

# EUCAST guidance document on Infective Endocarditis:

## Reporting of antimicrobial susceptibility testing results

**November 2025**

[minor revision adding screening criteria for benzylpenicillin]

### Background

Infective endocarditis is a severe condition requiring standardised and multidisciplinary management both for diagnosis and treatment. Correct targeted treatment is crucial to reduce mortality and morbidity. Historically, international and local guidelines have included MIC breakpoints to inform antibiotic choice and dosing – these breakpoints have been poorly documented and are methodologically challenging, often bisecting or disregarding the wild-type population. In 2023, the European Society of Cardiology (ESC) published updated guidelines for management of endocarditis (1). Herein, the MIC informed antibiotic treatment regimens are replaced by guidelines based on the S-I-R categorisation obtained when EUCAST methodology and clinical breakpoints are used.

The purpose of this document is to give guidance and background information on the EUCAST breakpoints and recommended testing of endocarditis isolates. Clinical guidance on treatment, including recommended dosing regimens, is provided in the ESC guidelines or national guidelines.

Antimicrobial treatment of endocarditis requires the use of high dosages for a prolonged period to ensure appropriate antimicrobial exposure. Because of reduced antimicrobial penetration into vegetations, the dosages used in endocarditis are often higher than the EUCAST standard and high dosages and these dosages are not based on pharmacokinetics/pharmacodynamics (PK/PD). The concept of standard dosages (S) and high dosages (I) can therefore not be applied here. Thus, EUCAST endocarditis breakpoints do not include an I-category, but presuppose that the dosages recommended in the ESC guidelines (1) are used.

EUCAST has reviewed the agents covered in the ESC guidelines for viridans group streptococci (table 7), other *Streptococcus* spp., *Staphylococcus* spp. (table 8), *Enterococcus* spp. (table 9), *Haemophilus influenzae* and *Kingella kingae* as well as agents used for oral follow-up treatment (table S9) (1). Endocarditis-breakpoints are based on epidemiological cut-off values (ECOFFs). One exception is the breakpoint for benzylpenicillin in combination treatment for viridans group streptococci, see below. Only when endocarditis breakpoints differ from the breakpoint for other indications, are they included in the breakpoint table as an additional line.

### General recommendations

Antimicrobial susceptibility testing can be performed by either disk diffusion or an MIC method, as described in the breakpoint tables. However, reporting of an MIC in the case of endocarditis is not necessary.

When ceftriaxone is used in combination with aminopenicillins for treatment of endocarditis with *Enterococcus* spp., EUCAST does not recommend testing for ceftriaxone, as the expected phenotype is resistant and does not predict clinical outcome. A method that would predict clinical utility of the combination is not available.

### Oral follow-up treatment

For oral antimicrobials used in follow-up treatment of endocarditis where clinical breakpoints are not given (e.g. moxifloxacin for *Enterococcus* spp. and moxifloxacin and rifampicin for viridans group streptococci), acquired resistance should be excluded using ECOFFs. Isolates should not be reported as susceptible, but as either “devoid of”, when belonging to the wild type, or “in possession

of”, when non-wild type, resistance mechanisms. This is explained in the associated note in the breakpoint tables.

EUCAST has not included a similar recommendation and note for rifampicin and *Enterococcus* spp. because of the high ECOFF for *E. faecalis* (8 mg/L) and the lack of clinical evidence of efficacy.

### Viridans group streptococci

Benzylpenicillin 1U disk can be used to screen for  $\beta$ -lactam resistance. Screen-negative isolates (inhibition zone  $\geq 21$ mm) can be reported susceptible to the following relevant  $\beta$ -lactams: benzylpenicillin, ampicillin, amoxicillin, cefotaxime, ceftriaxone, and carbapenems). For screen-positive isolates, the agent intended for treatment should be subjected to antimicrobial susceptibility testing.

The ESC guidelines, and several national guidelines, recommend the use of benzylpenicillin/amoxicillin/ceftriaxone in combination with gentamicin for isolates which by previous breakpoints (EUCAST breakpoint tables up to 2024) were categorized as benzylpenicillin susceptible, increased exposure. The clinical evidence for this recommendation is weak and based on smaller retrospective studies (2). A French retrospective study including 414 cases of streptococcal endocarditis demonstrated a higher mortality in patients with viridans group streptococci endocarditis with an amoxicillin MIC between 0.25 and 2 mg/L compared to when MIC  $\leq 0.125$  mg/L (3). The outcome was not improved when amoxicillin was combined with an aminoglycoside. A large Spanish retrospective study with 914 viridans group streptococci endocarditis cases, compared outcome in patients with benzylpenicillin susceptible streptococci (n=688, PEN S with MIC  $\leq 0.125$  mg/L) and susceptible, increased exposure (n=226, PEN-I) (4). Only 48 patients (21.2%) in the PEN-I group received benzylpenicillin in combination with an aminoglycoside, whereas 72 (31.9%) received cephalosporin monotherapy and 67 (29.6%) cephalosporin in combination with an aminoglycoside. There was no significant difference in mortality or relapse in the two groups. However, outcome was not evaluated in relation to the MIC of benzylpenicillin.

EUCAST acknowledges that the evidence for treatment with benzylpenicillin of viridans group streptococci with benzylpenicillin MIC 0.5 - 1 mg/L (inhibition zones 12-20 mm) is not clear. Therefore, these isolates should not be reported as susceptible, but rather with a comment that benzylpenicillin, when used for such isolates, should be combined with other active therapy. In the breakpoint table, this is displayed as an extra line for “Benzylpenicillin (endocarditis, in combination with other antimicrobial treatment)” with bracketed breakpoints.

Isolates with a benzylpenicillin disk diffusion test inhibition zone  $< 12$  mm, corresponding to an MIC  $> 1$  mg/L, should be reported as resistant to benzylpenicillin.

### References

1. Delgado, Victoria et al. 2023 ESC Guidelines for the management of endocarditis. European heart journal vol. 44,39 (2023): 3948-4042. doi:10.1093/eurheartj/ehad193
2. Knoll, Bettina et al. Infective endocarditis due to penicillin-resistant viridans group streptococci. Clinical infectious diseases vol. 44,12 (2007): 1585-92. doi:10.1086/518174
3. Pilmis, B et al. Be careful about MICs to amoxicillin for patients with Streptococci-related infective endocarditis. International journal of antimicrobial agents vol. 53,6 (2019): 850-854. doi:10.1016/j.ijantimicag.2019.03.002
4. Escrichuela-Vidal, Francesc et al. Impact of Intermediate Susceptibility to Penicillin on Antimicrobial Treatment and Outcomes of Endocarditis Caused by Viridans and Gallolyticus Group Streptococci. Clinical infectious diseases vol. 77,9 (2023): 1273-1281. doi:10.1093/cid/ciad375