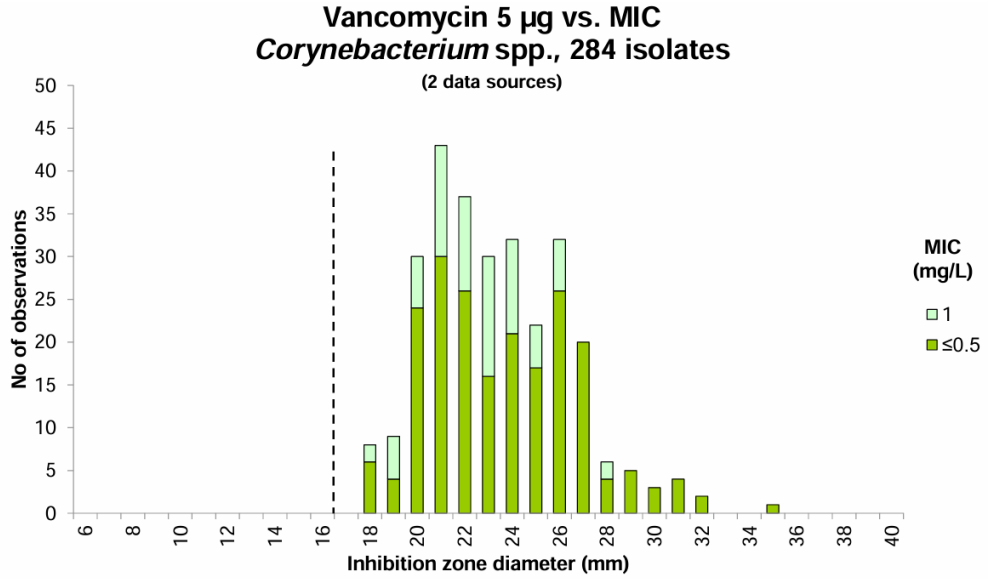
Corynebacterium: Dalbavancin (NRL data)



Dalbavancin MICs must be determined in the presence of polysorbate-80 (0.002% in the medium for broth dilution methods; agar dilution methods have not been validated). Follow the manufacturers' instructions for commercial systems.





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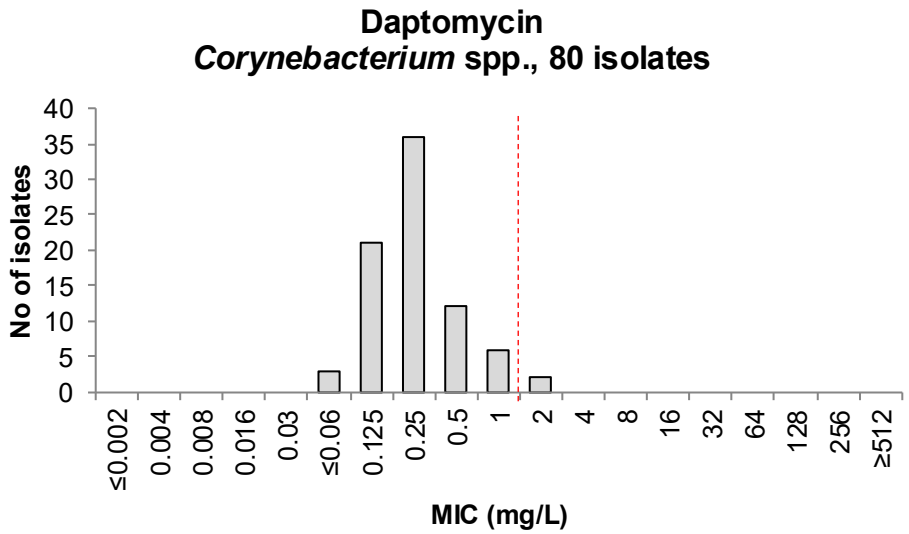
Corynebacterium: Daptomycin (NRL data)



Daptomycin MICs must be determined in the presence of Ca^{2+} (50 mg/L in the medium for broth dilution methods; agar dilution methods have not been validated).
Follow the manufacturers' instructions for commercial systems.

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Do you recommend screening for linezolid resistance in enterococci in urine samples?

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Important question:
Are you interested in finding all LRE[1]?

What is the concequence of finding LRE[1]	Norway	Sweden	Denmark	Finland	Iceland
Send it to the reference laboratory	Yes	Yes	Yes	No	Yes
It is notifiable	Yes	No	No	No	No
It requires hospital infection prevention measures	Yes	No[2]	No[2]	No	No[3]
Are there **national** recommendations to screen for LRE in urine samples?	Yes	No[4]	No	No	Yes

[1] Linezolid resistant enterococci

[2] Often decided on a local level (SE), varies from region to region (DK)

[3] "Not yet been actively decided, but cases have been community so not yet been an issue"

[4] Not a national recommendation, but many labs include linezolid for urine samples

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If the answer is **yes**, lets find all LRE!

- If you want to discover most possible LRE, screening for linezolid resistance in all clinical samples, including urine samples (also from outpatients) is warranted

- This is based on the Norwegian experience:

LRE epidemiology in Norway

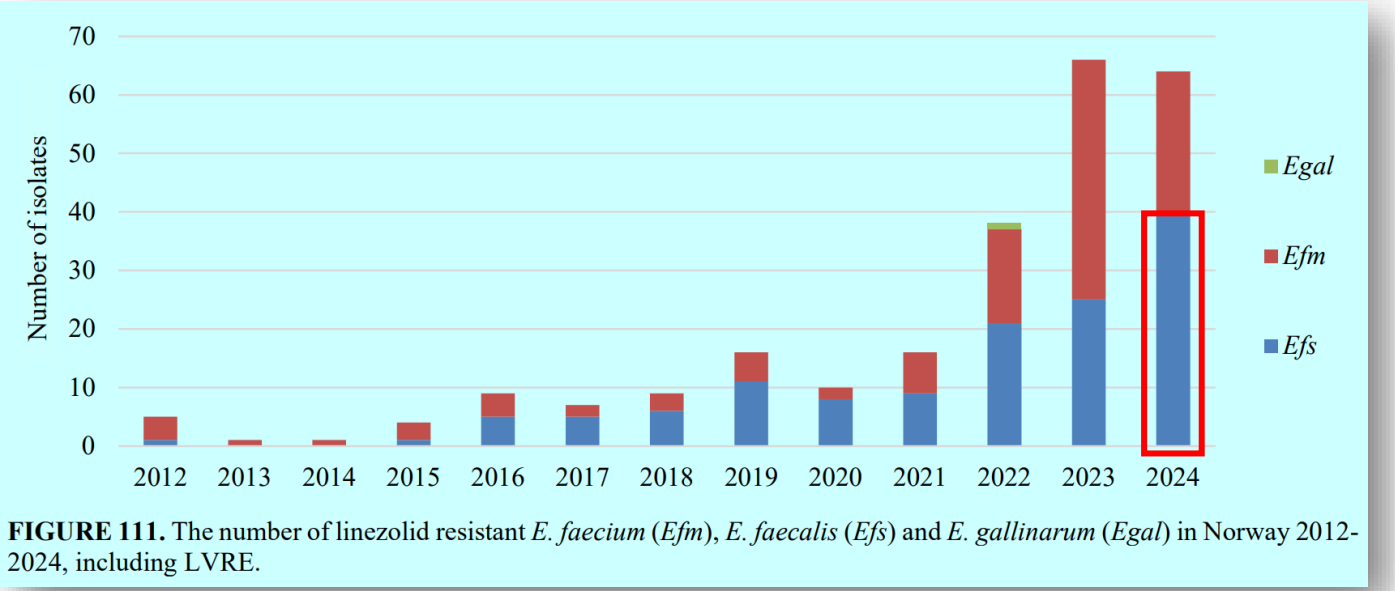

FIGURE 111. The number of linezolid resistant *E. faecium* (*Efm*), *E. faecalis* (*Efs*) and *E. gallinarum* (*Egal*) in Norway 2012-2024, including LVRE.

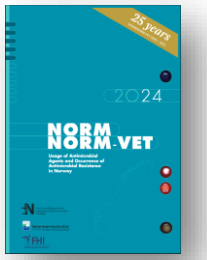

TABLE 86. Species, resistance mechanism and sequence type among LRE in N

Species	Resistance mechanism	
E. faecalis (n=40)	*optrA* (n=39)	ST16 (n= ST476 (n= ST1259 (ST376 (n= ST1116 (ST16 (n=
	poxtA-Ef (n=1)	
E. faecium (n=24)	23S rDNA G2576T mutation (n=13)	ST17 (n=
	poxtA/poxA-Ef (n=7)	ST80 (n=
	optrA (n=3)	ST80 (n=
	optrA+G2576T (n=1)	ST80 (n=

Often localised on mobile genetic elements!

Norwegian LRE 2012-2023 (n=181):

- 47% (85/181) from urine
- 22% (39/181) from outpatients
  - Outpatients: 77% from urine

Data from Kristin Hegstad, Reference laboratory for LRE, Norway

"We find 1-3 linezolid R isolates per year, usually in random, otherwise susceptible community urine samples."

Kristján Orri Helgason, Reykjavik, Iceland

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If the answer is **no**, we are not so interested in LRE

- There is probably no need to routinely screen for linezolid resistance in urine samples – only if needed for treatment (e.g. VRE in a patient with pyelonephritis)

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We have problems with too large zones for *S. aureus* NCTC 12493 (methicillin resistant) and cefoxitin 30 µg.
What can we do?

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S. aureus NCTC 12493

- Extended quality control strains
  - Complementary to the EUCAST routine QC strains recommended for detection of specific resistance mechanisms.
  - Extended QC should be performed with any change in the susceptibility testing system (with each new batch of disks or medium) and/or monthly.

Methicillin resistance in *Staphylococcus aureus*

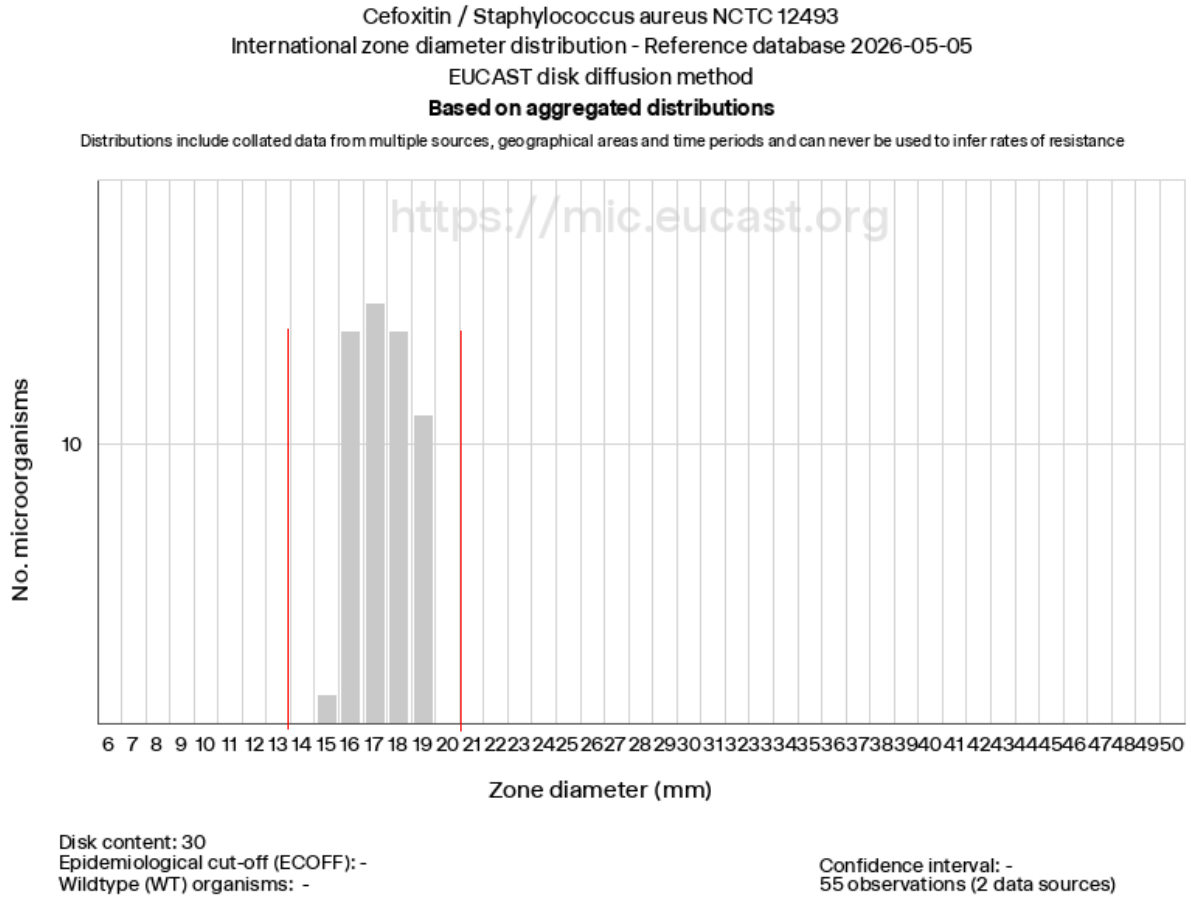
***Staphylococcus aureus* NCTC 12493**

(CCUG 67181)

Methicillin resistant (MRSA), *mecA* positive

Antimicrobial agent	**Disk content (µg)**	**Target susceptibility[1]**	**Range[2] (mm)**	**Comments**
Cefoxitin	30	R	***14-20***	

S. aureus NCTC 12493 and cefoxitin 30 µg

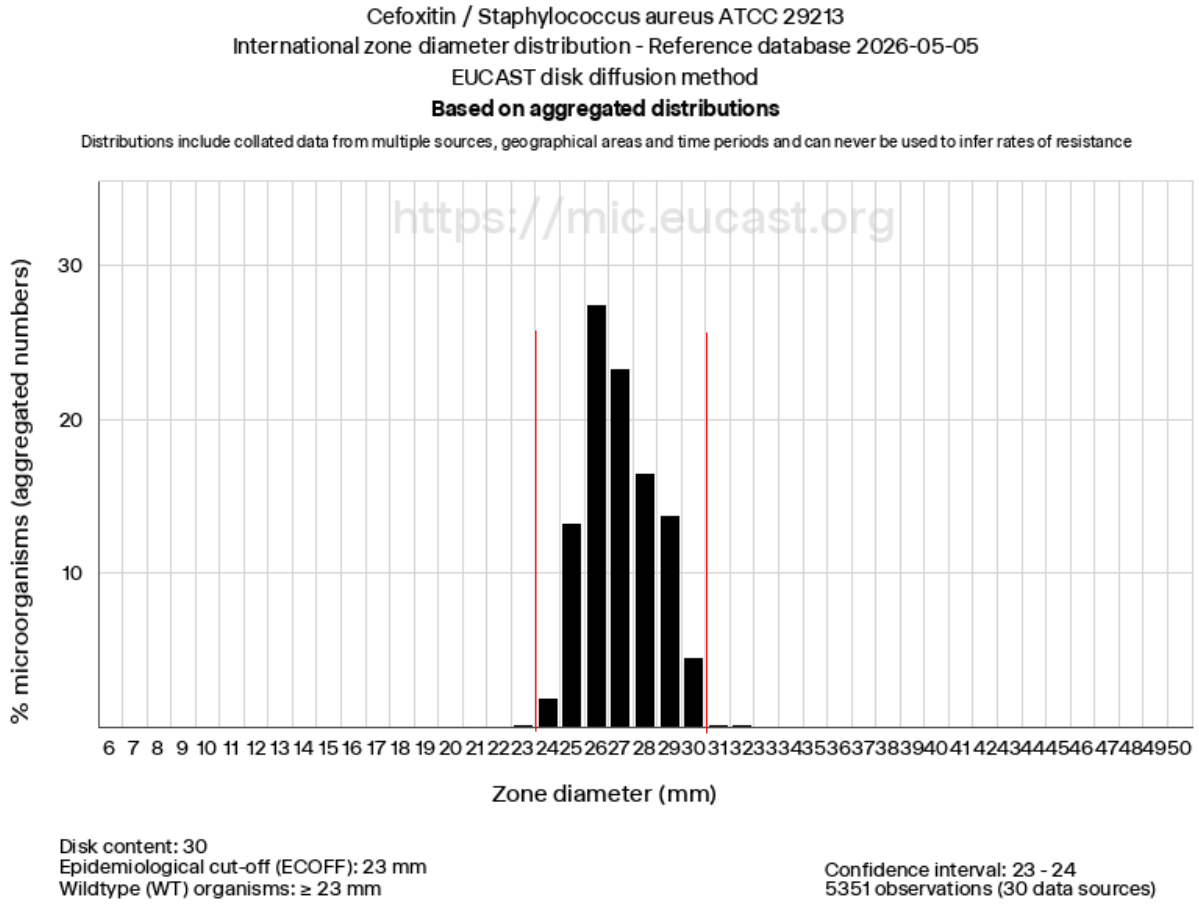


***S. aureus* NCTC 12493 and cefoxitin 30 µg**

	BBL	Bio-Rad	Oxoid
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16	1		
17	3		3
18	2	2	3
19		4	
20			
21			
22			
23			
24			
25			
26			

Target = R

S. aureus ATCC 29213 and cefoxitin 30 µg



Some agar-related differences

S. aureus ATCC 29213	FOX30	MH agar
	25	BBL
	25	BBL
	26	Bio-Rad
	26	Bio-Rad
	28	Oxoid
	27	Oxoid
EUCAST target	**27**	
EUCAST range	**24-30**	

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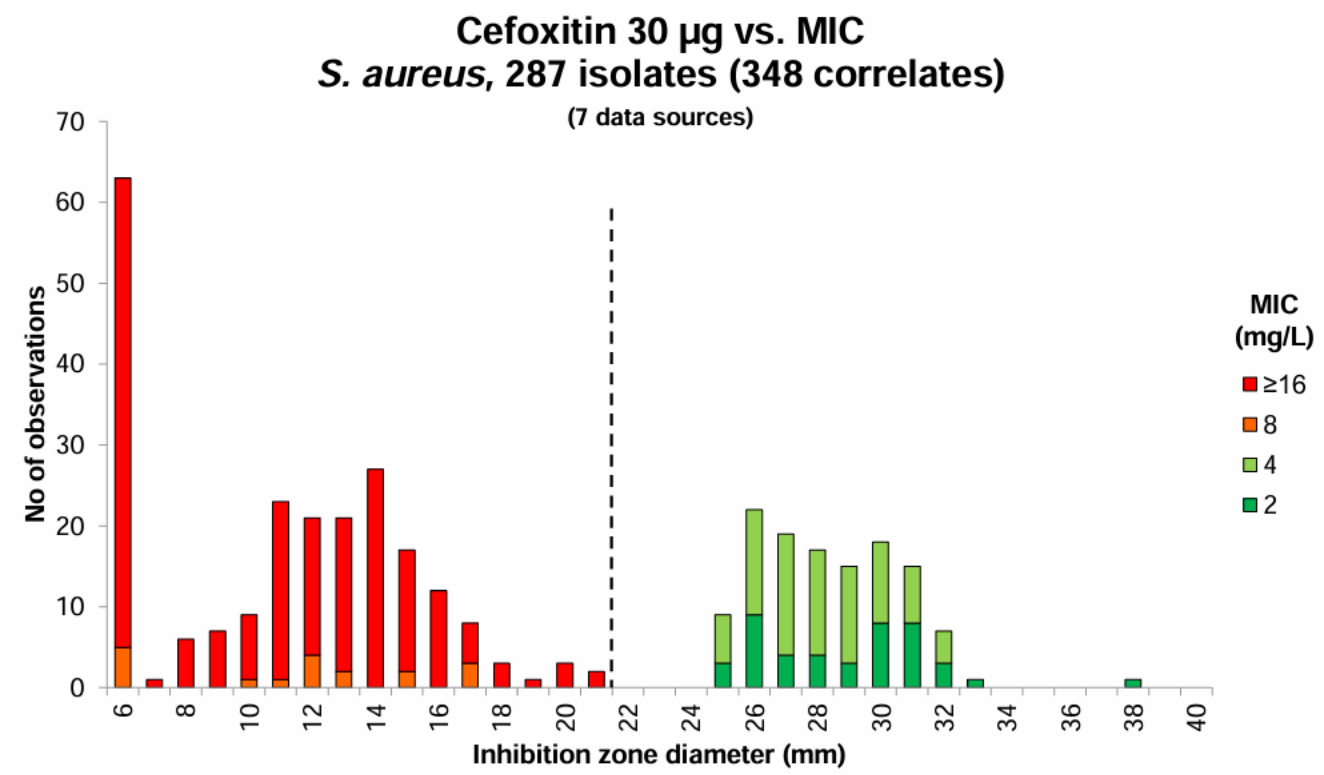
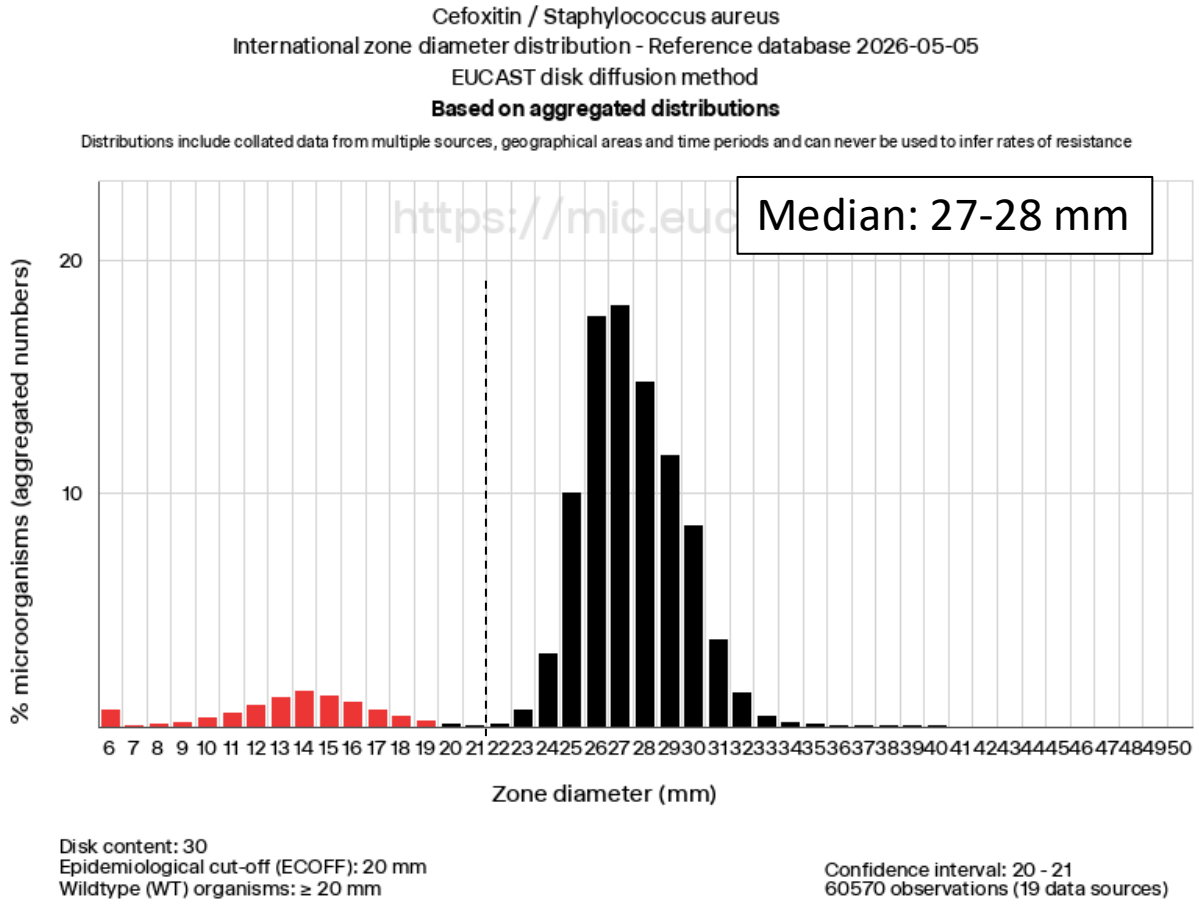
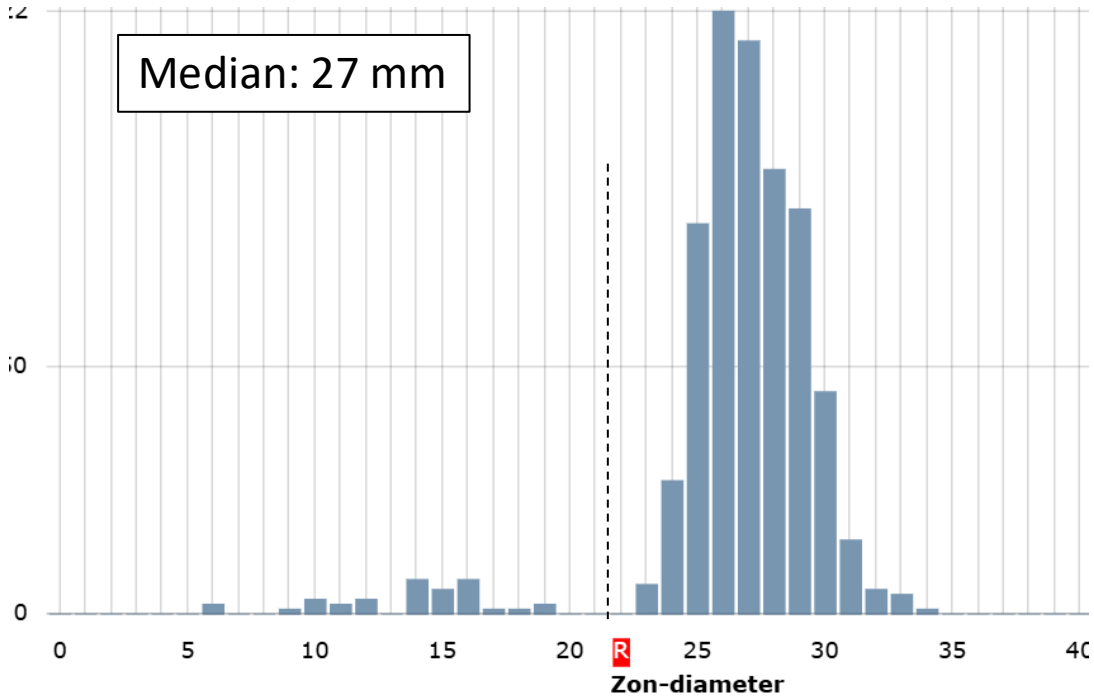
S. aureus and cefoxitin – clinical isolates

- EUCAST breakpoints are calibrated to testing on MH agar from at least two manufacturers



S. aureus and cefoxitin – clinical isolates





Systemic difference? Local ATU (*mec* PCR)?

In the document
"When there are no breakpoints",
why is the interpretive basis for the aminopenicillins only for IV administration for aerobes, whereas this specification does not apply to anaerobes?

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EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

EUCAST guidance on

When there are no breakpoints in breakpoint tables?

2024-02-29, cefiderocol added September 2024

Table 1. Antimicrobial agents relevant for the treatment of aerobic bacteria with guidance for bacteria lacking breakpoints in standard EUCAST breakpoint tables.

Determine an MIC and compare with numerical values to assess the microbiological activity of the agent against the species. The clinical use of agents for which MIC-values are higher than those listed below should be discouraged, while agents for which the MIC is the same or lower can be considered for therapy. Avoid reporting isolates S, I or R – instead add a comment to discourage or consider therapy. The proposed values are based on (i) a compromise between current EUCAST susceptible (S or I) breakpoints for species already in the tables, (ii) wild type distributions for microorganisms when available and (iii) PK/PD cut-off values.

	MIC-values above which therapy with the agent should be discouraged		
Agents and notes for aerobic bacteria	**Gram-positive organisms**	**Gram-negative organisms**	**Notes**
Benzylpenicillin	0.25	0.5	If a beta-lactamase is detected, report resistant without further testing.
Ampicillin, Amoxicillin, Ampicillin-sulbactam, Amoxicillin-clavulanic acid (IV only)	0.5	8	The breakpoint of 8 mg/L pertains to intravenous high dose administration. If a beta-lactamase is detected, the value is only valid for amoxicillin-clavulanic acid and ampicillin-sulbactam.
Piperacillin-tazobactam	1	8	Species specific breakpoints for gram-positive

Table 2. Antimicrobial agents relevant for the treatment of anaerobic bacteria with guidance for bacteria lacking breakpoints in standard EUCAST breakpoint tables.

Determine an MIC and compare with numerical values to assess the microbiological activity of the agent against the species. The clinical use of agents for which MIC-values are higher than those listed below should be discouraged, while agents for which the MIC is the same or lower can be considered for therapy. Avoid reporting isolates S, I or R - instead add a comment to discourage or consider therapy. The proposed values are based on (i) a compromise between current EUCAST susceptible (S or I) breakpoints for anaerobic species already in the tables, (ii) wild type distributions for microorganisms when available and (iii) PK/PD cut-off values.

Agents and notes for anaerobic bacteria	MIC-values above which therapy with the agent should be discouraged	
Benzylpenicillin	0.5	Breakpoints for anaerobic bacteria in the breakpoint table are 0.06 – 0.5 mg/L. If a beta-lactamase is detected, report resistant without further testing.
Amoxicillin	0.5	Breakpoints for anaerobic bacteria in the breakpoint table are 0.25 – 0.5 mg/L. If a beta-lactamase is detected, report resistant without further testing.
Amoxicillin-clavulanic acid	0.5	Breakpoints for anaerobic bacteria in the breakpoint table are 0.25 – 0.5 mg/L.

Back to the question (when no bp's):

Why is the interpretive basis for the aminopenicillins only IV administration for aerobes, whereas this is not specified for anaerobes?

Call a friend*:

- The easy answer is that all the bp for anaerobes are ecoff based:
  - Hence, if there is clinical evidence supporting oral use, then the bp will also apply oral formulations (unless serious infection).
  - Oral step-down and oral therapy for mild infections usually ok ☺
- This guidance document will be discussed further in the EUCAST steering committee meeting in June
- In general, the table with the R-bp has gotten far to much influence.
  - It should be interpreted as just one of many considerations in the expert evaluation of the MIC value…

*Christoffer Lindemann, EUCAST/Norway

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