



# AST and reporting of endocarditis isolates

NordicAST workshop Malmö  
May 29th, 2024

Barbara Holzkecht  
Dept. of Clinical Microbiology  
Copenhagen University Hospital – Herlev and Gentofte

EUCAST work lead by Christoffer Lindemann, Bergen, Norway



## Agenda

- Short introduction to endocarditis
- Principles for EUCAST endocarditis breakpoints
  - Short reminder about 2 important concepts: ECOFF and I-category
- The most important species and agents: proposed breakpoints and recommendations for testing
  - Viridans Group Streptococci vs. betalactams!
- Oral step-down treatment
- Reporting: an example

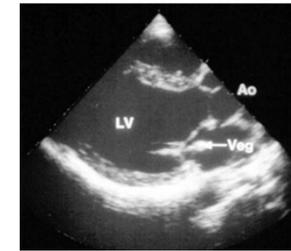


## Infective endocarditis: a short introduction

### Difficult diagnosis

Imaging of the heart valves

Microbiology: positive blood cultures (species and nr of sets)



### Secondary involvement of many organs

Embolic events: brain, spine, lungs, ...

Vasculitis

### High mortality

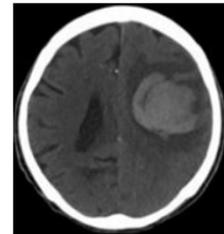
### Treatment

Surgery, if indicated

Antibiotics: traditionally 4-6 weeks high dose i.v. / recently: partial p.o. (POET trial)

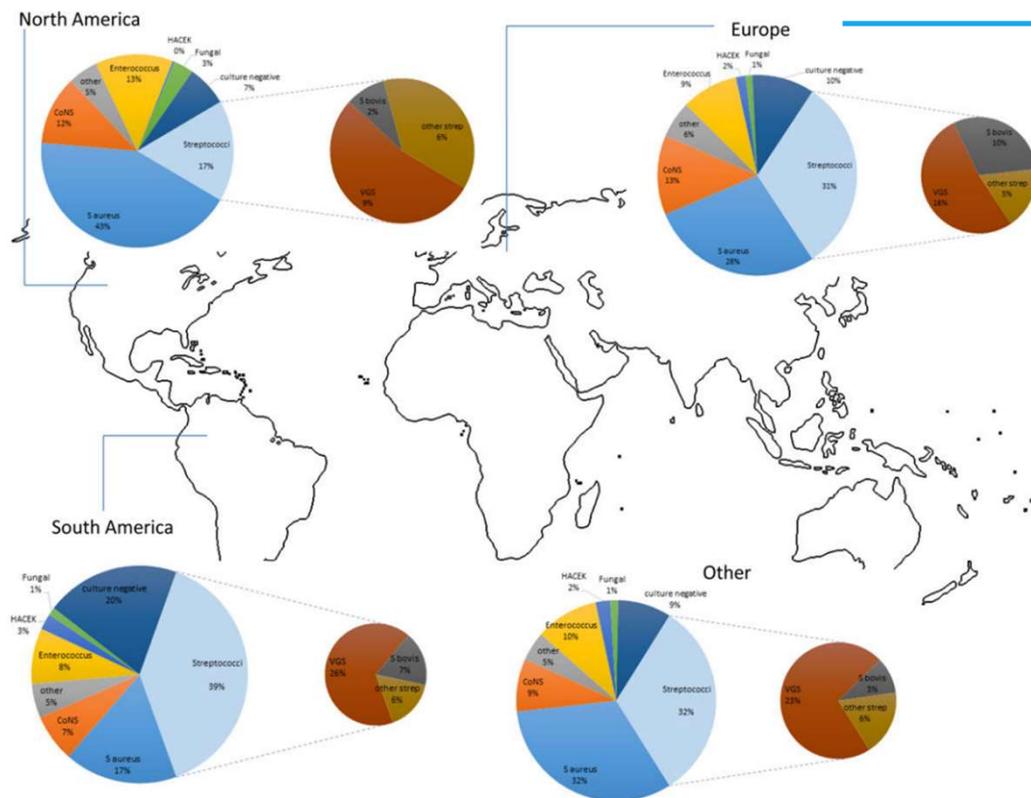
Multidisciplinary endocarditis team

Images from: Holland et al. Nat Rev Dis Primers. 2016;2:16059.





# Infective endocarditis: etiology



Europe	
Streptococci	31%
<i>S. aureus</i>	28%
CoNS	13%
Culture negative	10%
<i>Enterococcus</i> spp.	9%
HACEK	2%
Fungal	1%
Other	6%

Holland et al. Nat Rev Dis Primers. 2016;2:16059.

Data derived from: Murdoch et al. Arch Intern Med. 2009 March 9; 169(5): 463–473. d



# European treatment guidelines and implications for breakpoints and reporting

 European Heart Journal (2015) 36, 3075–3123  
doi:10.1093/eurheartj/ehv319

**ESC GUIDELINES**

## 2015 ESC Guidelines for the management of infective endocarditis

The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC)

Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM)

Authors/Task Force Members: Gilbert Habib\* (Chairperson) (France), Patrizio Lancellotti\* (co-Chairperson) (Belgium), Manuel J. Antunes (Portugal), Maria Grazia Bongiorno (Italy), Jean-Paul Casalta (France), Francesco Del Zotti (Italy), Raluca Dulgheru (Belgium), Gebrine El Khoury (Belgium), Paola Anna Erba<sup>a</sup> (Italy), Bernard Jung (France), Jose M. Miro<sup>b</sup> (Spain), Barbara J. Mulder (The Netherlands), Edyta Plonska-Gosciniak (Poland), Susanna Price (UK), Jolien Roos-Hesselink (The Netherlands), Ulrika Snygg-Martin (Sweden), Franck Thuny (France), Pilar Tornos Mas (Spain), Isidre Vilacosta (Spain), and Jose Luis Zamorano (Spain)

Document Reviewers: Cetin Erol (CPG Review Coordinator) (Turkey), Petros Nihoyannopoulos (CPG Review Coordinator) (UK), Victor Aboyans (France), Stefan Agewall (Norway), George Athanassopoulos (Greece), Saide Aytakin (Turkey), Werner Benzer (Austria), Héctor Bueno (Spain), Lidewij Broekhuizen (The Netherlands), Scipione Carerj (Italy), Bernard Cosyns (Belgium), Julie De Backer (Belgium), Michele De Bonis (Italy), Konstantinos Dimopoulos (UK), Erwan Donat (France), Heinz Drexel (Austria), Frank Arnold Flachskampf (Sweden), Roger Hall (UK), Sigrun Halvorsen (Norway), Bruno Hoen<sup>b</sup> (France), Paulus Kirchhof (UK/Germany).



 ESC European Society of Cardiology  
European Heart Journal (2023) 00, 1–95  
https://doi.org/10.1093/eurheartj/ehad193

**ESC GUIDELINES**

## 2023 ESC Guidelines for the management of endocarditis

Developed by the task force on the management of endocarditis of the European Society of Cardiology (ESC)

Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Nuclear Medicine (EANM)

Authors/Task Force Members: Victoria Delgado\*<sup>†</sup>, (Chairperson) (Spain), Nina Ajmone Marsan<sup>‡</sup>, (Task Force Co-ordinator) (Netherlands), Suzanne de Waha<sup>‡</sup>, (Task Force Co-ordinator) (Germany), Nikolaos Bonaros<sup>⊙</sup> (Austria), Margarita Brida<sup>⊙</sup> (Croatia), Haran Burri<sup>⊙</sup> (Switzerland), Stefano Caselli<sup>⊙</sup> (Switzerland), Torsten Doenst<sup>⊙</sup> (Germany), Stephane Ederhy<sup>⊙</sup> (France), Paola Anna Erba<sup>†</sup> (Italy), Dan Foldager (Denmark), Emil L. Fosbøl<sup>⊙</sup> (Denmark), Jan Kovac (United Kingdom), Carlos A. Mestres<sup>⊙</sup> (South Africa), Owen I. Miller<sup>⊙</sup> (United Kingdom), Jose M. Miro<sup>⊙</sup><sup>2</sup> (Spain), Michal Pazdernik<sup>⊙</sup> (Czech Republic), Maria Nazarena Pizzi<sup>⊙</sup> (Spain), Eduard Quintana<sup>⊙</sup><sup>3</sup> (Spain), Trine Bernholdt Rasmussen<sup>⊙</sup> (Denmark), Arsen D. Ristić<sup>⊙</sup> (Serbia), Josep Rodés-Cabau (Canada), Alessandro Sionis<sup>⊙</sup> (Spain), Liesl Joanna Zühlke<sup>⊙</sup> (South Africa), Michael A. Borger<sup>⊙</sup><sup>†</sup>, (Chairperson) (Germany), and ESC Scientific Document Group

Including dosing related to MIC breakpoints for viridans group streptococci

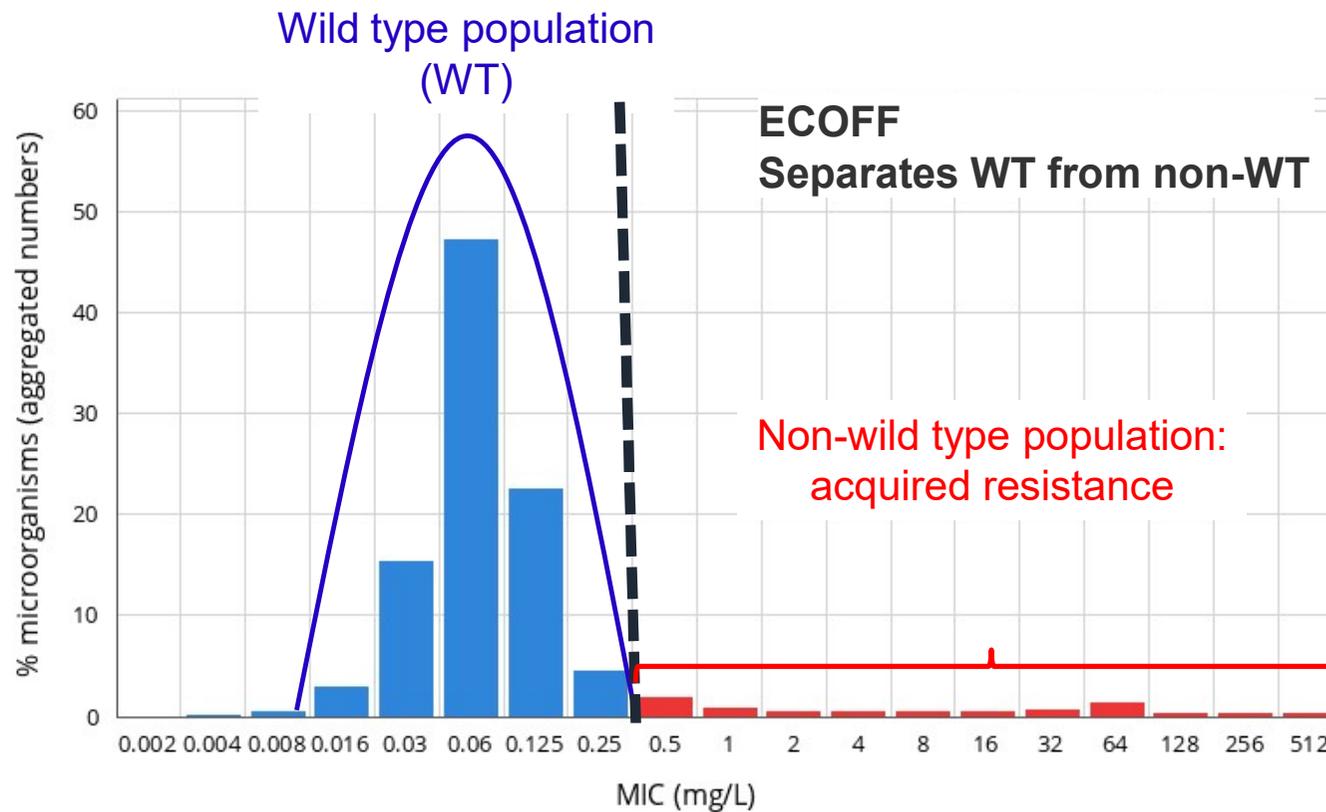
Referring to EUCAST's SIR-categorization and terminology

Delgado et al.

Eur Heart J. 2023 Oct 14;44(39):3948-4042.

# Two important concepts:

## 1. Epidemiological cut-off values (ECOFF)





## Two important concepts: 2. the I-category

EUCAST breakpoints relate to specified dosages:

### Dosages used to define breakpoints

Cephalosporins	Standard dosage	High dosage
Ceftriaxone	2 g x 1 iv	2 g x 2 iv or 4 g x 1 iv

<i>Streptococcus pneumoniae</i>							
Cephalosporins <sup>1</sup>	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Ceftriaxone (indications other than meningitis)	0.5	2			Note <sup>A</sup>	Note <sup>A</sup>	

"S = Susceptible, standard dosing regimen" (MIC ≤0,5 mg/L) can be treated with standard dosage

"I = Insusceptible, Increased exposure" (MIC 1-2) can be treated with high dosage



## **EUCAST endocarditis breakpoints: principles**

Endocarditis-dosages are often higher than EUCAST high dose  
→ no I-category (same principle as for meningitis-breakpoints)



## EUCAST endocarditis breakpoints: principles

Endocarditis-dosages are often higher than EUCAST high dose  
→ no I-category (same principle as for meningitis-breakpoints)

Endocarditis-breakpoints for agents mentioned in tables in ESC-guidelines for

*Staphylococcus* spp.

*Enterococcus* spp.

*Streptococcus* A,B,C,G

*Streptococcus pneumoniae*

Viridans group streptococci

*Haemophilus influenzae*

*Kingella kingae*

Agents without clinical breakpoints, but used for oral step-down treatment: notes



## ***Staphylococcus* spp.**

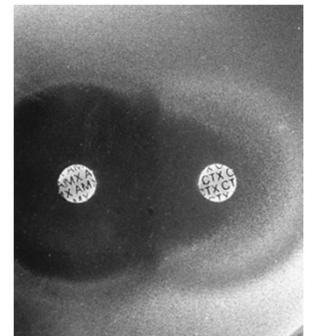
All relevant clinical breakpoints apply for endocarditis

- Cefoxitin screening for presence of *mecA/mecC* for  $\beta$ -lactam treatment
- (Penicillin susceptibility not mentioned in the ESC-guidelines apart from oral step-down treatment)
- Vancomycin and rifampicin: clinical breakpoints = ECOFFs



## ***Enterococcus* spp.**

- Ampicillin / Amoxicillin iv  
proposed breakpoint ( $S \leq 4/R > 4$  mg/L) = ECOFF  
see also current EUCAST consultation "Proposed change of breakpoints for aminopenicillins in enterococci"
- Ceftriaxone  
used in combination with aminopenicillins for *E. faecalis* endocarditis  
testing not recommended
- Daptomycin  
→ EUCAST guidance document



Mainardi et al. AAC  
1995 Sep;39(9):1984-7.



## Streptococcus A,B,C,G

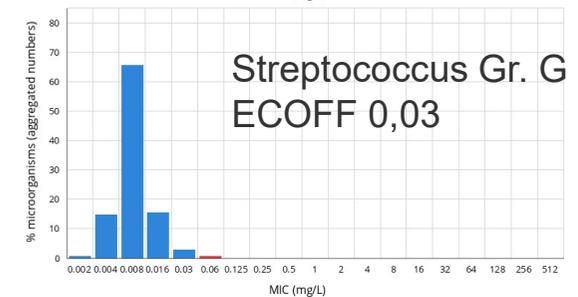
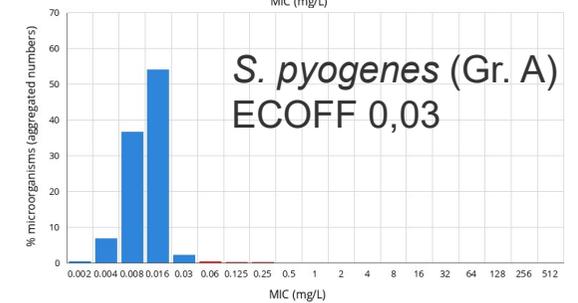
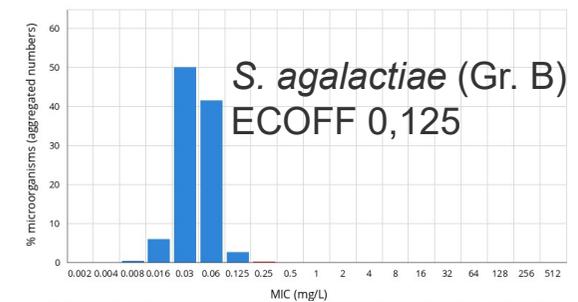
Benzylpenicillin is the mainstay of treatment!

Clinical breakpoint  $S \leq 0,25 / R > 0,25$  mg/L

Endocarditis breakpoints ECOFF-based:

*S. agalactiae* (Gr. B):  $S \leq 0,125 / R > 0,125$  mg/L

other:  $S \leq 0,03 / R > 0,03$  mg/L



## *Streptococcus pneumoniae*

Endocarditis breakpoints same as meningitis  
breakpoints

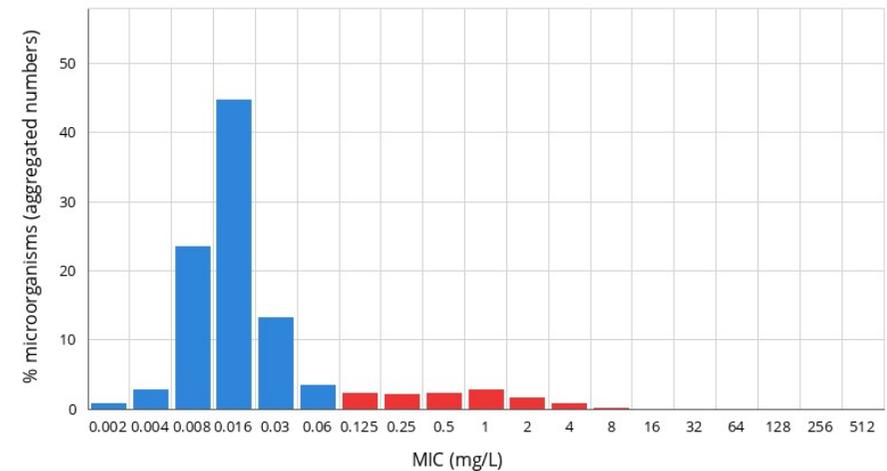
Benzylpenicillin:  
ECOFF-based:  $S \leq 0,06 / R > 0,06$  mg/L

Ampicillin/Amoxicillin i.v.:  $S \leq 0,5 / R > 0,5$  mg/L

Ceftriaxone/Cefotaxime:  $S \leq 0,5 / R > 0,5$  mg/L

Benzylpenicillin / *Streptococcus pneumoniae*  
International MIC distribution - Reference database 2024-05-19  
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:  $\leq 0.06$  mg/L

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



## Viridans group streptococci / $\beta$ -lactams

### Treatment guidelines and clinical data

ESC guidelines 2015: benzylpenicillin MIC  $\leq 0,125$  mg/L: monotherapy  
benzylpenicillin MIC 0,25 - 2 mg/L: combination with gentamicin  
ESC guidelines 2023: refers to EUCAST S-category for monotherapy  
(current EUCAST breakpoints: S  $\leq 0,25$ / R  $> 2$  mg/L)

Sparse clinical data in favour of combination benzylpenicillin +AG for Pen I-group:

Retrospective data from Mayo clinic 1967-2006: 29 patients, cure rate 90%

Knoll et al. Clin Infect Dis 2007;44: 1585–1592

Spanish cohort study 2008-2018, 226 with benzylpenicillin MIC 0,25 - 2 mg/L

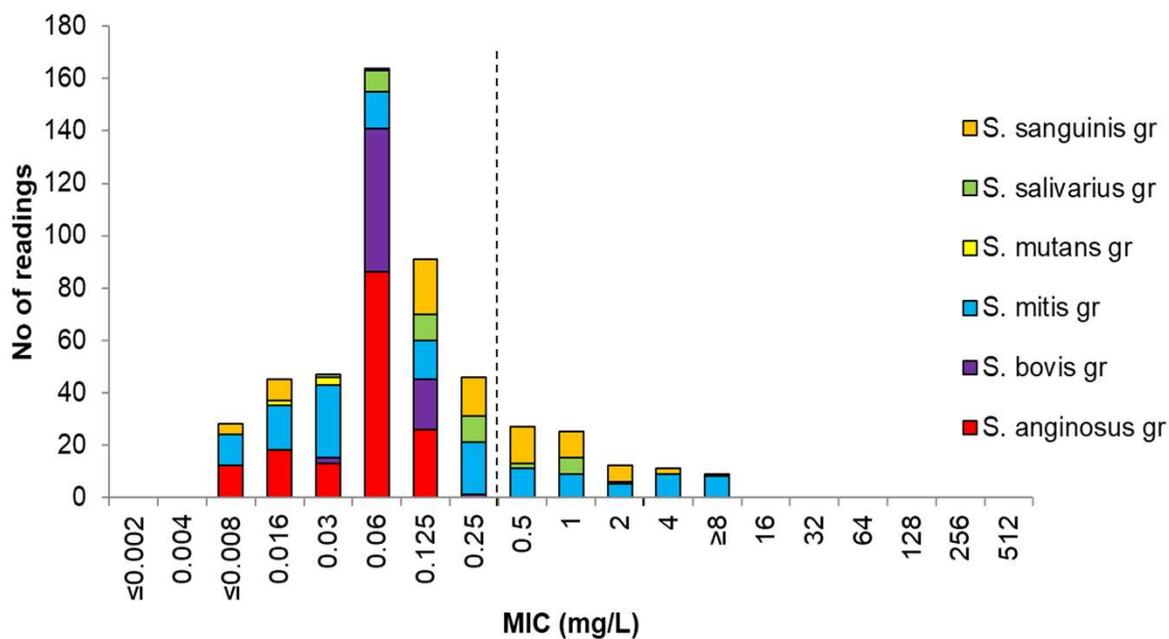
No difference in in-hospital mortality monotherapy vs. combination therapy

Majority treated with cephalosporins

Escrhuela-Vidal Clin Infect Dis. 2023 Nov 11;77(9):1273-1281.

# Viridans group streptococci / $\beta$ -lactams MIC distributions

**Benzylpenicillin MIC**  
Viridans group streptococci, 505 isolates



Common ECOFF: 0,25 mg/L

Figure: Erika Matuschek, EDL

Based on data from Plainvert, Matuschek et al. Microbiol Spectr. 2023 Jun 15;11(3):e0016023. 15



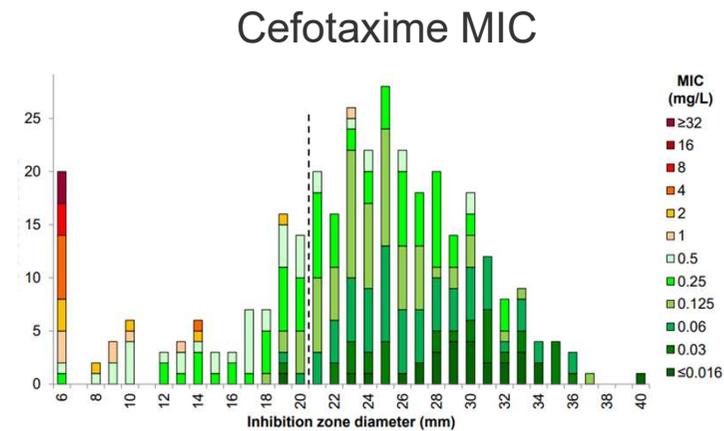
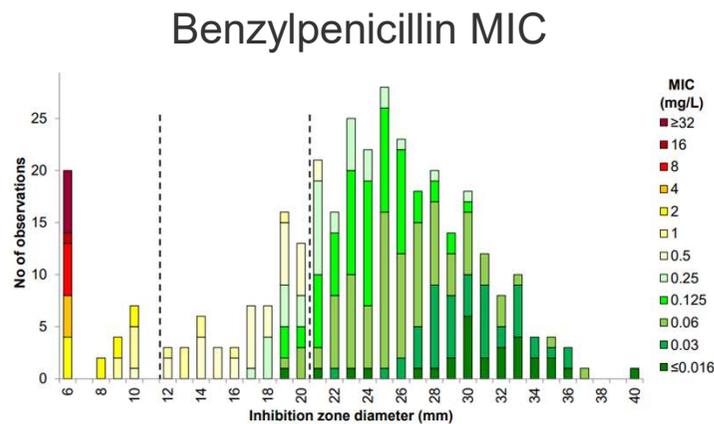
## Viridans group streptococci / $\beta$ -lactams

### Proposal for endocarditis breakpoints

Benzympenicillin	$S \leq 0,25 / R > 0,25$ mg/L
Ampicillin iv, Amoxicillin iv	$S \leq 0,5 / R > 0,5$ mg/L
Cefotaxime, Ceftriaxone	$S \leq 0,5 / R > 0,5$ mg/L

# Viridans group streptococci / $\beta$ -lactams Testing

Benzylpenicillin 1 unit disk screening (cut-off 21mm) versus

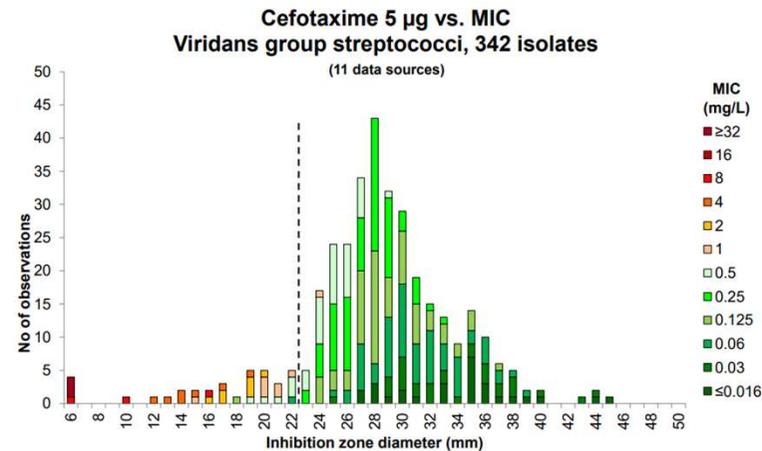
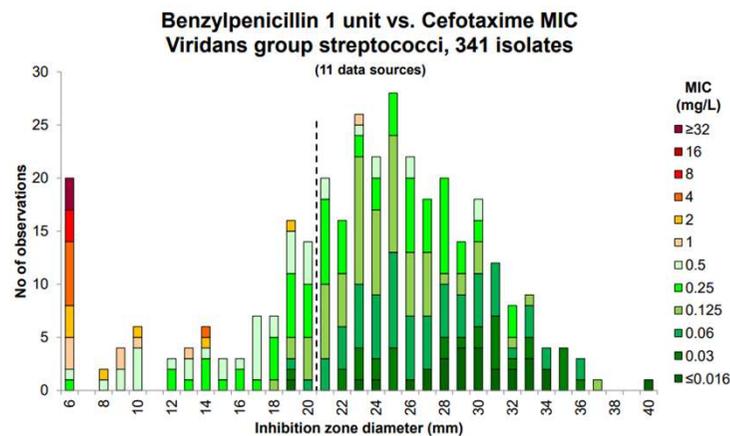


Good sensitivity: If screening negative, report S for relevant  $\beta$ -lactams

[https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST\\_files/Disk\\_criteria/Validation\\_2024/Viridans\\_group\\_streptococci\\_v\\_6.1\\_January\\_2024.pdf](https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Disk_criteria/Validation_2024/Viridans_group_streptococci_v_6.1_January_2024.pdf)

# Viridans group streptococci / $\beta$ -lactams Testing

Benzylpenicillin 1 unit disk screening cut-off 21mm:



Lower specificity for agents other than benzylpenicillin, eg. cefotaxime:

→ test for relevant agent, e.g. cefotaxime disk

## Agents for oral step-down therapy

- POET principle: combination therapy (watch dosing regimens!)
- For some species/agent combinations without clinical breakpoint: ECOFF given in Note
- (exception: Enterococcus spp. / Rifampicin)

**Table S9** Combinations of antibiotics for oral step-down treatment

Penicillin-and methicillin-susceptible <i>S. aureus</i> & CoNS	Methicillin-susceptible <i>S. aureus</i> & CoNS	Methicillin-resistant CoNS	<i>E. faecalis</i>	Penicillin-susceptible streptococci	Penicillin-resistant streptococci
Amoxicillin 1 g × 4 Rifampin 600 mg × 2	Dicloxacillin 1 g × 4 Rifampin 600 mg × 2	Linezolid 600 mg × 2 Fusidic acid 750 mg × 2	Amoxicillin 1 g × 4 Moxifloxacin 400 mg × 1	Amoxicillin 1 g × 4 Rifampin 600 mg × 2	Linezolid 600 mg × 2 Rifampin 600 mg × 2
Amoxicillin 1 g × 4 Fusidic acid 750 mg × 2	Dicloxacillin 1 g × 4 Fusidic acid 750 mg × 2	Linezolid 600 mg × 2 Rifampin 600 mg × 2	Amoxicillin 1 g × 4 Linezolid 600 mg × 2	Amoxicillin 1 g × 4 Moxifloxacin 400 mg × 1	Moxifloxacin 400 mg × 1 Rifampin 600 mg × 2
Moxifloxacin 400 mg × 1 Rifampin 600 mg × 2	Moxifloxacin 400 mg × 1 Rifampin 600 mg × 2		Amoxicillin 1 g × 4 Rifampin 600 mg × 2	Amoxicillin 1 g × 4 Linezolid 600 mg × 2	Linezolid 600 mg × 2 Moxifloxacin 400 mg × 1
Linezolid 600 mg × 2 Rifampin 600 mg × 2	Linezolid 600 mg × 2 Rifampin 600 mg × 2		Linezolid 600 mg × 2 Moxifloxacin 400 mg × 1	Linezolid 600 mg × 2 Rifampin 600 mg × 2	
Linezolid 600 mg × 2 Fusidic acid 750 mg × 2	Linezolid 600 mg × 2 Fusidic acid 750 mg × 2		Linezolid 600 mg × 2 Rifampin 600 mg × 2	Linezolid 600 mg × 2 Moxifloxacin 400 mg × 1	

ESC guidelines. Delgado et al. Eur Heart J. 2023 Oct 14;44(39):3948-4042.



## Reporting of endocarditis isolates: How we handle it in our department

Capital Region of Denmark: weekly multidisciplinary conference  
→ diagnostic, surgical referral and antimicrobial treatment plans

Personal contact from cardiologist, when endocarditis is diagnosed

Reporting:

- "Endocarditis panel" and specific instructions for reporting
- SIR-categorization without further specification, when breakpoints available
- Gentamicin high-level resistance reports with comment
- Comment regarding oral step-down treatment, when breakpoints are not set
- (For now: reporting of benzylpenicillin MIC for streptococci, as still part of Danish guidelines.)



## Take home

- Endocarditis breakpoints consultation coming soon
  - General Consultation during 2024
  - Breakpoints in the v15.0 table
- Same principles as meningitis breakpoints
  - No I-category
  - Mostly ECOFF-based breakpoints
- Proposition for viridans group streptococci / betalactams:
  - No I-category for benzylpenicillin
  - Benzylpenicillin screening works well
  - No need for MIC testing