SWAB guidelines for the antimicrobial treatment of infective endocarditis

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SWAB infective endocarditis guideline committee

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The present text provides an update of the 2019 SWAB guidelines on the treatment of infective endocarditis. Notable changes to the text have been highlighted.

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Overview of antimicrobial treatment regimens

Table 1.1.1. Empirical therapy, native valve, subacute presentation

Situation	Recommendation
Native valve, subacute presentation	Amoxicillin ~~12g~~ 12000mg/day in 6 doses or by continuous infusion + Ceftriaxone ~~4g~~ 4000mg/day in 2 doses
Native valve, subacute presentation *Non-severe penicillin allergy*	~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels of 15-20mg/l) or by continuous infusion (serum concentration 20-25mg/l)~~ Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist + Ceftriaxone ~~2g~~ 2000mg/day in 1 dose
Native valve, subacute presentation *Severe penicillin allergy*	Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist

Table 1.1.3. Empirical therapy, native valve, acute presentation

Situation	Recommendation
Native valve, acute presentation	Flucloxacillin ~~12g~~ 12000mg/day in 6 doses or by continuous infusion
Native valve, acute presentation *Non-severe penicillin allergy*	Cefazolin ~~6g~~ 6000mg/day in 3 doses or by continuous infusion
Native valve, acute presentation *Severe beta-lactam allergy*	Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels of 15-20mg/l) or by continuous infusion (serum concentration 20-25mg/l)~~

Table 1.2.3. Empirical therapy, prosthetic valve

Situation	Recommendation
Prosthetic valve	Flucloxacillin ~~12g~~ 12000mg/day in 6 doses or by continuous infusion + Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels of 15-20mg/l) or by continuous infusion (serum concentration 20-25mg/l)~~
Prosthetic valve *Non-severe penicillin allergy*	Cefazolin ~~6g~~ 6000mg/day in 3 doses or by continuous infusion + Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~/l) or by continuous infusion (serum concentration 20-25mg/l)~~
Prosthetic valve *Severe penicillin allergy*	Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist

Table 2.1.1 Viridans group streptococci including *S. gallolyticus*, penicillin MIC ≤~~0.125~~ 0.25 mg/ml - native valve

Situation	Recommendation
Native valve	Penicillin 12 million units/day in 6 doses or by continuous infusion for 4 weeks*
Native valve *Non-severe penicillin allergy*	Ceftriaxone ~~2g~~ 2000mg/day in one dose for 4 weeks*
Native valve *Severe beta-lactam allergy*	Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels of 15-20mg/l) or by continuous infusion (serum concentration 20-25mg/l)~~ for 4 weeks*

Native valve – 2 week treatment (only in uncomplicated IE)	Penicillin 12 million units/day in 6 doses or by continuous infusion for 2 weeks + Gentamicin 3mg/kg/day in 1 dose for 2 weeks. Perform therapeutic drug monitoring when using gentamicin.
Native valve – 2 week treatment (only in uncomplicated IE) *Non-severe penicillin allergy*	Ceftriaxone ~~2g~~ 2000mg/day in one dose for 2 weeks + Gentamicin 3mg/kg/day in 1 dose for 2 weeks. Perform therapeutic drug monitoring when using gentamicin.

~~* Gentamicin not recommended~~

Table 2.1.2 Viridans group streptococci including *S. gallolyticus*, penicillin MIC ≤~~0.125~~ 0.25 mg/ml - prosthetic valve

Situation	Recommendation
Prosthetic valve	Penicillin 12 million units/day in 6 doses or by continuous infusion for 6 weeks*
Prosthetic valve *Non-severe penicillin allergy*	Ceftriaxone ~~2g~~ 2000mg/day in one dose for 6 weeks~~*~~
Prosthetic valve *Severe beta-lactam allergy*	Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels of 15-20mg/l) or by continuous infusion (serum concentration 20-25mg/l)~~ for 6 weeks*

~~* Gentamicin not recommended~~

Table 2.2.1 Viridans group streptococci including *S. gallolyticus*, penicillin MIC >0.250 – 1 ~~2~~ mg/l - native valve

Situation	Recommendation
Native valve	Penicillin 18 million units/day in 6 doses or by continuous infusion for 4 weeks + Gentamicin 3mg/kg/day in 1 dose for 2 weeks. Perform therapeutic drug monitoring when using gentamicin.
Native valve *Non-severe penicillin allergy*	Ceftriaxone ~~2g~~ 2000mg/day in one dose for 4 weeks + Gentamicin 3mg/kg/day in 1 dose for 2 weeks. Perform therapeutic drug monitoring when using gentamicin.
Native valve *Severe beta-lactam allergy*	Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist

	~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels 15-20mg/l) or by continuous infusion (plateau concentration 20-25mg/l)~~ for 4 weeks ¥

¥ Gentamicin not recommended if vancomycin is used

Table 2.2.2 Viridans group streptococci including *S. gallolyticus*, penicillin MIC >0.250 – 1 ~~2~~ mg/l - prosthetic valve

Situation	Recommendation
Prosthetic valve	Penicillin 18 million units/day in 6 doses or by continuous infusion for 6 weeks + Gentamicin 3mg/kg/day in 1 dose for 2 weeks. Perform therapeutic drug monitoring when using gentamicin.
Prosthetic valve *Non-severe penicillin allergy*	Ceftriaxone ~~2g~~ 2000mg/day in one dose for 6 weeks + Gentamicin 3mg/kg/day in 1 dose for 2 weeks. Perform therapeutic drug monitoring when using gentamicin.
Prosthetic valve *Severe beta-lactam allergy*	Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels 15-20mg/l) or by continuous infusion (plateau concentration 20-25mg/l)~~ for 6 weeks. ¥

¥ Gentamicin not recommended if vancomycin is used

Table 2.3.1 *Streptococcus pneumoniae*, penicillin MIC ≤ 0.06 mg/l

Situation	Recommendation
Native valve or prosthetic valve	Treatment guidelines for viridans group streptococci can be used, with the exception of the two week treatment schedule.

Table 2.3.2 *β-haemolytic streptococci (e.g. S. agalactiae, S. dysgalactiae)*

Situation	Recommendation
Native valve or prosthetic valve	Treatment guidelines for viridans group streptococci can be used, with the exception of the two week treatment schedule.
Native valve or prosthetic valve	Addition of 2 weeks of gentamicin 3mg/kg/day may be considered. Treatment should be discontinued if signs of toxicity occur.

Table 2.4.1 Viridans group streptococci including *S. gallolyticus*, penicillin MIC ≤0.25mg/l

Situation	Recommendation
Native valve	Consider oral stepdown treatment if the patient meets criteria for IV-oral switch (see chapter on oral treatment)

Native valve	Oral stepdown treatment consists of amoxicillin 1g four times per day
Prosthetic valve	Consider oral stepdown treatment if the patient meets criteria for IV-oral switch (see chapter on oral treatment)
Prosthetic valve	Oral stepdown treatment consists of amoxicillin 1g four times per day

Table 3.1.1 *Staphylococcus aureus* or CNS, methicillin sensitive – native valve

Situation	Recommendation
Native valve	Flucloxacillin ~~12g~~ 12000mg/day in 6 doses or by continuous infusion for 6 weeks~~*~~
Native valve *Non-severe beta-lactam allergy OR decreased renal function or acute kidney injury*	Cefazolin ~~6g~~ 6000mg/day in 3 doses or by continuous infusion for 6 weeks~~*~~
Native valve *Severe beta-lactam allergy*	Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels of 15-20mg/l) or by continuous infusion (serum concentration 20-25mg/l)~~for 6 weeks*

~~* Gentamicin not recommended~~

Table 3.1.2 *Staphylococcus aureus* or CNS, methicillin sensitive – prosthetic valve

Situation	Recommendation
Prosthetic valve	Flucloxacillin ~~12g~~ 12000mg/day in 6 doses or by continuous infusion for 6 weeks + Rifampicin 900mg ~~1200~~ day in 2 doses for 6 weeks + Gentamicin 3mg/kg/day in 1 dose for 2 weeks. Perform therapeutic drug monitoring when using gentamicin.†
Prosthetic valve *Non-severe beta-lactam allergy*	Cefazolin ~~6g~~ 6000mg/day in 3 doses or by continuous infusion for 6 weeks + Rifampicin 900mg ~~1200~~ day in 2 doses for 6 weeks + Gentamicin 3mg/kg/day in 1 dose for 2 weeks. Perform therapeutic drug monitoring when using gentamicin.†
Prosthetic valve *Severe beta-lactam allergy*	Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing:

	loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels of 15-20mg/l) or by continuous infusion (serum concentration 20-25mg/l)~~for 6 weeks + Rifampicin 900mg ~~1200~~ day in 2 doses for 6 weeks + Gentamicin 3mg/kg/day in 1 dose for 2 weeks. Perform therapeutic drug monitoring when using gentamicin.†

† Gentamicin should be discontinued if signs of toxicity occur

Table 3.2.1 *Staphylococcus aureus* or CNS, methicillin resistant – native valve

Situation	Recommendation
Native valve	Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels of 15-20mg/l) or by continuous infusion (serum concentration 20-25mg/l)~~for 6 weeks*
Native valve	If vancomycin cannot be given, replacing vancomycin with daptomycin 10mg/kg/day in 1 dose might be an option if susceptible. Combination therapy with daptomycin and fosfomycin iv ~~12g~~ 12000mg/day or ceftaroline iv 1800mg/day is recommended in patients with persistent bacteraemia under daptomycin monotherapy. Decide the optimal treatment regimen in consultation with a medical microbiologist or infectious disease specialist or with an endocarditis team.

* Gentamicin not recommended

Table 3.2.2 *Staphylococcus aureus* or CNS, methicillin resistant – prosthetic valve

Situation	Recommendation
Prosthetic valve	Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels of 15-20mg/l) or by continuous infusion (serum concentration 20-25mg/l)~~ for 6 weeks +

	Rifampicin 900mg ~~1200~~ day in 2 doses for 6 weeks + Gentamicin 3mg/kg/day in 1 dose for 2 weeks. Perform therapeutic drug monitoring when using gentamicin.†
Prosthetic valve	If vancomycin cannot be given, replacing vancomycin with daptomycin 10mg/kg/day in 1 dose might be an option if susceptible. Combination therapy with daptomycin and fosfomycin iv ~~12g~~ 12000mg/day or ceftaroline iv 1800mg/day is recommended in patients with persistent bacteraemia under daptomycin monotherapy. Decide the optimal treatment regimen in consultation with a medical microbiologist or infectious disease specialist or with an endocarditis team.

† Gentamicin should be discontinued if signs of toxicity occur

Table 3.3.1 *Staphylococcus aureus* or CNS

Situation	Recommendation
Native valve	Routine use of oral stepdown treatment is not recommended
Prosthetic valve	Routine use of oral stepdown treatment is not recommended

Table 4.1.1 *Enterococcus* spp., amoxicillin susceptible, no high level aminoglycoside resistance (HLAR)

Situation	Recommendation
Native valve or Prosthetic valve	Amoxicillin ~~12g~~ 12000mg/day in 6 doses or by continuous infusion for 6 weeks + Ceftriaxone ~~4g~~ 4000mg/day in 2 doses for 6 weeks or by continuous infusion‡
Native valve or Prosthetic valve	Amoxicillin ~~12g~~ 12000mg/day in 4-6 doses or by continuous infusion for 6 weeks + Gentamicin 3mg/day in 1 dose for 6 weeks. Perform therapeutic drug monitoring when using gentamicin.

‡ First choice regimen

Table 4.1.2 *Enterococcus* spp., amoxicillin susceptible, HLAR

Situation	Recommendation
Native valve or Prosthetic valve	Amoxicillin ~~12g~~ 12000mg/day in 6 doses or by continuous infusion for 6 weeks + Ceftriaxone ~~4g~~ 4000mg/day in 2 doses for 6 weeks or by continuous infusion

Table 4.2.1 *Enterococcus* spp., amoxicillin resistant or amoxicillin allergy, no HLAR

Situation	Recommendation

Native valve or Prosthetic valve	Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels of 15-20mg/l) or by continuous infusion (serum concentration 20-25mg/l)~~ for 6 weeks + Gentamicin 3mg/day in 1 dose for 4-6 weeks. Perform therapeutic drug monitoring when using gentamicin.

Table 4.2.2 *Enterococcus* spp., amoxicillin resistant or amoxicillin allergy, HLAR

Situation	Recommendation
Native valve or Prosthetic valve	Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels of 15-20mg/l) or by continuous infusion (serum concentration 20-25mg/l)~~ for 6 weeks

Table 4.3.1 *Enterococcus* spp., amoxicillin resistant or amoxicillin allergy and vancomycin resistant or vancomycin allergy

Situation	Recommendation
Native valve or Prosthetic valve	Daptomycin iv 12mg/kg day in 1 dose for 6 weeks + Fosfomycin iv ~~12g~~ 12000mg/day in 3 doses or by continuous infusion for 6 weeks Decide the optimal treatment regimen in consultation with a medical microbiologist or infectious disease specialist or with an endocarditis team.

Table 4.4.1 Enterococcus faecalis, amoxicillin MIC ≤1 and susceptible to moxifloxacin

Situation	Recommendation
Native valve	Consider oral stepdown treatment if the patient meets criteria for IV-oral switch (see chapter on oral treatment)
Native valve	Oral stepdown treatment consists of: Amoxicillin 1gr four times per day + Moxifloxacin 400mg once daily

Prosthetic valve	Routine use of oral stepdown treatment is not recommended

Table 5.1.1 HACEK spp. – native valve

Situation	Recommendation
Native valve	Ceftriaxone ~~2g~~ 2000mg/day in 1 dose for 4 weeks
Native valve	Amoxicillin ~~12g~~ 12000mg/day in 6 doses or by continuous infusion for 4 weeks

Table 5.1.2 HACEK spp. – prosthetic valve

Situation	Recommendation
Prosthetic valve	Ceftriaxone ~~2g~~ 2000mg/day in 1 dose for 6 weeks
Prosthetic valve	Amoxicillin ~~12g~~ 12000mg/day in 6 doses or by continuous infusion for 6 weeks

Table 6.1.1 *Cutibacterium ~~(Propionibacterium)~~* spp.

Situation	Recommendation
Native valve or Prosthetic valve	Penicillin 12-18 million units/day in 6 doses or by continuous infusion for 6 weeks˚
Native valve or Prosthetic valve *Non-severe penicillin allergy*	Ceftriaxone ~~4g~~ 4000mg/day in 2 doses for 6 weeks˚
Native valve or Prosthetic valve *Severe beta-lactam allergy*	Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels of 15-20mg/l) or by continuous infusion (serum concentration 20-25mg/l)~~ for 6 weeks˚

˚ Consider adding rifampicin 900mg ~~1200~~/day in 2 doses in selected cases of prosthetic valve *Cutibacterium* endocarditis

Table 7.1.1 Culture negative endocarditis

Situation	Recommendation
Native valve	Amoxicillin ~~12g~~ 12000mg/day in 6 doses or by continuous infusion for 6 weeks + Ceftriaxone ~~4g~~ 4000mg/day in 2 doses for 6 weeks + Doxycycline 200mg/day in 1 or 2 doses for 6 weeks Δ
Prosthetic valve	Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels of 15-20mg/l) or by continuous infusion (serum concentration 20-25mg/l)~~ for 6 weeks + Ceftriaxone ~~2g~~ 2000mg/day in 1 dose for 6 weeks + Doxycycline 200mg/day in 1 or 2 doses for 6 weeks Δ

Δ Consider stopping doxycycline if additional tests for intracellular microorganisms (e.g.: *Coxiella*, *Bartonella*) are negative

0. What is new in this guideline compared to the guidelines of 2019?

- Textual changes to methodology section to reflect 2025 update and deletion of no longer relevant sections of the 2019 guidelines (chapters 1-3)
- Converted all dosages in grams to milligrams
- Added sections on oral step-down treatment (chapter 7 for general information, chapters 9, 10 and 11 specifically for streptococci, staphylococci and enterococci)
- Added further justification for choice of empirical treatment regimens (chapter 8)
- Adjusted penicillin MIC cut-offs for viridans group streptococci to conform to new EUCAST breakpoints
- Changed strength of recommendation for adjunctive rifampicin and gentamicin for staphylococcal prosthetic valve endocarditis (chapter 10)
- Added fosfomycin and ceftaroline as possible adjunctive therapy to daptomycin for staphylococcal endocarditis (chapter 10)
- Added fosfomycin as recommended adjunctive therapy to daptomycin for enterococcal endocarditis (chapter 11)
- Adjusted dosing of rifampicin from 1200mg/day to 900mg/day (chapter 10)
- Added section on suppressive therapy (chapter 17)
- Added updated recommendations on endocarditis prophylaxis (chapter 20)

1. Introduction

Infective endocarditis is a potentially lethal infection of the cardiac endothelium which can lead to the formation of valvular vegetations, intracardiac abscesses, destruction of cardiac structures and extracardiac complications. Endocarditis is a highly heterogenic disease that can be caused by a multitude of organisms with a myriad of signs, symptoms and complications. Endocarditis is also an ~~rare~~ uncommon disease, with an estimated annual incidence of ~~3 to~~ 9 to 14 per 100.000 persons per year (1, 2).

The rarity of the disease and the multiple treatment options warrant guidelines to support clinicians in the management of patients with endocarditis This guideline aims to provide clinicians guidance in choosing the best antibiotic strategy for patients with endocarditis ~~The present text replaces the previous SWAB guideline on infective endocarditis which dates from 2003 (3).~~

The present text provides an update of the 2019 SWAB guidelines on the treatment of infective endocarditis. Notable changes to the text have been highlighted.

2. Scope and validity of the guideline

The scope of this guideline encompasses the antimicrobial treatment of endocarditis in adult patients, with the exception of pregnant women. The treatment of endocarditis in children is beyond the scope of this guideline.
Treatment advice is based on the causative organism, patient specific factors, type of valve involved and presence of a cardiac implantable electronic device. This guideline is meant to guide physicians in choosing the appropriate antimicrobial therapy for the patient with infective endocarditis. The target audience includes, but is certainly not limited to: cardiologists, cardiothoracic surgeons, internists infectious disease specialists and medical microbiologists.

Endocarditis is a disease with a plethora of different causative microorganisms, not all of which are covered in this guideline. This guideline intends to provide comprehensive recommendations for the most common manifestations of the disease, but is not meant to describe treatment advice for every possible causative pathogen. For microorganisms not covered in this guideline, we refer clinicians to the latest available literature and other published guidelines.

Diagnosis of endocarditis and indications for surgical treatment lie beyond the scope of this guideline. For these topics, we refer to the guidelines on surgical treatment of the European Society of Cardiology (ESC), American Heart Association (AHA) and American Association for Thoracic Surgery (AATS) (4-7). ~~Prophylactic use of antibiotics to prevent endocarditis from invasive medical or dental procedures is also not discussed in this guideline.~~

~~The guideline articulates the prevailing professional standard in infective endocarditis and contains general recommendations for the antibiotic treatment of adults. It is likely that most of these recommendations are also applicable to children, but this has not been formally evaluated. It is possible that these recommendations are not applicable in an individual patient case. The applicability of the guideline in clinical practice is the responsibility of the treating physician. There may be facts or circumstances which, in the interest of proper patient care, non-adherence to the guideline is desirable.~~

The guideline articulates the prevailing professional standard in 2026 and contains general recommendations for the antibiotic treatment of hospitalized adults. It is likely that most of these

recommendations are also applicable to children, but this has not been formally evaluated.
It is possible that these recommendations are not applicable in an individual patient case. The applicability of the guideline in clinical practice is the responsibility of the treating physician. There may be facts or circumstances which, in the interest of proper patient care, non-adherence to the guideline is desirable.

SWAB intends to revise their guidelines every 5 years. The potential need for earlier revisions will be determined by the SWAB board at annual intervals, on the basis of an examination of current literature. Therefore, in 2031 or earlier if necessary, the guideline will be reevaluated.
-In addition to this planned update cycle, the guideline committee is available to provide modular updates to the guideline in the event of scientific publications leading to necessary change in practice. ~~If necessary, the guidelines committee will be reconvened to discuss potential changes. When appropriate, the committee will recommend expedited revision of the guideline to the SWAB board.~~

3. Methods

The guideline committee consisted of members delegated by their respective professional bodies; the Dutch Society for Infectious Diseases, Netherlands Society for Medical Microbiology, the Netherlands Society of Internal Medicine, the Netherlands Society of Cardiology, the Netherlands Society for Thoracic Surgery and the Dutch Association of Hospital Pharmacists. No patient input was sought for the development of this guideline.

This guideline was developed according to the SWAB tool guideline development and the AGREE-II tool for guideline development (8, 9). The guideline committee used the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for antimicrobial susceptibility.

For the 2019 version of the guideline, the guideline committee compared the 2015 versions of the European Society of Cardiology (ESC) and the American Heart Association (AHA) and used these guidelines as source material for the SWAB guideline, augmented with recommendations based on reviews of published literature. For a complete overview of methodology used and literature searches performed, we refer to the 2019 version of the SWAB guideline and its appendices (10).
For the 2025 update, the guideline committee compared the 2019 SWAB guidelines to the 2023 ESC guidelines (7). Recommendations that differed from the 2023 ESC guideline, including the addition of oral treatment, were collected by the coordinator and discussed by the guideline committee. After plenary discussion the guideline committee could decide to resolve the discrepancy by committee or perform review of published literature. Furthermore, the guideline committee identified additional subjects for literature review to add to or update the guideline: these included revision of nephrotoxic combinations of antibiotics and a section on indications for suppressive therapy was added.

~~The committee used the latest guidelines of the European Society of Cardiology (ESC) and the American Heart Association (AHA) as source material for the new SWAB guideline (4, 5). The recommendations on antimicrobial therapy in these two guidelines were compared to each other and provided the basis for the new SWAB guideline. Comparison was on three levels: the recommendation itself, the strength of the recommendation and the level of evidence.~~

~~Discrepancies between the ESC and AHA guidelines were classified in three subcategories: I: same recommendation but different strength of recommendation or different level of evidence; II: different recommendation; and III: recommendation not given in one of the two guidelines. Class II and III discrepancies where then discussed in the committee, where the decision was made to either choose one recommendation based on the current Dutch practices (e.g.: aminoglycosides are always dosed once daily in the Netherlands) or to do a literature review, using the references given in the respective guidelines and relevant literature gained from a new literature search. Only recommendations on antimicrobial therapy were compared.~~

~~Altogether, we identified 94 recommendations on antimicrobial therapy in the two guidelines. In 57 of these 94 recommendations, the advice of AHA and ESC differed (level II discrepancy), and in 18 instances a recommendation was missing in one of the two guidelines (level III discrepancy). In 19 recommendations the guidelines were in agreement. The level II and III discrepancies were then clustered in overlapping categories, leading to 26 clustered discrepancies (appendix A). Among these discrepancies, fourteen were deemed clear enough to come to a decision in the committee. For three discrepancies, consultation with an external expert was sought. For nine discrepancies, the guideline committee decided to do a review of available and new literature. The guideline committee added two subjects for additional literature review: treatment of cardiac implantable electronic device endocarditis (only CIED endocarditis is discussed, pocket infections fall beyond the scope of the guideline) and the treatment of endocarditis caused by *Cutibacterium* (formerly *Propionibacterium*) species. The guideline committee decided not to copy the recommendations on treatment for nutritionally deficient streptococci due to the extreme rareness of this condition. Treatment for fungal endocarditis was also not add to this guideline for the same reason~~. For the section on cardiac implantable electronic device endocarditis, the guideline committee based its advice on the 2015 British Society of Antimicrobial Chemotherapy (BSAC) guidelines and the 2010 AHA guidelines for the treatment of cardiac implantable electronic devices(11, 12), supplemented with a review of newly published literature since publication of these guidelines.

For the review of the literature, references quoted in the respective guidelines were complemented with articles on the subject indexed in PubMed until 07 November 2024. ~~January, 2015 and January, 07-.~~ Broad search terms were used (see appendix B for details) and all articles were screened by the coordinator based on title and abstract for full text review. Full text review of selected articles was carried out by members of the guideline committee working in groups of at least two ~~pairs of two~~, which led to a recommendation that was discussed by the full guideline committee and adopted after consensus was reached.

~~When recommendations given by the ESC and AHA were concordant, no new literature search was done, but the recommendation was discussed in the guideline committee and incorporated into the new guideline.~~

For classification of the strength of the recommendation the GRADE system was used (13). The GRADE system is a method of classifying quality of evidence and the strength of the accompanying recommendation. The strength of recommendations was graded as Strong or Weak, taking the quality of evidence, patients' values, resources and costs, and the balance between benefits, harms and burdens into account (Figure 1). Quality of evidence is inherently linked to the strength of the recommendation: higher quality evidence leads to more certainty on effect of the intervention. Unfortunately, high quality of evidence is rare in infective endocarditis. Despite the overall low quality of evidence, the guideline committee is of the opinion that low quality of evidence does not necessarily lead to a weak recommendation(14). ~~For example the evidence for treating *S. aureus* (MSSA) endocarditis with flucloxacillin is based on moderate to low quality evidence. Nevertheless,~~

~~the accumulated evidence and experience in the field leads to the strong recommendation that flucloxacillin should be used as the first line drug.~~ A strong recommendation means the guideline committee is confident that the advice should lead to a desirable result in most patients, while a weak recommendation means there is considerable uncertainty on the effect of the intervention(13). The GRADE system differs from the rating scales used by the ESC and AHA for classifying strength of recommendation and level of evidence. In cases where the guidelines were in full agreement and no new literature search was performed the strength of recommendation and level of evidence provided in the ESC and AHA were translated to the GRADE system. This meant that level I and IIa recommendations were adopted as “strong” recommendations.

When a new review of the literature was performed, the guideline committee assessed the strength of the recommendation and the level of evidence (or confidence) as described in the GRADE system based on the original studies. In reviewing the guidelines and cited literature, we found no studies meeting the GRADE criteria for high evidence. The highest level of evidence in this guideline is thus scored as moderate quality evidence. When no new review of the primary literature was performed we adapted the level of evidence cited in the ESC or AHA. Level B evidence was scored as ‘moderate’ quality evidence and Level C evidence as ‘low’ or ‘very low’. If the ESC and AHA guidelines differed on how the evidence was scored, the higher of the two was used.

For the 2025 update of the guideline, we compared the 2023 ESC Guidelines on the diagnosis and treatment of endocarditis to the 2019 SWAB guidelines(7). Recommendations that differed from the ESC guidelines were kept unchanged in the absence of new research, in addition new differences or new recommendations in the ESC guideline were discussed in the guideline committee. The guideline committee subsequently either decided to implement a change based on the evidence provided in the ESC guideline or perform a new literature search. For the literature search, Medline (PubMed) was searched for relevant articles based on title and abstract by the coordinator. No date restriction was used. Articles deemed possibly relevant were subsequently send to subcommittees of two or three committee members who selected articles based on the full texts and used these data for a recommendation, together with a rating of confidence based on the GRADE methodology. These recommendations were discussed by the full guideline committee and adopted after consensus was reached.

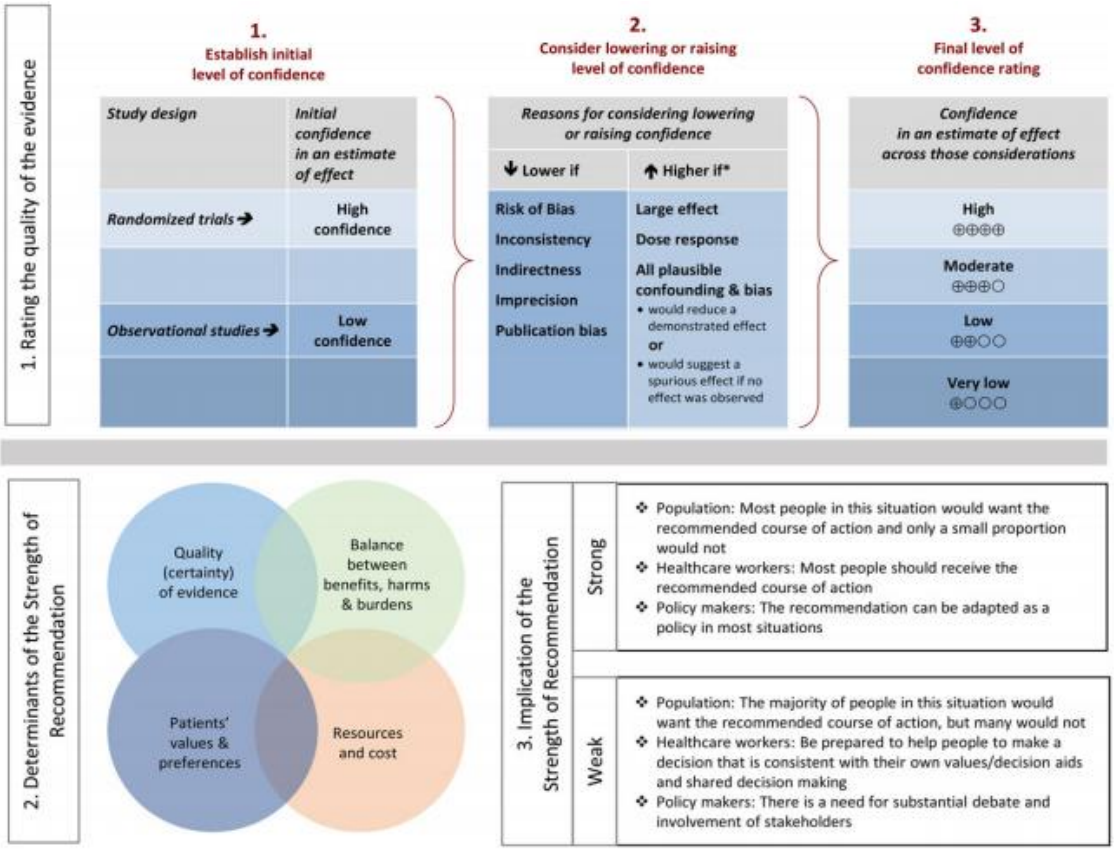

Figure 1 Approach and implications to rating the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology

Preparation of the guideline text was carried out by the guideline committee. After consultation with the members of these professional societies, the definitive guideline was drawn up by the delegates and approved by the board of SWAB.

4. Implementation

After final approval, the guideline and appendices are published through the SWAB website at (https://wwww.swab.nl/richtlijnen). The guideline committee intends to publish an executive summary in a peer reviewed journal. The new guideline forms the basis of the treatment recommendations in the online national antimicrobial guide (SWAB-ID) for the prophylaxis and treatment of infectious diseases in hospitals. SWAB-ID is updated at least twice yearly, incorporating all SWAB guideline recommendations. Every hospital in the Netherlands has been offered the opportunity to obtain a custom, localized version of SWAB-ID as a local or regional online antimicrobial guide. Updates of the national version of SWAB-ID, including new guidelines, are distributed to the localized SWAB-ID guides. The implementation of national and local SWAB-ID antimicrobial guidelines and adherence to the recommendations are secured by the national Antimicrobial Stewardship Program that has been established by SWAB, the Health Inspectorate (IGJ) and the Ministry of Health (VWS) since 2013. In each hospital, an Antimicrobial Stewardship

Team (A-team) is charged with implementation and monitoring of guidelines on a daily basis. ~~Adherence to guidelines and recommendations is reported to the SWAB National Stewardship Monitor.~~ SWAB will also notify antimicrobial stewardship teams (A-teams) of publication of the new guideline. The local A-teams or antibiotic committees can then implement the new guidelines into the local antimicrobial guides.

No significant barriers are expected in the implementation of this guideline. All antibiotic regimens recommended are part of the normal hospital formulary and hospitals regularly update their local antimicrobial guidelines after publication of a new SWAB guideline. ~~The recommendations given in this new guideline are mostly concordant with the already widely used 2015 ESC guidelines, which will facilitate acceptance and implementation~~. No additional funding is required to implement the recommendations in this guidelines.

5. General principles of antimicrobial treatment of infective endocarditis

Infective endocarditis is a heterogeneous disease that requires a multidisciplinary approach. A medical microbiologist and/or infectious disease specialist should always be consulted to determine the optimal treatment, and management discussions should preferably happen in an Endocarditis Team.

Infective endocarditis requires long term treatment with ~~intravenous~~ antibiotics. Traditionally, IV antibiotics for the full treatment duration was the norm, but this paradigm has shifted after publication of the landmark POET trial (15). This update reflects this paradigm change by incorporating oral treatment for selected patients with endocarditis Treatment duration is 6 weeks in most patients, but can be longer or shorter in selected patients, depending on the causative micro-organism, the duration of bacteraemia and result of valve cultures when available. Bacteraemia in endocarditis can last despite adequate treatment, and excised heart valves can harbour viable bacteria even after blood cultures have sterilized. Both the ESC and AHA guidelines recommend that treatment duration should be based on the first negative culture result and/or should start on the day of surgery in case valve culture is still positive. In clinical practice, if follow-up cultures are missing or are delayed when the patient is clinically improving, the last day of a positive blood culture may be a reasonable surrogate marker.

Treatment of prosthetic valve endocarditis differs in many, but not all cases from native valve endocarditis. Treatment for prosthetic valve endocarditis may be longer and can consist of multiple antimicrobial agents. whereof note, when the document states 'prosthetic valves', it refers to both bioprosthetic-valves and mechanical valves since bioprosthetic valves contain metal susceptible to biofilm formation just like mechanical prosthetic valves.

Whether patients who underwent valve surgery for native valve endocarditis should be treated postoperatively as native valve endocarditis or as prosthetic valve endocarditis after valve surgery is subject of debate. The ESC guidelines recommend continuing the regimen for native valve endocarditis, while the AHA guidelines are less strong in their recommendation and state that this may be considered. In the absence of evidence for one over the other, the guideline committee follows the ESC guidelines in this situation and recommends that in patients with native valve endocarditis treated with surgery the regimen for native valve endocarditis should be continued. A recent retrospective study supports the practice of using the regimen for native valve endocarditis in patients with *Staphylococcus aureus* endocarditis who undergo valve replacement (16). The exception to this recommendation being that in patients who undergo valve replacement but have persistent positive blood cultures after valve replacement should be considered at risk for developing endocarditis of the newly placed valvular prosthesis. In these patients the guideline committee is of the opinion that switching to a regimen for prosthetic valve endocarditis may be reasonable.

Many beta-lactam agents can be administered intermittently or by continuous infusion. There are no studies demonstrating that continuous infusion of beta-lactam agents leads to better clinical outcomes in patients with IE, but there is circumstantial evidence to suggest an advantage of continuous infusion. One study linked longer dosing intervals of penicillin in streptococcal endocarditis with an increased chance of treatment failure and a ~~recent~~ systematic review found continuous infusion of beta-lactam agents was associated with better pharmacodynamics and pharmacokinetic outcomes (17, 18). Additionally, continuous infusion allows for easier administration, creating an advantage for both health care providers and patients. Continuous infusion of a beta-lactam should always be preceded by a loading dose of the equivalent of one

intermittent dose (e.g: for continuous infusion of flucloxacillin iv 12000mg day, the loading dose should be 2000mg).

For vancomycin and gentamicin, dosing should always be performed based on therapeutic drug monitoring (TDM) based on local TDM guidelines and/or in consultation with a hospital pharmacist (19, 20).

Recommendation 1	**Strength of recommendation**	**Quality of evidence**
The day of blood culture sterilisation should be considered day 1 of adequate treatment.	Strong	Very low

Recommendation 2	**Strength of recommendation**	**Quality of evidence**
In patients who undergo valve surgery for endocarditis, day 1 of treatment is the day of blood culture sterilisation and not the day of surgery only when valve culture remains negative.	Strong	Very low

Recommendation 3	**Strength of recommendation**	**Quality of evidence**
If intra-operative cultures are positive, the day of surgery should be counted as day 1 of treatment.	Strong	Very low

Recommendation 4	**Strength of recommendation**	**Quality of evidence**
Patients with native valve endocarditis who undergo valve surgery, should stay on the treatment regimen for native valve endocarditis if intra-operative cultures are negative.	Weak	Very low

Recommendation 5	**Strength of recommendation**	**Quality of evidence**
If blood cultures remain positive after valve surgery in a patient with native valve endocarditis and a prosthetic valve has been placed or if intra-operative cultures are positive, a regimen for prosthetic valve endocarditis should be considered. ~~seems reasonable.~~	Weak	Very low

6. Allergies to first choice antibiotics and toxicity

The majority of patients with infective endocarditis can be treated with a beta-lactam antibiotic. In the general population, up to 10% of patients report a penicillin or beta-lactam allergy, in practice only a small proportion of these patients have a clinically significant allergy.

There are several ways to classify beta-lactam allergies: based on type of allergy (e.g.: IgE vs non-IgE mediated), severity, type of reaction, time of onset (e.g. acute vs delayed), and combinations of the aforementioned. Subsequently different management strategies exist. The guideline committee has decided to classify allergies as either non-severe or severe, allowing A-teams to adapt the guideline to the system currently in use in their hospital. In this guideline, non-severe penicillin allergy refers to cases that can be given a cephalosporin such as cefazolin or ceftriaxone, while severe beta-lactam allergy is meant for patients in whom a cephalosporin is not an option. For guidance on cross-reactivity between antibiotics we refer to the SWAB Guidelines on Approach to suspected Antibiotic Allergy (21). In patients with a severe allergy, consultation with an allergist or dermatologist is appropriate. In controlled settings a drug challenge or drug desensitization may be an option.

In general, it is preferable to use a beta-lactam antibiotic for two reasons: 1) the beta-lactam antibiotics are preferable over the other classes of antibiotics (e.g.: vancomycin) and 2) the alternative antibiotics are in general best held in reserve from an antimicrobial stewardship perspective.

7. Oral treatment of endocarditis

Endocarditis has traditionally been treated with IV antibiotics for the full course of treatment. Although small retrospective studies had shown that oral stepdown treatment may be feasible, the 2018 POET randomized clinical trial provided stronger evidence for oral treatment as a serious treatment option in patients with endocarditis (15). The 2023 version of the ESC guidelines have incorporated the results of the POET trial and provide options for oral stepdown treatment for all common microorganisms (7).

The SWAB guideline committee has carefully appraised the literature supporting oral stepdown treatment for endocarditis and agrees with the ESC guidelines that oral stepdown treatment may be feasible for select patients. Specifically, oral stepdown treatment is now recommended as an option, provided certain safety criteria are met, for patients with streptococcal endocarditis and for those with native valve endocarditis caused by *Enterococcus faecalis*. The literature appraisal and species-specific recommendations for oral stepdown therapy are detailed in the respective chapters for each microorganism.

For both streptococcal and native valve *E. faecalis* endocarditis, oral stepdown treatment can be considered if the following safety criteria are met:

- Local Endocarditis Team approves oral stepdown
- MIC criteria are met (see chapters on streptococcal and enterococcal IE)
- ≥10 days treatment with relevant IV antibiotics and (if applicable) ≥ 7 days after valves surgery
- Satisfying response to treatment: no fever >2 days, CRP <25% of max measured value or <20 mg/L and leukocytes <15 x 109/L
- No other indication for continued IV antibiotics
- No BMI >40 or decreased gastrointestinal uptake

- No evidence of new indication for surgery on repeated imaging within two days of IV to oral switch. For native valves a good quality TTE can suffice, for prosthetic valves a TOE or good quality TTE combined with cardiac CT is recommended

The above criteria are adapted from the POET trial and the 2023 ESC guidelines (7, 15). A notable difference is that the guideline committee believes a good quality TTE can replace the need for a repeat TEE before switching to oral stepdown treatment. In patients with prosthetic valves or with aortic valve endocarditis with possible involvement of the aortic root, cardiac CT may be a reasonable alternative to TEE to rule out abscesses, but can of course not be used for functional evaluation of the involved valve.

~~Shortly before the finalization of this guideline, a randomized controlled trial on the partial oral treatment of infective endocarditis was published (22) . This trial of 400 patients with left sided IE caused by streptococci, staphylococci and enterococci found that consolidation therapy with a combination of oral antibiotics was non-inferior to continued intravenous therapy. Patient selection was strict and patients were treated with a median of 17 days of intravenous therapy before randomization occurred. The results are mainly carried by native valve endocarditis caused by streptococci, and subgroups of specific but vulnerable patient groups were very small (e.g. only 7 patients with *S. aureus* prosthetic valve endocarditis received oral antibiotics). The guideline committee is of the opinion that this trial is very interesting but insufficient proof to widely alter clinical practice. Based on current evidence and experience, partial oral treatment should be restricted to patients with native valve streptococcal endocarditis in whom the disadvantages of prolonged intravenous therapy outweigh the potential risk of insufficiently treating the endocarditis. Also, partial oral treatment should preferably happen in a research setting.~~

8. Empirical therapy

Empirical therapy for endocarditis should cover the most likely causative agents for endocarditis. Clinically, there are several important distinctions that can help decide the most appropriate empirical therapy. Native valve and prosthetic valve endocarditis share the common causative agents: streptococci, *S. aureus*, ~~enterococci~~ *Enterococcus faecalis* and HACEK (*Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella*) group bacteria, while prosthetic valve endocarditis can also be caused by coagulase negative staphylococci and *Cutibacterium* spp. A second distinction can be made by either acute or subacute presentation. Acute endocarditis is often due to *Staphylococcus aureus* or non-viridans group streptococci, while a subacute course of protracted, intermittent, fever and general malaise (endocarditis lenta) is more often the result of viridans streptococci, enterococci and HACEK bacteria.

The ESC and AHA give different recommendations for empirical therapy: the ESC provides clear antibiotic regimens, while the AHA only advises which microorganisms should be covered by empirical therapy but refrains from pre-defined treatment schedules. The pathogens described by the AHA are covered by the ESC treatment regimens. Of note, the ESC does not make a distinction based on symptom duration, and differentiates between native valve IE, early and late prosthetic valve endocarditis and place of acquisition (hospital acquired versus community acquired, or healthcare associated).

The guideline committee prefers the ESC approach of providing specific treatment regimens, but also underscores the significance of symptom duration in the choice of empirical therapy. For this reason the guideline committee has decided to propose new regimens for empirical therapy.

It is vital that multiple blood cultures have been collected before the start of empirical therapy.

The guideline committee sees little benefit in delaying empirical treatment in patients with a high suspicion of infective endocarditis, but recognizes that in patients with a low index of suspicion, waiting for the results of blood culture may be prudent.

For subacute native valve endocarditis, the most common microorganisms are streptococci, enterococci and the HACEK group bacteria. In rare cases, *S. aureus* is also able to present with a more subacute presentation. Amoxicillin combined with high dosed ceftriaxone provides adequate coverage for these bacteria. In patients with a non-severe allergy to penicillin, a combination of vancomycin for enterococci and staphylococci and ceftriaxone for streptococci and HACEK bacteria covers most microorganisms. In patients unable to tolerate cephalosporins, vancomycin monotherapy is an option, but consultation with a medical microbiologist and/or infectious disease specialist is advised.

Acute native valve endocarditis or endocarditis associated with IV drug use is most often caused by *S. aureus*, followed by streptococci. Flucloxacillin provides the best coverage against *S. aureus* while also providing adequate treatment for streptococci and therefore is the drug of choice in these patients. Cefazolin and vancomycin are the alternatives in patients with allergies. In rare cases, endocarditis in patients who inject drugs is caused by Gram-negative bacteria, these are not covered in this empiric regimen.

The spectrum of bacteria causing prosthetic valve endocarditis includes the causes of native valve endocarditis, but also includes coagulase negative staphylococci (CNS) and more rarely *Cutibacterium spp* and these should be covered in the empirical therapy of prosthetic valve endocarditis. Optimal *S. aureus* coverage with flucloxacillin is preferable since this the most virulent microorganism and treatment of methicillin susceptible *S. aureus* bacteraemia with vancomycin is associated with a worse outcome. A combination of vancomycin and flucloxacillin covers all common causative agents apart from the HACEK group. In patients with a non-severe penicillin allergy, flucloxacillin may be substituted by cefazolin, while in patients with a severe beta-lactam allergy, vancomycin monotherapy is preferred.

The guideline committee has chosen empirical regimens without gentamicin, because gentamicin is rarely indicated as definite treatment. Adding it to empirical therapy would expose many patients to a potentially toxic and unnecessary agent.

These recommendations are based on national antimicrobial susceptibility patterns for the most prevalent bacteria. It is notable that French and German national guidelines for empiric treatment of native valve endocarditis recommend amoxicillin combined with cefazolin instead of amoxicillin combined with ceftriaxone. (23) The SWAB guideline prefers ceftriaxone as the second drug since in the empirical situation endocarditis is often one of several diagnoses considered, which warrants the broader antimicrobial spectrum provided by ceftriaxone over the (theoretical) better activity of cefazolin against *S. aureus*.

Causative agent: empirical therapy
Setting: native valve, subacute presentation

Recommendation 6	**Strength of recommendation**	**Quality of evidence**

Amoxicillin ~~12g~~ 12000mg/day in 6 doses or by continuous infusion + Ceftriaxone 2dd2gr in 2 doses	Weak	Very low

Causative agent: empirical therapy
Setting: native valve, subacute presentation, non-severe penicillin allergy

Recommendation 7	**Strength of recommendation**	**Quality of evidence**
~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels of 15-20mg/l) or by continuous infusion (serum concentration 20-25mg/l)~~ Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist + Ceftriaxone iv ~~2g~~ 2000mg/day in 1 dose	Weak	Very low

Causative agent: empirical therapy
Setting: native valve, subacute presentation, severe beta-lactam allergy

Recommendation 8	**Strength of recommendation**	**Quality of evidence**
~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels of 15-20mg/l) or by continuous infusion (serum concentration 20-25mg/l)~~ Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist	Weak	Very low

Causative agent: empirical therapy

Setting: native valve, acute presentation or IV drug use

Recommendation 9	Strength of recommendation	Quality of evidence
Flucloxacillin iv ~~12g~~ 12000mg/day in 6 doses or by continuous infusion	Weak	Very low

Causative agent: empirical therapy
Setting: native valve, acute presentation or IV drug use, non-severe penicillin allergy

Recommendation 10	Strength of recommendation	Quality of evidence
Cefazolin iv ~~6g~~ 6000mg/day in 3 doses or by continuous infusion	Weak	Very low

Causative agent: empirical therapy
Setting: native valve, acute presentation, severe beta-lactam allergy

Recommendation 11	Strength of recommendation	Quality of evidence
~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels of 15-20mg/l) or by continuous infusion (serum concentration 20-25mg/l)~~ Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist	Weak	Very low

Causative agent: empirical therapy
Setting: Prosthetic valve

Recommendation 12	Strength of recommendation	Quality of evidence
~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels of 15-20mg/l) or by continuous infusion (serum concentration 20-25mg/l)~~ Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses)	Weak	Very low

Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist + Flucloxacillin iv ~~12g~~ 12000mg/day in 6 doses or by continuous infusion		

9. Treatment of endocarditis caused by streptococci

Streptococci are among the most common causative agents of endocarditis. Streptococci are classified in several different ways, based on the haemolytic pattern on blood-agar plates and the presence of Lancefield-antigens. The most important streptococcal agents of endocarditis are the viridans streptococci, a group of streptococci part of the normal human oral microbiome. Apart from viridans group streptococci and the related *S. gallolyticus* (formerly *S. bovis*), endocarditis can also be caused by pneumococci and β-haemolytic streptococci. In the Netherlands, streptococci are almost always susceptible to penicillin (Minimal Inhibitory Concentration [MIC] ≤0.250 ~~125~~ mg/l) (24). Penicillin- intermediate resistant streptococci (MIC >0.250 ~~2~~ 1 mg/l) can still be treated with penicillin, but require a higher dose of penicillin and the addition of gentamicin. Penicillin resistant streptococci (MIC >1 ~~2~~ mg/l) are rare in the Netherlands and should be treated with vancomycin.

The ESC and AHA guidelines differ on four points on the treatment of streptococcal endocarditis, the most important difference being when to consider an isolate less susceptible to penicillin and what penicillin dosage to use in these cases. The guideline committee decided to follow the ESC guidelines when considering an isolate penicillin- intermediate resistant. Due to concerns of toxicity when using very high doses of penicillin and the lack of clinical studies demonstrating the effect of very high doses, the guideline committee advises a maximum dose of 18 million units of penicillin per day (the ESC and AHA use a maximum penicillin dose of 24 million units per day).

In general, native valve endocarditis caused by viridans streptococci can be treated with 4 weeks of beta-lactam monotherapy. In selected patients 2 weeks of combination therapy with a beta-lactam and gentamicin can be used. Two week treatment should only be attempted in patients with uncomplicated native valve endocarditis, as defined by the following criteria (3, 25, 26):

1. MIC penicillin ≤0.25 ~~125~~ mg/l,
2. no contraindications or high resistance against aminoglycosides,
3. no cardiac complications such as heart failure, aortal insufficiency or disturbed conductance,
4. no thromboembolic complications,
5. native valve,
6. no vegetations >5 mm,
7. clinical response within seven days,
8. the current episode of endocarditis is not a relapse

Prosthetic valve endocarditis requires 6 weeks of treatment. The addition of gentamicin is only advised in cases of decreased penicillin susceptibility.

The ESC and AHA guidelines also differ on the addition of gentamicin in patients with prosthetic valve endocarditis caused by streptococci. The ESC advises treatment only with penicillin, while the AHA states that adding two weeks of gentamicin should be considered (IIb recommendation). The literature cited in both guidelines does not support either of these recommendations and a review of literature published since has not resulted in new information. Considering the potentially significant toxicity of gentamicin, the guideline committee does not advise ~~routinely~~ adding gentamicin in patients with streptococcal prosthetic valve IE, thus following the ESC guideline.

If vancomycin is used in treating penicillin intermediate resistant streptococci, the ESC guidelines advise adding gentamicin for two weeks, as would be done when using a beta-lactam antibiotic. The AHA guidelines do not advise adding gentamicin to vancomycin in this scenario. The literature cited in both guidelines does not support either of these recommendations and a review of literature

published since has not resulted in new information. As stated before, taking in to account the potential toxicity of gentamicin and the lack of evidence or rationale for its addition here, the guideline committee does not advise adding gentamicin to vancomycin when treating penicillin intermediately susceptible streptococci.

For endocarditis caused by *Streptococcus pneumoniae*, both guidelines advise treatment to be the same as treatment for viridans streptococci, while the ESC warns that the two week regimen is not validated for *S. pneumoniae*. The guideline committee agrees with the ESC.

Endocarditis caused by β-haemolytic streptococci, such as *S. agalactiae*, *S. dysgalactiae* and *S. pyogenes*, is a rare entity and the treatment advice from both guidelines is based on case series and retrospective cohorts. There is a discrepancy between the two guidelines with regards to the addition of gentamicin to beta-lactam therapy. The ESC only recommends adding 2 weeks of gentamicin for endocarditis caused by *S. agalactiae* (group B streptococcus) prosthetic valve IE, while the AHA recommends it for group B, C and G endocarditis in all cases. Literature on this subject is scarce, and the AHA recommendations appear mainly based on older case series(27, 28), one of which shows a survival benefit from combination therapy. Two later retrospective cohorts (30 and 49 patients) demonstrate no benefit from adding an aminoglycoside (29, 30). All studies in this field are severely limited by their retrospective designs and possible confounding by indication. The guideline committee concludes that there is no data to support adding gentamicin to standard therapy in endocarditis caused by β-haemolytic streptococci but no data to recommend against it either, and addition should be up to the discretion of the endocarditis team If gentamicin is added, careful consideration needs to be paid to renal and cochlear function and treatment should be discontinued if signs of toxicity occur.

For both the 2023 ESC guidelines and the 2025 update of the SWAB guidelines, the MIC breakpoints for penicillin sensitivity have been changed to conform with the 2025 EUCAST guidance document on clinical breakpoints for streptococci. In practice, this means that viridans group streptococci with a penicillin MIC of ≤0.25mg/l are considered susceptible to penicillin and can be treated with penicillin monotherapy, while streptococci with a penicillin MIC of >0.25 – 1 can be treated with penicillin combined with gentamicin. For streptococci with a penicillin MIC >1, vancomycin is the preferred antibiotic treatment.

For pneumococci, the EUCAST breakpoint for susceptible has been lowered to ≤0.06mg/L, the SWAB guideline committee has decided in collaboration with the CRG (committee on antimicrobial susceptibility of the SWAB) to follow EUCAST here and recommend penicillin for endocarditis caused by *S. pneumoniae* only in isolates with a penicillin MIC of ≤0.06mg/L.

Oral stepdown treatment for streptococcal endocarditis

Before publication of the POET trial, smaller studies had demonstrated that oral stepdown treatment for streptococcal endocarditis could be an alternative to continued IV treatment (31). Within the POET trial, 196 patients with streptococcal endocarditis were randomized, 24% of whom had a prosthetic valve. Although underpowered to demonstrate non-inferiority of oral stepdown treatment for the streptococcal endocarditis, this trial provided strong evidence that oral stepdown treatment could be safe in this population. Since the POET trial, two cohort studies have provided additional support for oral treatment. One retrospective study from France included 170 patients with streptococcal endocarditis of whom 91 (54%) received oral stepdown treatment after a median of 14 days IV treatment and found no differences in mortality in multivariate analysis for all microorganisms combined, but did not perform a species specific analysis (32). The POETry registry

from Denmark was a prospective cohort after implantation of the POET trial protocol and included another 232 non-randomized patients with streptococcal endocarditis, again showing no excess mortality (33).

Based on the absolute number in both randomized trils and cohort studies with adequate design and follow-up, the SWAB guideline committee considers oral stepdown treatment for streptococcal endocarditis a safe alternative to continued IV treatment. This recommendation applies to both native and prosthetic valve endocarditis by streptococci, although the evidence base for prosthetic valve endocarditis is lower than for native valve endocarditis due to lower absolute number of patients with prosthetic valve endocarditis treated. Since the majority of patients included in previous studies had endocarditis caused by viridans group streptococci or *S. gallolyticus*, the recommendation for oral stepdown treatment is applicable only to these streptococci (and for example, not for beta-hemolytic streptococci).

For oral regimens, the ESC guidelines recommend combination treatment with two from different classes of active antibiotics, based on the regimens used in the POET trial (7, 15). The rationale for using two antibiotics in the POET trial was to reduce the risk of effective monotherapy (15). However, the regimens used for streptococci do not show synergism in vitro, and the plasma concentrations of amoxicillin measured in patients included in the POET trial exceeded the PK/PD target of >50% fT>MIC for all patients (34). Additionally, retrospective studies with amoxicillin monotherapy also demonstrate good results (31, 32). Therefore, the guideline committee recommends amoxicillin monotherapy for oral stepdown treatment of streptococcal endocarditis.

For amoxicillin dosing, we recommend the regimen used in the POET trial of amoxicillin 1gr four times per day, as this has been shown to provide plasma amoxicillin concentrations needed to attain the desired PK/PD targets (34, 35). Although amoxicillin absorption may reach saturation at doses above 750mg three times per day, and hence the advised dosage may be higher than necessary, the guideline committee prefers the clinically proven regimen used by the POET trial, noting that treatment discontinuation due to side-effects was very rare in this study (15, 36, 37).

Causative agent: Viridans group streptococci, including *S. gallolyticus*, penicillin MIC ≤~~0.125~~ 0.25 mg/l
Setting: native valve

Recommendation 13	**Strength of recommendation**	**Quality of evidence**
Penicillin iv 12 million units/day in 6 doses or by continuous infusion for 4 weeks	strong	moderate
~~Routinely adding gentamicin to the treatment of streptococcal IE is not advised~~	~~strong~~	~~moderate~~

Causative agent: Viridans group streptococci including *S. gallolyticus*, penicillin MIC ~~≤0.125~~ 0.25 mg/l
Setting: native valve, non-severe penicillin allergy

Recommendation 14	**Strength of recommendation**	**Quality of evidence**
Ceftriaxone iv ~~2g~~ 2000mg/day in one dose for 4 weeks	strong	moderate
~~Routinely adding gentamicin to the treatment of streptococcal IE is not advised~~	~~strong~~	~~moderate~~

Causative agent: Viridans group streptococci including *S. gallolyticus*, penicillin MIC ~~≤0.125~~ 0.25 mg/l
Setting: native valve – 2 week treatment (only in uncomplicated IE, see main text)

Recommendation 15	**Strength of recommendation**	**Quality of evidence**
Penicillin iv 12 million units/day in 6 doses or by continuous infusion for 2 weeks + Gentamicin 3mg/kg/day in 1 dose for 2 weeks. Perform therapeutic drug monitoring when using gentamicin.	strong	moderate

Causative agent: Viridans group streptococci including *S. gallolyticus*, penicillin MIC ~~≤0.125~~ 0.25 mg/l
Setting: native valve – 2 week treatment, non-severe penicillin allergy (only in uncomplicated IE, see main text)

Recommendation 16	**Strength of recommendation**	**Quality of evidence**
Ceftriaxone iv ~~2g~~ 2000mg/day in one dose for 2 weeks + Gentamicin iv 3mg/kg/day in 1 dose for 2 weeks. Perform therapeutic drug monitoring when using gentamicin.	strong	moderate

Causative agent: Viridans group streptococci including *S. gallolyticus*, penicillin MIC ~~≤0.125~~ 0.25
Setting: native valve, severe beta-lactam allergy

Recommendation 17	**Strength of recommendation**	**Quality of evidence**
Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses)	strong	low

Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels 15-20mg/l) or by continuous infusion (plateau concentration 20-25mg/l)~~ for 4 weeks		
Gentamicin not recommended if vancomycin is used	strong	low

Causative agent: Viridans group streptococci including *S. gallolyticus*, penicillin MIC >0.250 – 1 ~~2~~ mg/l
Setting: native valve

Recommendation 18	**Strength of recommendation**	**Quality of evidence**
Penicillin iv 18 million units/day in 6 doses or by continuous infusion for 4 weeks + Gentamicin iv 3mg/kg/day in 1 dose for 2 weeks. Perform therapeutic drug monitoring when using gentamicin.	strong	moderate

Causative agent: Viridans group streptococci including *S. gallolyticus*, penicillin MIC >0.250 – 1 ~~2~~ mg/l
Setting: native valve, non-severe penicillin allergy

Recommendation 19	**Strength of recommendation**	**Quality of evidence**
Ceftriaxone iv ~~2g 2g~~ 2000mg/day in one dose for 4 weeks + Gentamicin iv 3mg/kg/day in 1 dose for 2 weeks. Perform therapeutic drug monitoring when using gentamicin.	strong	moderate

Causative agent: Viridans group streptococci including *S. gallolyticus*, penicillin MIC >0.250 – 1 ~~2~~ mg/l
Setting: native valve, severe beta-lactam allergy

Recommendation 20	**Strength of recommendation**	**Quality of evidence**
Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels 15-20mg/l) or by continuous infusion (plateau concentration 20-25mg/l)~~ for 4 weeks	strong	moderate
Gentamicin not recommended if vancomycin is used	strong	low

Causative agent: Viridans group streptococci including *S. gallolyticus*, penicillin MIC ≤~~0.125~~ 0.25mg/l
Setting: prosthetic valve

Recommendation 21	**Strength of recommendation**	**Quality of evidence**
Penicillin iv 12 million units/day in 6 doses or by continuous infusion for 6 weeks	strong	moderate
~~Routinely adding gentamicin to the treatment of streptococcal IE is not advised~~	~~strong~~	~~moderate~~

Causative agent: Viridans group streptococci including *S. gallolyticus*, penicillin MIC ≤~~0.125~~ 0.25
Setting: prosthetic valve, non-severe penicillin allergy

Recommendation 22	Strength of recommendation	Quality of evidence
Ceftriaxone iv ~~2g 2g~~ 2000mg/day in one dose for 6 weeks	strong	moderate
~~Routinely adding gentamicin to the treatment of streptococcal IE is not advised~~	~~strong~~	~~moderate~~

Causative agent: Viridans group streptococci including *S. gallolyticus*, penicillin MIC ~~≤0.125~~ 0.25
Setting: prosthetic valve, severe beta-lactam allergy

Recommendation 23	Strength of recommendation	Quality of evidence
Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels 15-20mg/l) or by continuous infusion (plateau concentration 20-25mg/l)~~ for 6 weeks	strong	moderate
Gentamicin not recommended if vancomycin is used	strong	low

Causative agent: Viridans group streptococci including *S. gallolyticus*, penicillin MIC >0.250 – 1 ~~2~~
Setting: prosthetic valve

Recommendation 24	Strength of recommendation	Quality of evidence
Penicillin iv 18 million units/day in 6 doses or by continuous infusion for 6 weeks + Gentamicin iv 3mg/kg/day in 1 dose for 2 weeks. Perform therapeutic drug monitoring when using gentamicin.	strong	moderate

Causative agent: Viridans group streptococci and *S. gallolyticus*, penicillin MIC >0.250 – 1 ~~2~~
Setting: prosthetic valve, non-severe penicillin allergy

Recommendation 25	**Strength of recommendation**	**Quality of evidence**
Ceftriaxone iv ~~2g~~ 2000mg/day in one dose for 6 weeks + Gentamicin iv 3mg/kg/day in 1 dose for 2 weeks. Perform therapeutic drug monitoring when using gentamicin.	strong	moderate

Causative agent: Viridans group streptococci and *S. gallolyticus*, penicillin MIC >0.250 – 1 ~~2~~
Setting: prosthetic valve, severe beta-lactam allergy

Recommendation 26	**Strength of recommendation**	**Quality of evidence**
Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels 15-20mg/l) or by continuous infusion (plateau concentration 20-25mg/l)~~ for 6 weeks	strong	moderate
Gentamicin not recommended if vancomycin is used	strong	low

Causative agent: Viridans group streptococci and *S. gallolyticus*, penicillin MIC >1 ~~2~~ mg/l
Setting: native valve or prosthetic valve

Recommendation 27	**Strength of recommendation**	**Quality of evidence**
Depending on susceptibility, vancomycin or ceftriaxone may be an option. Decide the optimal treatment regimen in consultation with a medical microbiologist or infectious disease specialist or with an endocarditis team.	strong	Not applicable

Causative agent: *Streptococcus pneumoniae, penicillin MIC ≤0.06*
Setting: native valve or prosthetic valve

Recommendation 28	**Strength of recommendation**	**Quality of evidence**
Treatment guidelines for viridans group streptococci can be used. The two week schedule is not applicable.	strong	low

Causative agent: *Streptococcus pneumoniae, penicillin MIC >0.06*
Setting: native valve or prosthetic valve

Recommendation 29	**Strength of recommendation**	**Quality of evidence**
Treat with either ceftriaxone or vancomycin based on susceptibility testing. Decide the optimal treatment regimen in consultation with a medical microbiologist or infectious disease specialist or in an endocarditis team.	strong	low

Causative agent: β-haemolytic streptococci (e.g. *S. agalactiae*, *S. dysgalactiae*)
Setting: native valve or prosthetic valve

Recommendation 30	**Strength of recommendation**	**Quality of evidence**
Treatment guidelines for viridans group streptococci can be used. The two week schedule is not applicable.	strong	low
Addition of 2 weeks of gentamicin 3mg/kg/day in 1 dose may be considered. Treatment should be discontinued if signs of toxicity occur.	weak	low

Causative agent: Viridans group streptococci including *S. gallolyticus*, penicillin MIC ≤0.25mg/l
Setting: native valve

Recommendation 31	**Strength of recommendation**	**Quality of evidence**
Consider oral stepdown treatment if the patient meets criteria for IV-oral switch (see chapter on oral treatment)	Weak	Moderate
Oral stepdown treatment consists of amoxicillin 1gr four times per day	Weak	Moderate

Causative agent: Viridans group streptococci including *S. gallolyticus*, penicillin MIC ≤0.25mg/l
Setting: prosthetic valve

Recommendation 32	**Strength of recommendation**	**Quality of evidence**
Consider oral stepdown treatment if the patient meets criteria for IV-oral switch (see chapter on oral treatment)	Weak	Low
Oral stepdown treatment consists of amoxicillin 1gr four times per day	Weak	Low

10. Treatment of endocarditis caused by staphylococci

S. aureus is currently the most frequent cause of endocarditis and is associated with high morbidity and mortality. Endocarditis caused by coagulase-negative staphylococci (CNS) is rare and mainly occurs on prosthetic material. In the Netherlands, *S. aureus* is generally methicillin susceptible, in contrast with methicillin resistance in CNS. Historically, gentamicin was added to *S. aureus* native valve endocarditis as a synergetic agent based on in vitro studies and clinical observations of reduction of duration of bacteraemia. However, adjunctive gentamicin in native valve *S. aureus* endocarditis does not result in better clinical outcomes but does lead to an increased incidence of kidney injury (38, 39). Therefore, routine administration of gentamicin in staphylococcal native valve endocarditis is no longer recommended.

The recommendations for treatment of staphylococcal endocarditis differ slightly between the ESC and AHA guidelines. The ESC recommends 4 to 6 weeks of treatment for native valve endocarditis by staphylococci, while the AHA recommends 6 weeks for all patients. Based on current Dutch practices in the treatment of complicated *Staphylococcus aureus* bacteraemia, the guideline committee decides to recommend a 6 week regimen in all cases. Both the ESC and AHA recommend (flu)cloxacillin dosed at 12 grams per 24 hours, divided in 4-6 equal doses. The guideline committee has added continuous infusion of 12 grams per day as an alternative, noting that continuous infusion has potential pharmacokinetic advantages and is often easier to administer.

There is a growing body of evidence indicating that cefazolin may be preferable to flucloxacillin for treatment of *Staphylococcus aureus* bacteraemia (including endocarditis), due to a lower incidence of kidney injury(40) . Indeed, the 2023 ESC guidelines present cefazolin as an alternative option next to flucloxacillin for treatment of methicillin susceptible staphylococcal endocarditis. In the absence of randomized data however, the guideline committee keeps the recommendation of flucloxacillin as first choice treatment, but stresses that cefazolin is an excellent alternative in patients with (high risk of) kidney injury or with decreased renal function.

The ESC guidelines advise an alternative, partially oral, regimen for staphylococcal endocarditis using clindamycin and cotrimoxazole. This recommendation is based on one non-randomized study in 31 patients published in a letter to the editor (41). The guideline committee does not include this treatment option in this guideline, since it lacks the required standard of evidence to be considered. A supportive argument to not include this regimen is a study that showed cotrimoxazole to be inferior to vancomycin in patients with MRSA bacteraemia (42).

The ESC en AHA guidelines both recommend daptomycin as an alternative to vancomycin in patients with staphylococcal endocarditis. However, daptomycin dosing differs; the ESC guidelines advise daptomycin 10mg/kg/day and the AHA ≥8mg/kg/day. The guideline committee has decided to follow the ESC guidelines and use 10mg/kg as the standard dosing regimen for daptomycin. The 2023 ESC guidelines further recommend combining daptomycin with a second agent. Rationale for this recommendation appears to be the prevention of antimicrobial resistance development under daptomycin therapy. A review of literature by the guideline committee revealed very limited evidence that daptomycin combined with a second agent leads to better outcomes than daptomycin monotherapy. The clinical studies that do exist are of low quality or have low precision for patients with endocarditis (43, 44). Therefore, the guideline committee does not recommend standard combination therapy when daptomycin is given for staphylococcal endocarditis. However, in cases with persistent bacteraemia under daptomycin monotherapy, adding a second agent to daptomycin may be considered, in accordance with the recommendation in the ESC guideline. Based on the very

limited available evidence, the best agents appears to be intravenous fosfomycin dosed at 12000 mg/day or ceftaroline 1800mg/day (44-46).

The AHA additionally recommends ciprofloxacin as an alternative for gentamicin in the case of prosthetic valve endocarditis caused by gentamicin resistant staphylococci. This advice is based on a single in vitro study but has no human data(47) . The guideline committee has decided not to include this recommendation.

Both the AHA and ESC state that rifampicin is an important adjunctive in the treatment of infected prosthetic material by staphylococci, despite acknowledging that the evidence for its benefit is limited. Rifampicin is thought to have a better penetration into vegetations and is active against bacteria in planktonic state, as seen in vegetations. Since publication of the 2019 SWAB guidelines, a systematic review and retrospective cohort study have questioned the efficacy of the addition of gentamicin and rifampicin in patients with staphylococcal prosthetic valve endocarditis (48, 49). To reflect this growing uncertainty, the guideline committee has decided to lower the strength of recommendation (from strong to weak) and level of evidence (from moderate to low) for the addition of these agents in patients with staphylococcal prosthetic valve endocarditis. The guideline committee recognizes that evidence for both rifampicin and gentamicin in staphylococcal prosthetic valve endocarditis is limited, but decided not to deviate from the ESC and AHA guidelines, which are in agreement on this subject.

There are no studies examining the appropriate dosing of rifampicin in patients with endocarditis. The 2019 version of the SWAB guideline followed the 2015 ESC guidelines with a dosing schedule of 1200mg in 2-3 doses per day. The 2023 version of the ESC guidelines has lowered the recommended dosage of rifampicin to 900mg taken in 3 doses per day, which is in line with the AHA guidelines. With no evidence to support either dosing schedule, the guideline committee follows the ESC in now recommending the lower rifampicin dosage to 900mg/day, but recommends dosing 450mg twice daily over 300mg thrice daily for of ease of use. ~~The AHA recommends dosing rifampicin three times daily to a total daily dose of 900mg, while the ESC recommends 900-1200mg over 2-3 doses per day. Rifampicin efficacy is likely concentration dependent and side effects do not seem more common after higher doses(50, 51). Therefore, the guideline committee advises dosing rifampicin at 1200mg in 2 doses. If side-effects or toxicity occur, a lower dose may be attempted.~~ Since resistance to rifampicin is thought to develop quickly, both guidelines recommend adding rifampicin only after a 3-5 days of therapy or after bacteraemia has been cleared.

The ESC guidelines advise to give gentamicin in a single dose, while the AHA guidelines recommend dividing the total daily dose over 2-3 separate gifts. Based on national standard practices and the lack of convincing clinical evidence for a multiple daily dosing regimen, the guideline committee recommends giving gentamicin as a single dose (48, 49) In staphylococci resistant to either gentamicin or rifampicin, adding this agent to the treatment regimen is ~~unnecessary~~ not recommended.

Oral stepdown treatment of staphylococcal endocarditis

For staphylococcal endocarditis, the evidence base for oral stepdown treatment is scarcer than for streptococcal endocarditis. Retrospective studies from before the POET trial mainly involved patients with right sided endocarditis associated with IV-drug use (31, 52). In the POET trial, 110 patients with staphylococcal endocarditis were randomized, with only 7 patients with staphylococcal prosthetic valve were included (15). Retrospective studies published after the POET trial, however positive,

also provide low quality evidence for the safety of oral stepdown treatment in staphylococcal endocarditis (32, 33, 53). Also, staphylococcal endocarditis is associated with higher mortality than endocarditis caused by other microorganisms (54). Therefore, the guideline committee advises against routine oral stepdown treatment for staphylococcal endocarditis.

Causative agent: *Staphylococcus aureus* or CNS, methicillin sensitive
Setting: native valve

Recommendation 33	**Strength of recommendation**	**Quality of evidence**
Flucloxacillin iv ~~12g~~ 12000mg/day in 6 doses or by continuous infusion for 6 weeks#	strong	moderate
Routinely adding gentamicin to the treatment of staphylococcal native valve endocarditis is not advised	strong	low

cefazolin iv ~~6g~~ 6000mg/day in 3 doses or by continuous infusion is an alternative in patients with decreased renal function or acute kidney injury

Causative agent: *Staphylococcus aureus* or CNS, methicillin sensitive
Setting: native valve, non-severe penicillin allergy

Recommendation 34	**Strength of recommendation**	**Quality of evidence**
Cefazolin iv ~~6g~~ 6000mg/day in 3 doses or by continuous infusion for 6 weeks	strong	moderate
Routinely adding gentamicin to the treatment of staphylococcal native valve endocarditis is not advised	strong	low

Causative agent: *Staphylococcus aureus* or CNS, methicillin sensitive
Setting: native valve, severe beta-lactam allergy

Recommendation 35	**Strength of recommendation**	**Quality of evidence**
Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels 15-20mg/l) or by continuous infusion (plateau concentration 20-25mg/l)~~ for 6 weeks	strong	moderate

Causative agent: *Staphylococcus aureus* or CNS, methicillin sensitive
Setting: prosthetic valve

Recommendation 36	**Strength of recommendation**	**Quality of evidence**
Flucloxacillin iv ~~12g~~ 12000mg/day in 6 doses or by continuous infusion for 6 weeks# + Rifampicin iv or po ~~1200~~ 900 mg/day in 2 doses for 6 weeks$ + Gentamicin iv 3mg/kg/day in 1 dose for 2 weeks. Perform therapeutic drug monitoring when using gentamicin. *	~~strong~~ weak	~~moderate~~ low

cefazolin iv ~~6g~~ 6000mg/day in 3 doses or by continuous infusion is an alternative in patients with decreased renal function or acute kidney injury

$ Rifampicin should be added after bacteraemia has been cleared

* Gentamicin should be discontinued if signs of toxicity occur.

Causative agent: *Staphylococcus aureus* or CNS, methicillin sensitive
Setting: prosthetic valve, non-severe penicillin allergy

Recommendation 37	**Strength of recommendation**	**Quality of evidence**
Cefazoli iv n ~~6g~~ 6000mg/day in 3 doses or by continuous infusion for 6 weeks + Rifampicin iv or po 900mg~~1200~~ day in 2 doses for 6 weeks$ + Gentamicin iv 3mg/kg/day in 1 dose for 2 weeks. Perform therapeutic drug monitoring when using gentamicin. *	~~strong~~ weak	~~moderate~~ low

$ Rifampicin should be added after bacteraemia has been cleared

* Gentamicin should be discontinued if signs of toxicity occur.

Causative agent: *Staphylococcus aureus* or CNS, methicillin sensitive
Setting: prosthetic valve, severe beta-lactam allergy

Recommendation 38	**Strength of recommendation**	**Quality of evidence**
Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels 15-20mg/l) or by continuous infusion (plateau concentration 20-25mg/l)~~ for 6 weeks + Rifampicin iv of po 900mg ~~1200~~ day in 2 doses for 6 weeks$ + Gentamicin iv 3mg/kg/day in 1 dose for 2 weeks. Perform therapeutic drug monitoring when using gentamicin. *	~~strong~~ weak	~~moderate~~ low

$ Rifampicin should be added after bacteraemia has been cleared
* Gentamicin should be discontinued if signs of toxicity occur.

Causative agent: *Staphylococcus aureus* or CNS, methicillin resistant
Setting: native valve

Recommendation 39	**Strength of recommendation**	**Quality of evidence**
Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels 15-20mg/l) or by continuous infusion (plateau concentration 20-25mg/l)~~ for 6 weeks	strong	moderate

Causative agent: *Staphylococcus aureus* or CNS, methicillin resistant
Setting: prosthetic valve

Recommendation 40	**Strength of recommendation**	**Quality of evidence**
Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels 15-20mg/l) or by continuous infusion (plateau concentration 20-25mg/l)~~ for 6 weeks+ Rifampicin iv or po 900mg ~~1200~~ day in 2 doses for 6 weeks$ + Gentamicin iv 3mg/kg/day in 1 dose for 2 weeks. Perform therapeutic drug monitoring when using gentamicin. *	~~strong~~ weak	~~moderate~~ low

$ Rifampicin should be added after bacteraemia has been cleared
*Gentamicin should be discontinued if signs of toxicity occur.

Causative agent: *Staphylococcus aureus* or CNS
Setting: native valve or prosthetic valve, methicillin resistant

Recommendation 41	**Strength of recommendation**	**Quality of evidence**
If vancomycin cannot be given, replacing vancomycin with daptomycin 10mg/kg/day in 1 dose might be an option if susceptible. Combination therapy with daptomycin and Fosfomycin ~~12g~~ 12000mg/day IV (in 3doses or by continuous infusion) or ceftaroline 1800mg/day (in 3 doses or by continuous infusion) IV is recommended in patients with persistent bacteraemia under daptomycin monotherapy. Decide the optimal treatment regimen in consultation with a medical microbiologist or infectious disease specialist or with an endocarditis team.	~~strong~~ weak	~~moderate~~ low

Causative agent: *Staphylococcus aureus* or CNS
Setting: native valve or prosthetic valve

Recommendation 42	**Strength of recommendation**	**Quality of evidence**
Routine use of oral stepdown treatment is not recommended	Weak	Low

11. Treatment of endocarditis caused by enterococci

Enterococci are part of the normal digestive flora and the causative agent of endocarditis in approximately 10-20% of all cases, more in the elderly (55). *E. faecalis* causes the majority of enterococcal IE, while *E. faecium* and other enterococci only rarely cause endocarditis (56). Enterococci have a natural tolerance against many antibiotics, including the penicillins, and are fully resistant to cephalosporins. *E. faecalis* is generally susceptible to amoxicillin, while >85% of *E. faecium* is amoxicillin resistant (57).

Traditionally, penicillin, amoxicillin or vancomycin together with an aminoglycoside has been used for the treatment of enterococcal endocarditis. This combination shows in vitro and in vivo synergetic activity against enterococci, however aminoglycoside toxicity in patients is a real concern. A combination of amoxicillin and ceftriaxone is equally effective. Ceftriaxone in itself is not effective against enterococci but by competitive binding to penicillin binding proteins (PBP's) it increases the effectiveness of amoxicillin (58).

Treatment duration of enterococcal endocarditis is 6 weeks. Both the ESC and AHA state that for enterococcal endocarditis with symptom duration less than 3 months, treatment with amoxicillin and gentamicin for 4 weeks may be sufficient, based on one single center retrospective study of low quality. The guideline committee advises 6 weeks of treatment, since enterococcal endocarditis is a severe and difficult to treat entity (59). Both the AHA and ESC guidelines offer ampicillin as the drug of choice for enterococcal IE, the guideline committee has adapted this to the Dutch clinical practice of using amoxicillin instead of ampicillin.

For endocarditis caused by *Enterococcus* spp., the AHA and ESC provide similar regimens, but with important differences. For a regimen containing amoxicillin and gentamicin, the ESC advises 2 to 6 weeks of gentamicin, while the AHA recommends 4 to 6 weeks of gentamicin. Both guidelines refer to the only two comparative studies done on this subject (60, 61), while the AHA additionally cites several studies demonstrating the efficacy of combination therapy versus beta-lactam monotherapy(56, 59) which don't address the duration of gentamicin administration. An additional search of the current publications revealed no new studies examining the effectiveness of the different regimes. The guideline committee has the opinion that the two comparative studies have severe methodological flaws and a biological rationale for the 2 week gentamicin regimen is lacking. Therefore, the guideline committee advises to add gentamicin for the full duration of therapy.

Amoxicillin + gentamicin and amoxicillin + ceftriaxone are considered equal choices in both the ESC and AHA, with a preference for amoxicillin + ceftriaxone in patients with impaired renal function and high level aminoglycoside resistance (HLAR, defined as gentamicin MIC ≥128mg/l). Taking into account the accumulated evidence and experience with amoxicillin + ceftriaxone and its favourable toxicity profile, the guideline committee prefers amoxicillin + ceftriaxone over amoxicillin + gentamicin. Ceftriaxone is dosed higher in enterococcal endocarditis than in streptococcal endocarditis. A biological rationale is lacking, but since the original studies were performed with the high dose of 4 gram ceftriaxone per day, the guideline committee recommends this dose.

If amoxicillin cannot be used due to resistance or beta-lactam intolerance, vancomycin combined with gentamicin is the preferred regimen. The evidence for alternatives to vancomycin is scarce, but the 2023 ESC guidelines recommend daptomycin combined with a second antibiotic. As with staphylococcal IE, the evidence for this practice is very limited. However, development of daptomycin resistance in enterococci has been described, and for this reason the guideline committee recommends using daptomycin in enterococcal endocarditis only when combined with a

second agent such as intravenous fosfomycin. Consultation with a medical microbiologist is always advised in these cases to determine the best treatment regimen. Dosing of daptomycin in enterococcal endocarditis is higher (12mg/kg/day) than in staphylococcal endocarditis (10mg/kg/day) based on higher MICs for daptomycin among enterococci(62). ~~. Both the ESC and AHA give several options, including daptomycin and linezolid. The accumulated evidence for both daptomycin and linezolid nearly exclusively stems from small retrospective cohorts or case reports. After reviewing the cited literature for these two options and a review of newly published literature, the guideline committee has decided not to provide a definitive advice on these cases, but advises consultation with a medical microbiologist or infectious disease specialist to determine the best available regimen on a case by case basis.~~

Oral treatment of enterococcal endocarditis

In addition to the POET trial (which included 97 patients with endocarditis caused by *E. faecalis*), there are now three additional retrospective studies comprising a total of 176 patients with enterococcal endocarditis, of whom 72 received oral step-down therapy (32, 33, 53). None of these studies found evidence of inferiority of oral therapy; however all studies were underpowered and were limited by their non-randomized design. Furthermore, the absolute number of patients with prosthetic valve endocarditis was very low. Based on this data, the guideline committee now recommends oral stepdown treatment in selected patients with native valve *E. faecalis* endocarditis. Given the remaining uncertainty about the effectiveness and safety in patients with prosthetic valve endocarditis—and the serious consequences of inadequate treatment of these infections— patients with prosthetic valve endocarditis by *E. faecalis* should still exclusively receive intravenous treatment.

Amoxicillin MICs are often higher for enterococci than for streptococci, leaving less room for inter-patient variation in amoxicillin absorption. To prevent treatment failure in patients with insufficient amoxicillin absorption, the guideline committee recommends combination therapy, as was used in the POET study. The preferred combination is amoxicillin 1000mg four times daily combined with moxifloxacin 400mg once daily (7, 15). This regimen can only be used if the amoxicillin MIC is ≤1mg/L and the *Enterococcus* strain is susceptible to moxifloxacin.

Causative agent: *Enterococcus* spp. Amoxicillin susceptible, no HLAR
Setting: native valve

Recommendation 43	**Strength of recommendation**	**Quality of evidence**
First choice: Amoxicillin iv 12g 12000mg/day in 6 doses or by continuous infusion for 6 weeks + Ceftriaxone iv ~~4g~~ 4000mg/day in 2 doses for 6 weeks	strong	low
Alternative regimen Amoxicillin iv ~~12g~~ 12000mg/day in 6 doses or by continuous infusion for 6 weeks + Gentamicin iv 3mg/day in 1 dose for 4-6 weeks Perform therapeutic drug monitoring when using gentamicin.	strong	low

Amoxicillin + ceftriaxone is preferred over amoxicillin + gentamicin for enterococcal endocarditis	~~weak~~ strong	low

Causative agent: *Enterococcus* spp. Amoxicillin susceptible, no HLAR
Setting: prosthetic valve

Recommendation 44	**Strength of recommendation**	**Quality of evidence**
First choice: Amoxicillin iv ~~12g~~ 12000mg/day in 6 doses or by continuous infusion for 6 weeks + Ceftriaxone iv ~~4g~~ 4000mg/day in 2 doses for 6 weeks	strong	low
Alternative regimen: Amoxicillin iv ~~12g~~ 12000mg/day in 6 doses or by continuous infusion for 6 weeks + Gentamicin iv 3mg/day in 1 dose for 6 weeks Perform therapeutic drug monitoring when using gentamicin.	strong	low
Amoxicillin + ceftriaxone is preferred over amoxicillin + gentamicin for enterococcal endocarditis	~~weak~~ strong	low

Causative agent: *Enterococcus* spp. Amoxicillin susceptible, HLAR
Setting: native valve or prosthetic valve

Recommendation 45	**Strength of recommendation**	**Quality of evidence**
Amoxicillin iv ~~12g~~ 12000mg/day in 6 doses or by continuous infusion for 6 weeks + Ceftriaxone iv ~~4g~~ 4000mg/day in 2 doses for 6 weeks	strong	low

Causative agent: *Enterococcus* spp. Amoxicillin resistant OR amoxicillin allergy, no HLAR
Setting: native valve or prosthetic valve

Recommendation 46	**Strength of recommendation**	**Quality of evidence**
Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels 15-20mg/l) or by continuous infusion (plateau concentration 20-25mg/l)~~ for 6 weeks + Gentamicin iv 3mg/day in 1 dose for 6 weeks Perform therapeutic drug monitoring when using gentamicin.	strong	low

Causative agent: *Enterococcus* spp. Amoxicillin resistant OR amoxicillin allergy, HLAR
Setting: native valve or prosthetic valve

Recommendation 47	**Strength of recommendation**	**Quality of evidence**
Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels 15-20mg/l) or by continuous infusion (plateau concentration 20-25mg/l)~~ for 6 weeks	strong	low

Causative agent: *Enterococcus* spp. Amoxicillin resistant OR amoxicillin allergy + vancomycin resistant or vancomycin allergy
Setting: native valve or prosthetic valve

Recommendation 48	**Strength of recommendation**	**Quality of evidence**
Daptomycin iv 12mg/kg day in 1 dose for 6 weeks + Fosfomycin iv ~~12g~~ 12000mg/day in 3 doses or by continuous infusion for 6 weeks*	Strong	very low

~~Decide the optimal treatment regimen in consultation with a medical microbiologist or infectious disease specialist or with an endocarditis team.~~		

* Decide the optimal treatment regimen in consultation with a medical microbiologist or infectious disease specialist or with an endocarditis team.

Causative agent: *Enterococcus faecalis*
Setting: native valve

Recommendation 49	**Strength of recommendation**	**Quality of evidence**
Consider oral stepdown treatment if the patient meets criteria for IV-oral switch (see chapter on oral treatment)	Weak	low
Oral stepdown treatment consists of: Amoxicillin 1000 mg four times per day + Moxifloxacin 400mg once daily *	Weak	low

* only if amoxicillin MIC is ≤1 and the strain is moxifloxacin susceptible

Causative agent: *Enterococcus faecalis*
Setting: prosthetic valve

Recommendation 50	**Strength of recommendation**	**Quality of evidence**
Routine use of oral stepdown treatment is not recommended	Weak	Low

Causative agent: *Enterococcus other than E. faecalis*
Setting: native valve or prosthetic valve

Recommendation 51	**Strength of recommendation**	**Quality of evidence**
Routine use of oral stepdown treatment is not recommended	Weak	Low

12. Treatment of endocarditis caused by HACEK species

The HACEK (*Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella*) group consists of a group of fastidious Gram-negative bacteria that is a part of the normal human oral microbiome. Less than 5% of all endocarditis cases is caused by HACEK bacteria(63). HACEK endocarditis often has a subacute presentation and identification of bacteria may take several days, since HACEK bacteria grow slowly. Both the ESC and AHA recommend ceftriaxone monotherapy as the preferred antimicrobial therapy. If the bacteria are susceptible to amoxicillin, both the ESC and AHA recommend treating with the agent, while the ESC additionally advises to add 2 weeks of gentamicin. After reviewing the literature there is little evidence for the use of gentamicin in HACEK endocarditis. In case of confirmed amoxicillin susceptibility, the guideline committee advises to use amoxicillin monotherapy and not to add gentamicin.

If ceftriaxone cannot be given due to severe beta-lactam allergy, both the ESC and the AHA recommend ciprofloxacin monotherapy. The guidelines differ slightly on ciprofloxacin dosing, with the ESC recommending high doses of ciprofloxacin (750mg two times daily orally) and the AHA recommending a standard dose (500mg two times daily orally or 400mg two times daily IV). References reported for these recommendations provide no clinical outcomes on use of ciprofloxacin as treatment option for HACEK endocarditis and a literature search resulted in no new evidence. The recommendations in the ESC and AHA guidelines are thus not based on any clinical data. Reported MIC's for fluoroquinolones in HACEK spp are generally low (below 0.25mg/l)(64), and standard dosing seems therefore sufficient. Since experience is limited, 6 weeks of ciprofloxacin is advised for both native valve and prosthetic valve endocarditis.

Causative agent: HACEK spp.
Setting: native valve

Recommendation 52	**Strength of recommendation**	**Quality of evidence**
Ceftriaxone iv ~~2g~~ 2000mg/day in 1 dose for 4 weeks	strong	low
Amoxicillin iv ~~12g~~ 12000mg/day in 6 doses or by continuous infusion for 4 weeks ◊	strong	low

◊ only if proven susceptible

Causative agent: HACEK spp.
Setting: prosthetic valve

Recommendation 53	**Strength of recommendation**	**Quality of evidence**
Ceftriaxone iv ~~2g~~ 2000mg/day in 1 dose for 6 weeks	strong	low
Amoxicillin iv ~~12g~~ 12000mg/day in 6 doses or by continuous infusion for 6 weeks ◊	strong	low

◊ only if proven susceptible

Causative agent: HACEK spp.
Setting: native valve or prosthetic valve, beta-lactam allergy

Recommendation 54	**Strength of recommendation**	**Quality of evidence**
Ciprofloxacin 800mg/day in 2 doses intravenously or 1000mg/day in 2 doses orally for 6 weeks	weak	Very low

13. Treatment of endocarditis caused by non-HACEK Gram-negative bacteria

Endocarditis caused by non-HACEK Gram-negative bacteria is rare and often associated with hospital admission(65). *Escherichia coli* and *Pseudomonas aeruginosa* cause the majority of cases. Both the ESC and AHA advice consultation with a medical microbiologist or ID-specialist and suggest 6 weeks of combination therapy with a beta-lactam and either an aminoglycoside or a fluoroquinolone. Both guidelines also advise early cardiac surgery to achieve cure. Due to the rarity of the disease, consultation with a medical microbiologists or infectious disease specialist is always advised.

Causative agent: non-HACEK Gram-negative bacteria
Setting: native valve or prosthetic valve

Recommendation 55	**Strength of recommendation**	**Quality of evidence**
For patients with endocarditis by non-HACEK Gram-negative bacteria, decide the optimal treatment regimen in consultation with a medical microbiologist or infectious disease specialist or with an endocarditis team.	Strong	Not applicable

14. Right-sided endocarditis

Right-sided endocarditis is a separate entity distinctly different from the more common left-sided endocarditi, and is most commonly caused by *S. aureus*. Right-sided endocarditis caused by *S. aureus* is strongly associated with IV-drug use, but infection of the tricuspid or pulmonic valve may also be seen in patients with congenital heart disease and indwelling cardiac devices.

For right-sided endocarditis by *S. aureus*, both the ESC and AHA advise that a shorter treatment schedule can be used, but only if the following criteria are fulfilled:

- *S. aureus* methicillin susceptible
- Rapid response (<96h) to antibiotic treatment
- Absence of metastatic foci outside the pulmonary system
- Absence of empyema from pulmonary septic emboli
- Vegetation size <20mm
- No cardiac abscesses
- Absence of severe immunosuppression (CD4 cells <200 cells/ml)
- Absence of concurrent left-sided IE
- Absence of cardiac prosthetic material

In these patients, two weeks of flucloxacillin may suffice. In patients not meeting these criteria, or patients who do not tolerate flucloxacillin, a standard 6 week regimen is advised. Both the AHA and ESC also mention a 4 week oral regimen for patients with right sided *S. aureus* endocarditis consisting of ciprofloxacin 2dd750mg and rifampicin 2dd300mg if IV therapy is not feasible. This recommendation is based on one small RCT (52) and a prospective cohort study (66) and may be attempted as a last resort in patients in whom IV therapy is not feasible.

It is unknown if the two week IV regimen can also be extrapolated to patients with isolated right-sided endocarditis caused by other bacteria. In these cases, optimal treatment should be determined in consultation with a medical microbiologist, infectious disease specialist and preferably discussed in an endocarditis team.

Causative agent: *S. aureus*
Setting: right-sided native valve, uncomplicated (see criteria above)

Recommendation 56	**Strength of recommendation**	**Quality of evidence**
Flucloxacillin iv ~~12g~~12g 12000mg/day in 6 doses or by continuous infusion for 2 weeks	weak	low

Causative agent: *S. aureus*
Setting: right-sided native valve, uncomplicated (see criteria above) and IV therapy impossible

Recommendation 57	**Strength of recommendation**	**Quality of evidence**
Ciprofloxacin 1500mg/day in 2 doses orally for 4 weeks + Rifampicin po 600mg/dag in 2 doses orally for 4 weeks	weak	Very low

Causative agent: bacteria other than *S. aureus*
Setting: right-sided endocarditis, native valve or prosthetic valve

Recommendation 58	**Strength of recommendation**	**Quality of evidence**
For patients with right sided endocarditis by bacteria other than *S. aureus*, decide the optimal treatment regimen in consultation with a medical microbiologist or infectious disease specialist or with an endocarditis team	Strong	Not applicable

15. Treatment of endocarditis caused by *Cutibacterium ~~(Propionibacterium)~~* spp.

Cutibacterium, ~~also known as *Propionibacterium*~~, spp almost exclusively infect prosthetic valves and CIEDs, though there are reports of native valve endocarditis (67). *C. acnes* is the most important pathogen, but other species have been reported as well. Because of the rarity of *Cutibacterium* endocarditis, there is little evidence on the best treatment, and neither the ESC nor the AHA mention it in the guidelines.

For the literature review, the available literature in Medline was searched for case series, cohort studies and reviews of previously published cases. The majority of published literature consists of case reports or case series, often with limited information on antimicrobial regimen and duration of follow-up.

The vast majority of published cases included surgery as part of treatment (67, 68), though cure through conservative treatment alone has also been described (67, 69).

In a cohort of 15 patients from the International Collaboration on Endocarditis (ICE) study most patients were treated with a beta-lactam agent with or without an aminoglycoside (69). In two retrospective cohort studies from the US with respectively 8 and 24 patients, most patients were treated with vancomycin or a cephalosporin (70, 71). In contrast, a more recent Dutch study with 13 patients (of which 12 underwent redo surgery) from a single centre, reported excellent results of treatment with penicillin alone (n=4) or penicillin in combination with rifampicin (n=7) (68).

There is data on the adjunctive use of rifampicin in treatment of *Cutibacterium* endocarditis in humans. In vitro studies report rifampicin as the most active agent against *C. acnes* biofilm (72), but it is unknown if this leads to improved clinical outcomes in human infection.

There were no comparative studies on the best antibiotic regimen for *Cutibacterium* endocarditis. The overall quality of evidence for any treatment option for *Cutibacterium* endocarditis is low to very low.

The guideline committee considers penicillin to be the drug of choice for *Cutibacterium* endocarditis based on its favourable side effect profile, narrow spectrum and lack of need for therapeutic drug monitoring. If penicillin cannot be used ceftriaxone is the alternative. No studies on ceftriaxone dosing in *Cutibacterium* endocarditis exist and for this reason the guideline committee argues that high dosed ceftriaxone may be preferable over normal dose ceftriaxone as is used in streptococcal endocarditis since *Cutibacterium* endocarditis is associated with more difficult to treat infections. In case penicillin or ceftriaxone cannot be used, vancomycin is the last line option. In selected patients (e.g.: inoperable, extensive paravalvular abscesses) rifampicin may be added in consultation with the endocarditis team.

Causative agent: *Cutibacterium* spp.
Setting: native valve or prosthetic valve

Recommendation 59	**Strength of recommendation**	**Quality of evidence**
Penicillin iv 12-18 million units/day in 6 doses or by continuous infusion for 6 weeks	Strong	Low

Causative agent: *Cutibacterium* spp.
Setting: native valve or prosthetic valve, non-severe penicillin allergy

Recommendation 53	**Strength of recommendation**	**Quality of evidence**
Ceftriaxone iv ~~4g~~ 4000mg/day in 2 doses for 6 weeks	Strong	Low

Causative agent: *Cutibacterium* spp.
Setting: native valve or prosthetic valve, severe beta-lactam allergy

Recommendation 60	**Strength of recommendation**	**Quality of evidence**
Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels 15-20mg/l) or by continuous infusion (plateau concentration 20-25mg/l)~~ for 6 weeks	Strong	Low

Causative agent: *Cutibacterium* spp.
Setting: prosthetic valve

Recommendation 61	**Strength of recommendation**	**Quality of evidence**
Consider adding rifampicin iv or po 900~~1200~~mg/day in 2 doses in selected cases	weak	Very low

16. Culture negative endocarditis

In 5 to 10% of the patients with endocarditis in the Netherlands, blood cultures do not show growth (73, 74). Negative blood cultures may be the result of prior antibiotic use, inappropriate or insufficient blood culture collection or the result of fastidious or obligate intracellular growing microorganisms that are difficult or even impossible to culture in normal blood culture systems.

HACEK group bacteria may take up to 7 days to grow in normal blood culture sets, while for *Cutibacterium* may take up to 14 days to grow (71, 75). Additionally, some streptococci (especially pneumococci) may be unculturable even after one (oral) dose of antibiotics.

Bacteria that do not grow in normal blood culture systems include intracellular bacteria such as *Tropheryma whipplei*, *Bartonella spp*, ~~*Mycoplasma* spp.~~, ~~*Legionella* spp~~, and *Coxiella burnetii*. These 'culture-negative' microorganisms are rare and their diagnosis requires serology or PCR.

~~The therapy of culture-negative endocarditis should cover the above mentioned pathogens.~~

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In patients with negative blood cultures after prior antibiotic use or inappropriate blood cultures the causative agent is most likely one of the common causes of endocarditis (staphylococci, streptococci and enterococci). On the other hand, in patients with culture negative endocarditis despite adequate blood culture collection and without prior antibiotic use, a microorganism that is difficult or impossible to detect with blood cultures is more likely.

~~It is important to distinguish between endocarditis caused by inappropriate blood culture collection or incubation and prior antibiotic use and endocarditi caused by microorganisms that cannot be revealed by routine culture methods, as the former is mostly covered by empirical therapy, while the latter may require a completely different treatment regimen. HACEK group bacteria and *Cutibacterium* may take up to 7 - 14 days before blood cultures are reported positive (71, 75), while some streptococci (especially pneumococci) are difficult to culture even after one dose of antibiotics . Bacteria that are not routinely cultured include *Tropheryma whipplei*, *Bartonella spp*, *Mycoplasma* spp., *Legionella* spp, and *Coxiella burnetii*. These 'culture-negative' microorganisms are rare and their diagnosis requires serology, or PCR. The therapy of culture-negative endocarditis should cover the above mentioned pathogens.~~

If additional testing (serology, PCR) reveals a causative micro-organism, the antibiotic regimen should be adjusted to provide optimal treatment for this pathogen.

On rare occasions endocarditis can also be caused by fungi not detected by routine blood culture, mycobacteria and by non-infectious causes (also known as non-bacterial thrombotic endocarditis or marantic endocarditis). These entities fall outside the scope of this guideline and are therefore not addressed here.

Treatment of culture negative endocarditis is dependent on many factors, and the AHA refrains from any specific treatment advice on culture negative endocarditis. The ESC only provides recommendations for the 'culture negative' organisms such as *Tropheryma whipplei* or *Coxiella burnetii*, but does not provide a recommendation for treatment when all additional tests are negative (5). The SWAB guideline committee has formulated treatment suggestions based on the

most common pathogens for both native and prosthetic valve endocarditis, with doxycycline added as therapy for intracellular bacteria.

When patients have started empirical therapy and no pathogen has been identified by blood culture, the switch from empirical therapy to a regimen directed to culture negative endocarditis related pathogens is recommended. When to make this switch is unclear from literature; there are no studies regarding this question, and the advice on when to switch is based on expert opinion.

It is important to stress that the treatment of culture negative endocarditis is dependent on many factors, including but not limited to: the type of valve involved; the duration of symptoms; the number of blood cultures collected prior to start of antimicrobial therapy; the results of additional cultures and serology; the clinical response to empirical therapy and available risk factors (e.g.: animal contact, preceding dental interventions). The regimens described below are meant as suggestions for therapy of culture negative endocarditis, and should always be discussed and adjusted in consultation with an infectious disease specialist or medical microbiologist and preferably in an endocarditis team.

Causative agent: culture negative endocarditis

Recommendation 62	**Strength of recommendation**	**Quality of evidence**
Always consult with a medical microbiologist or infectious disease specialist in patients with (suspected) culture negative endocarditis	Strong	Not applicable

Causative agent: culture negative endocarditis

Recommendation 63	**Strength of recommendation**	**Quality of evidence**
Consider switching from empirical therapy to therapy directed at culture negative endocarditis if conventional blood cultures (taken without antibiotic therapy) remain negative after 72 hours	Weak	Very low

Causative agent: culture negative endocarditis
Setting: Native valve

Recommendation 64	**Strength of recommendation**	**Quality of evidence**
Amoxicillin iv ~~12g~~ 12000mg/day in 6 doses or by continuous infusion for 6 weeks + Ceftriaxone iv ~~4g~~ 4000mg/day in 2 doses for 6 weeks + Doxycycline iv or po 200mg/day in 1 or 2 doses for 6 weeks Consider stopping doxycycline if additional tests for intracellular microorganisms (e.g.: *Coxiella*, *Bartonella*) are negative	Weak	Very low

Causative agent: culture negative endocarditis
Setting: Prosthetic valve

Recommendation 65	**Strength of recommendation**	**Quality of evidence**
Vancomycin iv (continuous dosing: loading dose 20mg/kg, followed by 35mg/kg/day via continuous infusion; intermittent dosing: loading dose 30mg/kg, followed by 35mg/kg/day in two separate doses) Therapeutic Drug Monitoring (TDM) is advised in relation to efficacy and toxicity. For guidance on TDM, see local TDM guidelines or consult with the consultant hospital pharmacist ~~Vancomycin 2000-3000mg/day in 2-3 doses (trough levels 15-20mg/l) or by continuous infusion (plateau concentration 20-25mg/l)~~ for 6 weeks + Ceftriaxone iv ~~2g~~ 2000mg/day in 1 dose for 6 weeks + Doxycycline iv or po 200mg/day in 1 or 2 doses for 6 weeks	Weak	Very low

Consider stopping doxycycline if additional tests for intracellular microorganisms (e.g.: *Coxiella*, *Bartonella*) are negative		

17. Suppressive therapy

There is no accepted definition of suppressive therapy and both lifelong and extended but not lifelong therapy, are often referred to as suppressive therapy Clinicians may decide to treat a patient with endocarditis with long-term suppressive antimicrobial therapy to prevent relapse of infection. The 2023 ESC or 2015 AHA guidelines provide no guidance on which patients benefit from this approach or how to provide it. For the 2025 revision, the SWAB guideline committee reviewed all available literature and found no good evidence to support the practice of suppressive therapy and found no randomized studies or high-quality cohort studies comparing patients with extended antimicrobial therapy to patients without (76, 77). Therefore the guideline committee cannot define the conditions under which suppressive therapy is indicated. In selected patients with a possible indication, it is recommended to decide the application of suppressive therapy and specific antimicrobial, dosage and duration always in consultation with the endocarditis team.

Recommendation 66	Strength of recommendation	Quality of evidence
Suppressive (lifelong or extended but not lifelong) therapy is not routinely recommended for patients with endocarditis and should only be started in highly selected patients after consultation with an endocarditis team.	Strong	Very low

18. Treatment Cardiac Implantable Electronic Devices endocarditis.

~~Cardiac implantable electronic device endocarditis is a relatively new entity. It's incidence increases~~ The incidence of cardiac implantable electronic device (CIED) endocarditis has been increasing with the increased use of cardiac implantable devices (78, 79). CIED infections cover a spectrum ranging from infections limited to the device pocket infections to more extensive disease with bacteraemia (11, 80, 81). The following chapter exclusively concerns CIED endocarditis: bloodstream infections due to an infected CIED. Isolated device pocket infections are not covered in this guideline. In general, device removal is always recommended, however this is not always feasible.

Timing of device removal:

The BSAC guidelines advice 'prompt' removal of infected devices without clarification. The AHA guidelines advise that "complete device removal should not be delayed, regardless of timing of initiation of antimicrobial therapy". There were no new studies that examined the opportune moment to remove an infected CIED. For several reasons, the guideline committee believes removal of the infected CIED should occur as soon as possible in all patients, regardless of preceding antimicrobial treatment and pathogen. First, removal of the device is essential for cure and treatment duration is mainly dictated by the moment of device removal, and prompt removal may thus reduce total length of antimicrobial therapy and hospital stay. Second, leaving an infected

device in place creates the risk of seeding from the infected device, leading to intra or extra cardiac infectious foci.

Recommendation 67

Situation	Recommendation	Strength of recommendation	Level of evidence
Infected CIED	Remove the infected CIED as soon as possible.	Strong	Very low

Duration of treatment after device removal

The optimal treatment duration for CIED infection after device removal is unknown.

When the infected device has been removed completely, there is no involvement of other cardiac structures (native or prosthetic valve) and there are no extracardiac metastatic foci, the AHA advises at least two weeks of IV treatment post extraction andtwo to four weeks if *S. aureus* is the causative agent. The BSAC guidelines also advise at least 2 weeks of post extraction treatment. These scenarios assume a favourable clinical course after antibiotic treatment and the absence of residual lesions on repeat echocardiography after device removal. A review of literature published since the 2015 BSAC guidelines identifies three studies reporting on treatment duration after device removal and outcomes(82-84). These were single center retrospective cohort studies, two of which used two week treatment after extraction with favourable results (83, 84). One study retrospectively compared 'short course' (median 2 weeks) versus 'long course' (4-6 weeks) antimicrobial treatment and reported no significant differences in death or relapse rates. One study reported exclusively on 6 weeks of post extraction treatment and found no relapse in all 40 patients treated (82).

In summary, two weeks of treatment post extraction in uncomplicated cases of device endocarditis may be reasonable.

If there is involvement of native or prosthetic valve or there are extracardiac metastatic foci a longer treatment duration is advised. The AHA guidelines advise 4-6 weeks post extraction. In contrast, the BSAC guidelines advise 4-6 weeks in total, regardless of the moment the device is removed, unless the infection is uncontrolled until the device is removed. The US guidelines also advise 4-6 weeks post extraction treatment if blood cultures taken after extraction remain positive.

Recommendation 68

Situation	Recommendation	Strength of recommendation	Level of evidence
- Infected CIED, vegetation on lead only or no visible vegetation - Complete removal of device. - No positive blood cultures after removal of device	Treat for 14 days with IV antibiotics after removal of device	Weak	Very low

- No extra cardiac foci or involvement of cardiac structures other than the infected device			

Recommendation 69

Situation	Recommendation	Strength of recommendation	Level of evidence
- Infected CIED - Complete removal of device. - No positive blood cultures after removal of device **AND** - Extra cardiac foci (e.g.: infected thrombus, vertebral osteomyelitis, peripheral abscess) **AND/OR** - Involvement of cardiac structures other than the infected device	Treat for a total of 4-6 weeks with IV antibiotics, with a minimum of 2 weeks after device removal, depending on causative microorganism and involved cardiac structure	Weak	Very low

Recommendation 70

Situation	Recommendation	Strength of recommendation	Level of evidence
- Infected CIED - Complete removal of device. **AND** - positive blood cultures after removal of device	Treatment duration depends on focus; but at least 4-6 weeks AFTER first negative blood culture and depending on causative microorganism	Weak	Very low

Treatment duration if device cannot be removed.

Complete removal of the infected device is essential for curing CIED-endocarditis. However, removing the CIED may be impossible due to comorbid conditions or patient refusal. In such cases, device salvage may be attempted. The AHA guidelines do not provide a clear advice on this subject, while the BSAC guidelines recommend a 6 week antibiotic regimen comparable to those used for prosthetic valve endocarditis. The BSAC guidelines summarize that device salvage can be successful in a varying but meaningful proportion of patients. Two recent cohort studies demonstrate high failure rates using medical therapy alone (84) or in combination with subsequent oral suppressive therapy (85). In summary, the cure for an infected CIED is almost always complete removal of the device. If this is not possible or successful, salvage therapy may be attempted. Repeat blood cultures taken after cessation of antibiotic therapy may be useful to identify relapses before disease onset occurs. If salvage therapy fails, removal of the infected device should be considered again. In those patients with a relapse after salvage therapy and no possibility to remove the device, oral suppressive therapy may be attempted.

Recommendation 71

Situation	Recommendation	Strength of recommendation	Level of evidence
- Infected CIED - Incomplete removal of device.	Treat for a total of 6 weeks after first negative blood culture with a regimen comparable to salvage therapy.	Weak	Very low

Recommendation 72

Situation	Recommendation	Strength of recommendation	Level of evidence
- Infected CIED - Incomplete removal of device.	Consider repeating blood cultures after cessation of antimicrobial therapy	Weak	Not applicable

Recommendation 73

Situation	Recommendation	Strength of recommendation	Level of evidence
- Infected CIED - Removal not possible	Attempt salvage therapy with the antibiotic regimen used for prosthetic valve endocarditis directed at the causative microbe.	Weak	Very low

Recommendation 74

Situation	Recommendation	Strength of recommendation	Level of evidence
- Infected CIED - Relapse after salvage therapy	Consider oral suppressive therapy	Weak	Very low

Timing of device replacement

After removal of an infected CIED a device-free interval before implantation of a new CIED is preferable. The AHA guidelines recommend at least 14 days of device free interval ~~after the last positive blood culture~~ in case of valvular vegetations. If vegetations are only seen on the lead, the AHA advises repeating blood cultures after device removal, and consider placement of a new device safe if blood cultures are negative after 72 hours.

The BSAC guidelines are less clear on the timing of device replacement and state that replacement should be delayed until symptoms and signs of systemic and local infection have resolved.

~~A considerable proportion of patients will need a temporary device as a bridge between removal of the infected CIED and placement of a new permanent device. The type and specific use of these temporary devices is beyond the scope of this guideline.~~

The committee found no new relevant literature on the timing of device replacement and, as such, is following the AHA guidelines. This advice corresponds with the recommendations in the 2015 ESC guidelines, which is mainly based on the AHA guidelines.

Recommendation 75

Situation	Recommendation	Strength of recommendation	Level of evidence
Infected CIED, no valvular vegetations	Delay reimplantation of a new device until blood cultures taken after device explanation have been negative for >72 hours	Weak	Very low

Recommendation 76

Situation	Recommendation	Strength of recommendation	Level of evidence
Infected CIED, valvular vegetations	Delay reimplantation of a new device for at least 14 days after device exttraction and and until blood cultures after extraction are negative	Weak	Very low

What specific treatment regimen should be used for the treatment of an infected CIED?

The AHA guidelines do not provide specific antimicrobial regimens for treating an infected CIED. The BSAC guidelines gives different treatment regimens for uncomplicated CIED infection (no

involvement of cardiac structures other than the CIED-lead, in the BSAC guidelines defined as ICED-LI) and complicated CIED infection (with involvement of cardiac structures other than the CIED-lead). For uncomplicated CIED infection, the treatment regimen is comparable to native valve endocarditis once the device is removed, albeit that the UK guidelines offer slightly different dosing regiments compared to the AHA an ESC guidelines(4, 5). For complicated CIED infections and salvage therapy, regimens comparable to prosthetic valve endocarditis are advised.

There are no studies evaluating the appropriate antimicrobial therapy in CIED infection. The guideline committee considers it reasonable to start with a regimen comparable to prosthetic valve endocarditis and attempt early device removal. If complete device removal is successful and there is no evidence of remaining infected prosthetic material, de-escalation to a regimen used for native valve endocarditis is appropriate, with duration based on blood cultures and wether there is involvement of any native valves or extra-cardiac infectious foci.

If device removal is not successful (parts of the infected leads remain) or there is evidence of involvement of other infected prosthetic materials, treatment as prosthetic valve endocarditis is appropriate.

Recommendation 77

Situation	**Recommendation**	**Strength of recommend ation**	**Level of evidence**
Infected CIED	Start with treatment for prosthetic valve endocarditis directed at the causative microbe.	Weak	Very low

Recommendation 78

Situation	**Recommendation**	**Strength of recommend ation**	**Level of evidence**
Infected CIED, after complete removal of device	De-escalate to treatment for native valve endocarditis directed at the causative microbe. (duration see above)	Weak	Very low

Recommendation 79

Situation	**Recommendation**	**Strength of recommend ation**	**Level of evidence**

Infected CIED, if complete removal of device is not possible or unsuccessful	Continue treatment with a regimen used for prosthetic valve endocarditis directed at the causative microbe. (duration see above)	Weak	Very low

~~**19. Changes from the previous endocarditis guideline**~~

~~The changes from the previous, 2003 version of the SWAB guidelines on the treatment of infective endocarditis are manifold. The most important changes are as follows:~~

- ~~Different regimens for empirical treatment~~
- ~~Dosing of penicillin in penicillin intermediate resistant streptococci has been adjusted~~
- ~~There is no more need for gentamicin in staphylococcal native valve endocarditis~~
- ~~Amoxicillin/ceftriaxone is now the first choice regimen for enterococcal endocarditis~~
- ~~Gentamicin is no longer recommended for HACEK endocarditis treated with amoxicillin~~
- ~~New chapters on culture negative endocarditis, *Cutibacterium* endocarditis and CIED endocarditis~~

20. Endocarditis prophylaxis

Endocarditis prophylaxis is only indicated in **patients with a high risk** of infective endocarditis who undergo **at-risk or-o-dental procedures**. Patients that do not have a high risk should not receive endocarditis prophylaxis, nor should patients with high risk receive endocarditis prophylaxis for interventions that are not at high risk of periprocedural bacteraemia.

Patients with a high risk of infective endocarditis:

- Patients with a history of infective endocarditis
- Patients with a prosthetic heart valve (both surgical and transcatheter valves, this also includes bioprostheses, allografts and conduits)
- Patients who have undergone valve repair/valvuloplasty with prosthetic material
- Patients with a ventricular assist device (LVAD)
- The following patients with congenital heart disease:
    - Cyanotic heart defect that is not surgically corrected (e.g.: *Tetralogy of Fallot*, *Transposition of Great Arteries*)
    - Congenital heart defects that have been treated with palliative shunts, conduits or other valvular prosthesis (e.g.: *Mustard procedure*, *Blalock-Taussig shunt, corrected Tetralogy of Fallot with pulmonary valve prosthesis*)
    - Fully corrected congenital heart defects with the use of prosthetic materials but without palliative shunts, conduits or valvular prosthesis: only during the first six months after surgery (e.g.: *atrial septal defect closed with patch*)
    - Corrected congenital heart defect but with a remaining leasion that prevents endothelialisation of the patch or device (e.g. *closed atrial septal defect but with mitral regurgitation directed towards the atrial septum*)

At risk oro-dental procedures

The following oro-dental procedures are at high risk of causing bacteraemia:

- Dental extraction
- Oro-dental surgery (e.g.: paradontal surgery, implant surgery, oral biopsy, tonsillectomy, adenoidectomy)
- Dental procedures involving the gingival tissue or periapical region (e.g.: root canal procedure, scaling)

Endocarditis prophylaxis is not indicated in other oral procedures, including but not limited to: application of local anaesthesia, applying, adjusting or removing orthodontic braces, natural loss of dentition and buccal or mucosal bleeding after trauma.

Endocarditis prophylaxis:

Endocarditis prophylaxis should preferably be given orally. Amoxicillin is first choice, with clindamycin being the alternative.

Adults: amoxicillin 2000mg orally or intravenously, 30-60 minutes prior to the procedure

In patients with a penicillin allergy or who received penicillin 7 days prior to the procedure use:

Clindamycin 600mg orally or intravenously, 30-60 minutes prior to the procedure

Additional notes:

1. The ESC guidelines do not recommend clindamycin as an alternative to penicillin in patients with a penicillin allergy. However, clindamycin has been the historic second choice for endocarditis prophylaxis in The Netherlands and the guideline committee sees no reason to change this.
2. The ESC guidelines recommend that additional coverage against enterococci during TAVR/TAVI placement and similar transcatheter valve procures as a class 2a, level C recommendation. Since the causal relationship between enterococcal endocarditis and TAVR/TAVI is dubious, the guideline committee does **not** recommend additional enterococcal coverage added to routine surgical prophylaxis.
3. Endocarditis prophylaxis is **not** indicated for surgical procedures other than oro-dental procedures. If a patient with a high risk of endocarditis (as defined above) undergoes a procedure with a high risk of periprocedural bacteraemia, preprocedural antibiotic prophylaxis according to local guidelines should be given.

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The SWAB employs strict guidelines with regard to potential conflicts of interests, as described in the SWAB Format for Guideline Development (www.swab.nl). All members of the guideline committee complied with the SWAB policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the guideline committee were provided the SWAB conflict of interest disclosure statement and were asked to identify ties to companies developing products or other parties that might be affected by the guideline. Information was requested regarding employment, honoraria, consultancies, stock ownership, research funding, and membership on company advisory committees. The panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict.

Potential conflicts are listed below:

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Dr. C.H.E. Boel	None
Drs. M.A. Funnekotter	None
Dr. I.J.E. Kouijzer	None
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Dr. N. Roescher	None
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Dr. W. Tanis	None
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22. List of abbreviations

AATS	American Association for Thoracic Surgery
AGREE	Appraisal of Guidelines for Research and Evaluation
AHA	American Heart Association
BSAC	British Society for Antimicrobial Chemotherapy
CIED	Cardiac Implantable Electronic Device
CNS	Coagulase Negative Staphylococci
CT	Computed Tomography
ESC	European Society of Cardiology
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HACEK	*Haemophilus spp, Aggregatibacter spp, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae*
HLAR	High Level Aminoglycoside Resistance
IE	Infective endocarditis
IV	Intravenous
IgE	Immunoglobulin E
MIC	Minimal Inhibitory Concentration
MSSA	Methicillin Susceptible *Staphylococcus aureus*
MRSA	Methicillin Resistant *Staphylococcus aureus*
NVE	Native Valve Endocarditis
PBP	Penicillin Binding Protein
PCR	Polymerase Chain Reaction
PO	Per os (orally)
PVE	Prosthetic Valve Endocarditis
Spp	Species (plural)
SWAB	Stichting Werkgroep Antibiotica Beleid/Dutch Working Pary on Antimicrobial Stewardship
TTE	Transthoracic echocardiography
TOE	Transoesophageal echocardiography

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Appendices

(separate documents)

Appendix A – Endocarditis prophylaxis guidelines (Dutch version)

Appendix B – Results of literature searches and answers to PICOs

APPENDIX A: Endocarditis profylaxe (Nederlandse vertaling, oktober 2025)

Endocarditis profylaxe is alleen geïndiceerd bij **patiënten met een hoog risico** op infectieuze endocarditis die een **at-risk oro-dentale procedure** moeten ondergaan. Patiënten zonder hoog risico hoeven geen endocarditis profylaxe te ontvangen en patiënten met een hoog risico op endocarditis die een ingreep ondergaan zonder hoog risico op perprocidurele bacteriëmie hoeven ook geen endocarditis profylaxe te krijgen.

Patiënten met een hoog risico:

- Patiënten die ooit eerder endocarditis hebben doorgemaakt
- Patiënten met een hartklepprothese (zowel chirurgisch als transcatheter ingebrachte kleppen, deze groep bevat dus ook alle bioprotheses, allografts en conduits)
- Patiënten met kunstmateriaal in situ na reparatie van een hartklep
- Patienten met een ventricular assist device (VAD) in situ
- Bepaalde aangeboren hartafwijkingen (AHA):
    - Onbehandelde cyanotische AHA (bijvoorbeeld: *Tetralogie van Fallot, Transpositie van de grote vaten*)
    - Bij patiënten die een ingreep hebben ondergaan waarbij palliatieve shunts, conduits of andere prothesen zijn geplaatst (bijvoorbeeld: *Mustard procedure, Blalock-Taussig shunt, gecorrigeerde Tetralogie van Fallot met een pulmonalisklep prothese*)
    - Volledig gecorrigeerde hartafwijking met gebruikmaking van prothese materiaal: alleen gedurende de eerste zes maanden na behandeling (bijvoorbeeld: *atrium-septum defect met afgesloten met een patch*)
    - Behandelde aangeboren hartafwijking met restafwijking ter plekke van een patch of device waardoor endothelialisatie wordt belemmerd (bijvoorbeeld: *gesloten atrium-septum defect maar mitralisklepinsufficiëntie met jet richting het atriale septum*)

At risk oro-dentale procedures

- Trekken van tanden
- Chirurgische ingrepen in de mond (waaronder parodontale chirurgie, kaakchirurgie, implantaatchirurgie, tonsillectomie en adenoïdectomie en orale biopsieën)
- Tandheelkundige ingrepen waarbij het tandvlees of het periapicale gebied van de tanden wordt gemanipuleerd (waaronder tandsteenverwijdering en wortelkanaalbehandelingen)

Het geven van antibiotische profylaxe specifiek gericht op het voorkomen van endocarditis is **niet** geïndiceerd bij andere ingrepen in de mondholte, zoals het geven van lokale anaesthesie, het aanbrengen/aanpassen/verwijderen van orthodontische apparatuur, natuurlijke uitval van gebitselementen en het optreden van bloeding van lippen/mucosa door een trauma.

Endocarditis profylaxe:

Endocarditis profylaxe wordt bij voorkeur oraal gegeven. Amoxicilline is de eerste keuze, met clindamycine als alternatief.

Volwassenen: amoxicilline 2000 mg per os of intraveneus, 30-60 minuten voor de ingreep.

In geval van penicilline allergie of behandeling met penicilline in de 7 dagen voorafgaand aan de ingreep:

Volwassenen: clindamycine 600 mg per os of intraveneus, 30-60 minuten voor de ingreep

A**anvullende opmerkingen**

1. ESC guideline geeft clindamycine niet meer als keuze bij allergie, echter de onderbouwing daarvoor is matig en in Nederland een geaccepteerde 2e keuze profylaxe, ook voor andere indicaties.
2. ESC guideline geeft aan dat bij TAVI en andere transcatheter valvulaire procedures enterokokken dekking overwogen moet worden als een klasse 2a, level C aanbeveling. Aangezien een causale relatie tussen plaatsen van TAVI en optreden van enterokokken endocarditis niet bewezen is, is het advies om **geen** amoxicilline toe te voegen aan de reguliere profylaxe.
3. Het geven van antibiotische profylaxe specifiek gericht op het voorkomen van endocarditis is **niet** geïndiceerd bij andere ingrepen dan at risk oro-dentale procedures.

   Indien een patiënt met een hoog risico op endocarditis (zie boven) een ingreep moet ondergaan waarbij er een risico bestaat op het optreden van een periprocedurele bacteriëmie, dient voorafgaand aan de procedure laagdrempelig te worden gestart met antibiotica volgens de geldende (lokale) richtlijnen.

Voor SWAB onderstaande hoofdstukken allemaal weglaten (dus alles in 1 hoofdstuk):

Home › Profylaxe

Endocarditis profylaxe

Titel ▲	Sectie	Menu positie
endocarditis profylaxe - ingrepen geïnfecteerd weefsel	Profylaxe	Endocarditis profylaxe
endocarditis profylaxe - ingrepen in de mondholte en de bovenste luchtwegen	Profylaxe	Endocarditis profylaxe
endocarditis profylaxe - ingrepen in de tractus digestivus	Profylaxe	Endocarditis profylaxe
endocarditis profylaxe - ingrepen in de tractus urogenitalis	Profylaxe	Endocarditis profylaxe

PICO 5: Endocarditis profylaxe voor niet-tandheelkundige ingrepen

Patients: Patiënten met een hoog risico op endocarditis die een niet-tandheelkundige ingreep (bijv ERCP, bronchoscopie) ondergaan

Intervention: Antibiotica proylaxe

Control: Geen antibiotica profylaxe

Outcome: Incidentie van endocarditis (primaire uitkomst), mortaliteit, optreden van adverse drug events

Artikel (auteur, jaar)	**Geeft artikel antwoord op de PICO, zo ja, beschrijf kort hoe**	**Indien antwoord op de PICO:** **Opmerkingen over kwaliteit van artikelen (vermeld iig studie design en aantal patiënten)**
Larry M. Baddour Circulation. 2023;148:1529–1541. DOI: 10.1161/CIR.000000000000118	Nee Review	In summary, we propose that there is sufficient evidence associating certain NDIPs with the subsequent occurrence of IE, in particular, in those at high IE risk, to warrant a reevaluation of IE prevention advice.
Briana Goddard, MD Urol Clin N Am 51 (2024) 467–474	Nee Opsomming van beperkte data	Best practice statements by the AUA and AHA do not recommend administering antibiotic prophylaxis for patients with artificial valves undergoing a GU procedure for the sole purpose of preventing infectious endocarditis.
Imre Janszky JACC VOL. 71, NO. 24, 2018	Nee Geen RCT All patients >20 years of age with a primary discharge diagnosis with International Classification of Diseases-10th Revision codes I33, I38, or I39 occurring between	several invasive nondental medical procedures are associated with a markedly increased risk for infective endocarditis. Health care professionals performing particularly risk-prone procedures should consider every possible preventive

	January 1, 1998, and December 31, 2011, in Sweden were included.	measure to decrease the excess risk.
Tejs Ehlers Klug Journal of Cardiovascular Pharmacology and Therapeutics 17(3) 298-302	Nee aim of the present study was to explore the incidence of bacteremia during elective and quinsy tonsillectomy in order to evaluate the antibiotic prophylaxis recommendations to patients at high risk of infective endocarditis who are undergoing tonsillectomy.	In all, 59% and 42% of electively and acutely tonsillectomized patients, respectively, had bacteremia with microorganisms that are predominant in bacterial endocarditis. These results challenge the distinction made by the European Society of Cardiology between elective and quinsy tonsillectomy, namely that antibiotic prophylaxis is the only recommendation to patients undergoing procedures to treat an established infection. Based on our findings, we advocate the use of amoxicillin with clavulanic acid in patients at high risk of developing infective endocarditis.
Amar R. Mohee BJU Int 2014; 114: 118–124	Nee The objectives of the present study were to assess if there was an association between urological procedures and thedevelopment of IE. A retrospective, case-control design was used to compare four distinct groups of patients with IE: (1) enterococcal IE, (2) CoNS IE, (3) *Streptococcus bovis*-group IE, (4) oral streptococcal IE.	The association between enterococcal IE and urological procedures raises questions about the pathogenesis of enterococcal IE. Can enterococcal IE result from bacteraemia caused by the procedure? Or, are patients who undergo urological procedures more likely to have an underlying urological pathology that causes repeated undetected bacteraemias in the period preceding the procedures? Both mechanisms may lead to the bacterial seeding of cardiac valves, but would warrant different approaches to prophylaxis

Mia M. Pries-Heje1,2 Current Cardiology Reports (2023) 25:1873–1881	Nee The aim of this review is to compare similarities and differences in current recommendations for antibiotic prophylaxis for IE by the three largest international societies, with consideration of some of the recent published works.	The question of whether to recommend antibiotic prophylaxis or not in certain patient populations remains unanswered and remains largely based on expert consensus opinion
Swiss expert group on Infective Endocarditis Prevention, Sendi Parhamab	Nee The Swiss societies of Infectious Diseases, Pediatric Cardiology and Cardiology and the Pediatric Infectious Disease Group of Switzerland present the current update on infective endocarditis prophylaxis in a joint initiative.	Gastrointestinal/genitourinary procedures – Antibiotic prophylaxis is not recommended for gastroscopy, colonoscopy, low-risk laparoscopic procedures on the biliary tract (see also recommendations for antimicrobial perioperative prophylaxis of Swissnoso 2015), cystoscopy, vaginal or caesarean delivery, or transoesophageal echocardiography. – In the case of an established infection, an empiric antibiotic regimen containing anti-enterococcal activity should be used.
YARDENA SIEGMAN-IGRA Scandinavian Journal of Infectious Diseases, 2010; 42: 208–21	Nee The purpose of this study was to explore the possible link between IE and GI and GU procedures and to examine the contribution of these procedures to the occurrence of IE in order to appreciate whether the removal of these procedures from the indications for IE prophylaxis was justified. In brief, data on	Hence, GI and GU procedures pose a non-negligible risk of acquisition of IE. Consequently, it is proposed here, that adults at high risk of IE who undergo surgical GI and GU procedures, receive prophylaxis that includes an anti-enterococcal agent In conclusion, GI and GU procedures pose a non-negligible risk of acquisition of

	all adults with culture-positive IE in a tertiary care university hospital in Tel Aviv were collected prospectively by reviewing all of the patients' medical records, with special attention to invasive procedures performed before the onset of IE symptoms. This database was currently reviewed and patients who had invasive procedures within the 3 months preceding the diagnosis of IE were the subject of the present study.	IE, having been associated with 9% (20 of 212) of IE episodes,
Martin H. Thornhill JACC VOL. 71, NO. 24, 2018	No EDITORIAL COMMENT op het artikel van Janszky	If the breadth of procedures associated with increased risk is confirmed by further studies, this will raise important questions for guideline committees about the benefits of recommending antibiotic prophylaxis prior to some of these procedures. However, broadening the scope of antibiotic prophylaxis to include all of these procedures is unlikely to be the solution. At least for those procedures where sterility should be easy to achieve and maintain, the solution is more likely to lay with improved sterile technique, infection control procedures and identifying systematic approaches for reducing health care–associated bacteremia rather than necessarily advocating antibiotic prophylaxis

Martin H Thornhill	Nee An admission was defined as a single continuous hospital stay (which could comprise several consultant episodes), where an International Classification of Diseases 10th Revision (ICD-10) primary or secondary diagnosis code I33.0, I33.9, I39.0, I39.1, I39.2, I39.3, I39.4 or I39.8, or a primary diagnosis code I38.X, was used for any consultant episode	We report a significant association between implantation of CIEDs, upper and lower GI endoscopy, bronchoscopy, and dental extractions (including surgical tooth removal), and subsequent IE. These procedures resulted in an additional 14.3–49.5 IE cases/100000 procedures in those at high IE risk and an additional 1.1–3.9 IE cases/100000 procedures in those at moderate risk. These data support a reconsideration of the possible role of preprocedural AP for these procedures in those at high IE risk.
Presentatie van Bruno Hoen ISCVID 2024 (met toestemming, zie bijlage)	Nee	Geeft beschouwing over de gevonden associaties (mn vanwege verkeerd gebruik van icd codes). In Frankrijk is de aanbeveling geschrapt.

Conclusie werkgroep:

Voor niet-tandheelkundige procedures is het bewijs voor endocarditisprofylaxe zeer zwak. Er zijn alleen associaties gevonden, welke niet altijd even logisch zijn (bv. verhoogd risico op endocarditis bij arteriële punctie). Daarnaast schort het aan de methodologie van de studies (Janszky, Thornhill) ptn zijn geïncludeerd obv ICD codes, terwijl dat dan niet altijd gaat om patiënten met bewezen endocarditis. Ook wordt het aantal patiënten dat antibiotica gegeven zou moeten worden hoog ingeschat, gezien de hoeveelheid aan genoemde procedures, en is niet zonder bijwerkingen, met dus onduidelijkheid in of dit überhaupt endocarditis gaat voorkomen.

In Frankrijk is de aanbeveling ‘Systemic antibiotic prophylaxis may be considered for high-risk patients undergoing an invasive diagnostic or therapeutic procedure of the respiratory, gastrointestinal, genitourinary tract, skin, or musculoskeletal systems’ niet overgenomen (presentatie Bruno Hoen, ISCVID). Voorstel van de werkgroep is om de aanbeveling in NL (het was ook slechts een ‘may be considerd’ IIB, level C in de ESC guideline) ook niet over te nemen.

APPENDIX B: Results of literature searches and answers to PICOs (October 2025)

Contents

PICO 1: Daptomycine monotherapie voor staphylokokken endocarditis

Patients: Patiënten met endocarditis door staphylokokken

Intervention: Daptomycine + een tweede middel

Control: Daptomycine als monotherapie

Outcome: Mortaliteit op alle tijdshorizons, therapiefalen, optreden van daptomycine resistentie.

Onderzochte literatuur met opmerkingen van de richtlijncommissie:

Artikel (auteur, jaar)	**Geeft artikel antwoord op de PICO, zo ja, beschrijf kort hoe**	**Indien antwoord op de PICO:** **Opmerkingen over kwaliteit van artikelen (vermeld iig studie design en aantal patiënten)**
Moise, 2013	Ja Figure 1: Treatment succes voor IE met of zonder beta-lactam combo-therapie (n = 11) 100 vs 70%, p = 1 (?!) Breder getrokken naar 'endvasculaire infecties' door S. aureus waar septische artritis, osteomyelitis en onbekende bron ook bij zaten:	Retrospectief, multicenter naar S. aurues bacteriëmie patiënten behandeld met daptomycine en met vooraf al beperkte nierfunctie (eGFR <50). Daptomycine 6mg/kg, combi therapie specifiek naar B-lactam uitgesplitist en alleen voor S. aureus. Kwaliteit studie: laag. Retrospectief onderzoek, geen standaard

	90% (9/10) treatment succes met combotherapie. 56% zonder (13/23), p = 0.061	doseringen, geen multivariable analyse. Precisie: laag: kleine aantallen, , veel ontbrekende uitkomsten
Durante-Mangoni, 2016	Ja Alinea 3.6: *In-hospital death and microbiological plus clinical failure did not differ according to whether patients received a partner antimicrobial to daptomycin or HDD monotherapy (data not shown).*	Prospectief single center cohort studie uit Italië, IE patiënten met definitie IE behandeld met dapto >6mg/kg. 55% CIED, 25% NV, 20% PV. 87% vd patiënten had staphylokokken IE (48% S epidermidis, 31% .> aureus). 11 patiënten met staphylokokken IE kregen naast dapto ook B-lactam (oxacilline of ampicilline) ter synergisme voor mediane duur van 21 dagen. Kwaliteit van de studie: Laag, geen duidelijke vergelijking, geen statistiek bedreven op vergelijking. Precisie: zeer laag: kleine aantallen. **TvdV: eigenlijk kun je met deze data niets zeggen over of dapto mono of combi therapie beter is. Auteurs hadden dit er ook niet in moeten zetten.**
Seaton, 2016	Nee, geen aparte data voor endocarditis of voor S. aureus gerapporteerd	Retrospectieve registry studie naar daptomycine gebruik in CORE en EU-CORE registries. Kwaliteit niet gescoord gezien geen antwoord op de PICO
Kale-Pradhan, 2020	Nee, geen aparte data voor daptomycine mono vs combo gerapporteerd. NB in de sysrev zit een studie die niet in de relevante artikelen zit dit dapto mono vs combo vergelijkt: Jorgensen 2020 CID. Deze is niet endocarditis specifiek, echter wel toegevoegd nu	Systematic review naar vanco+beta-lactam en dapto+beta-lactam versus mono vanco of mono dapto voor MRSA bacteriëmie of endocarditis
Jorgensen, 2020	Ja, combinatie therapie minder vaak composiet uitkomst van mortality of recurrence (23 vs 27%, p = 0.013).	Retrospectieve multicenter cohort studie van patiënten met MRSA SAB, n = 221. (35% endocarditis, 27% bone/joint, 20% SSTI, 25% lijninfectie). 43$ van de combinatie patiëten kreeg cefepime als B-lactam. Dapto dosering 8mg/kg. Kwaliteit studie: redelijk, observationeel onderzoek maar goede methoden met correctie voor confounders.

		Precisie: laag, niet alle patiënten endocarditis, grootste deel van populatie voldoet niet aan PICO.
Pujol, 2021	Ja, Geen significant verschil in composiet eindpunt, hoewel wel voordeel van combo therapie lijkt (RR 1.29 in voordeel van combo therapie). Geen verschil in mortaliteit Welvaker AE's, met name hartfalen, in de combo groep, waardoor vaker stoppen van de fosfomycine	RCT met dapto mono vs dapto + fosfo in MRSA SAB en IE. N = 155, IE = 18 (12%) Kwaliteit: goed, RCT van goede kwaliteit, hoge dosering daptomycine Precisie: laag, weinig patiënten met IE of andere intravasculaire infectie.
Cristina García de la Mària, 2023 DOI: 10.1080/14787210.2023.2174969	Ja, gaat in op dapto vs dapto + 2e middel (fosfomycine)	Review artikel, ook Miro als co-auteur Exploring therapeutic combinations has shown fosfomycin to have a unique mechanism of action and to be the most effective option in preventing the onset of resistance to and optimizing the efficacy of daptomycin, suggesting the synergistic combination of fosfomycin with daptomycin is a useful alternative treatment option for MSSA or MRSA IE

PICO 2: Daptomycine monotherapie voor enterokokken endocarditis

Patients: Patiënten met endocarditis door enterokokken

Intervention: Daptomycine + een tweede middel

Control: Daptomycine als monotherapie

Outcome: Mortaliteit op alle tijdshorizons, therapiefalen, optreden van daptomycine resistentie.

Onderzochte literatuur met opmerkingen van de richtlijncommissie:

Artikel (auteur, jaar)	**Geeft artikel antwoord op de PICO, zo ja, beschrijf kort hoe**	**Indien antwoord op de PICO:** **Opmerkingen over kwaliteit van artikelen (vermeld iig studie design en aantal patiënten)**
Lubbert, 2015	Twijfelachtig, niet gespecifieerd op endocarditis of bacteriëmie	Registry studie naar patiënten met enterokokken infectie. N = 472. 12% IE (n = 58). Dapto dosering 6mg/kg.

		Overall, clinical success rates were similar whether patients received no concomitant antibiotic therapy (78.0%) or any concomitant antibiotic therapy (77.3%).
Peghin, 2019	Geen verschil tussen mono en combinatie therapie voor mortality of relapse	Prospectief cohort van Enterokokken endocarditis, n = 43, 16 patiënten kregen daptomycine based regime, waarvan. Geen verschil tussen daptomycine combinatie (n = 11) en monotherapie groep (n = 5) in deze 16 patiënten Studie kwaliteit: laag, observationeel, geen correctie voor confounders Precisie: laag, kleine aantallen
Turnridge, 2020	Nee	EUCAST position paper voor achtergrond, noemt alleen getallen van Peghin 2019

PICO 3a: Orale uitbehandeling van endocarditis door streptokokken

Patients: Patiënten met endocarditis door streptokokken

Intervention: Orale therapie voor minimaal de laatste twee weken van de behandelduur (zowel mono als dubbeltherapie)

Control: IV therapie gedurende de hele behandelduur

Outcome: Mortaliteit (primaire uitkomst), composiet van mortaliteit & embolism en ongeplande cardiale chirurgie (conform eindpunt POET trial)

Onderzochte literatuur met opmerkingen van de richtlijncommissie:

Artikel (auteur, jaar)	**Geeft artikel antwoord op de PICO, zo ja, beschrijf kort hoe**	**Indien antwoord op de PICO:** **Opmerkingen over kwaliteit van artikelen (vermeld iig studie design en aantal patiënten)**
Al Omari (2014)	Uitkomstmaat = cure. RCT van Stamboulian: geen verschil in uitkomst (cure) tussen iv en iv-orale switch groep.	Lage kwaliteit, veel retrospectief, kleine aantallen, zeer oude studies met oude antibiotica keuzes. Systematic review (11 studies, waarvan 8 met streptokokken endocarditis) -Colli (2007): retrospectief, n=4 viridans strept, vanco+linezolid. 100% cure. -Chetty (1988): prospectief NVIE, n=9

		strep, amoxi per os, 87% cure. -Pinchas (1983): prospectief NVIE, n=11 viridans strep, amoxi per os 6 weken (+ probenecid eerste 4 wkn en streptomycine laatste 2 wkn), 90% cure. -Philips (1977): retrospectief, n=8 viridans strep, amoxi, 100% cure -Gray (1964): retrospectief, n=8 viridans step, ampicilline, 92% cure. -Champeau (1963): retrospectief NVIE, n=6 viridans strep, feneticillline, 80% cure. -Friedberg (1952): retrospectief NVIE, n=6 viridans strep, aureomycine, 36% cure. -Schein (1948): retrospectief NVIE, n=76 strep, sulfonamide, 10% cure. 1 trial: Stamboulian (1991); 30 NVIE (15 viridans, 15 bovis). iv: 4 weken ceftriaxon. switch: 2 weken ceftriaxon+2 weken amoxi per os. 100% cure. Toxicity niet genoemd.
Bock (2023), substudie POET.	Geen antwoord op PICO, wel op target levels orale antibiotica voor (o.a.) strep. Amoxi 4x1000mg: PTA 100%. Linezolid 2x600mg: PTA 92-100% (MIC), 67-84% (BP). Moxi 1x400mg: PTA 75-81% (MIC), 34-49% (BP). Rifamp 2x600mg: PTA 71-78% (MIC), 66% (BP).	Hoge kwaliteit studie. n=236 patienten, maar onduidelijk hoeveel streptokokken. PTA (probability of target attainment)
Brown (2020)	‘pharmacological data offer theoretical reassurance for the safety of oral therapy. This is coupled with a growing evidence base for non-inferiority of oral antimicrobials compared with prolonged parenteral therapy in practice.’	Geen meerwaarde. Review van papers die ook in deze tabel zijn opgenomen (één extra toegevoegd: Stamboulian et al. (1991).)
Demonchy (2011)	Partieel Seven IV-oral switches concerned streptococcal endocarditis, and consisted in monotherapy with amoxicillin (n = 4) or bitherapy chosen among amoxicillin, rifampin, or clindamycin. “favourable outcome” despite high frequency of complications and left sided IE.	Retrospectief, gericht op juist toepassen van antibiotica bij IE. Article on the quality of protocol adherence in infectious diseases (including IE). Total 66 IE patients. IV to oral was done (-against protocol!) in 29% of patients after 18 days (+/- 9) No correlation between IV to oral switch en mortaliteit.
El Dalati (2024)	Samengesteld eindpunt 90-dagen mortaliteit/recidief: n=2. Mediane iv duur: 18 dagen Mediane orale duur: 18 dagen	Lage kwaliteit. retrospectief, 32 patienten met IE (veel IVDU) die oraal uitbehandeld werden. n-5 streptokokken. Veelal dubbeltherapie: linezolid + amoxicilline, linezolid + levofloxacine, amoxicilline + levofloxacine.

Freling (2023)	Primaire uitkomstmaat: clinical succes dag 90. Geen verschil in uitkomsten tussen beide groepen.	Lage kwaliteit. multicenter, retrospectief. 257 pt met IE: -211 iv only (28.4% streptokokken), -46 iv-orale switch (21.7% streptokokken)
Heldman (1996)	Nee, alleen stafylokokken.	n.v.t. prospectief, RCT. rechtszijdige IE o.b.v. Stafylokokken
Iversen (2019)	Primaire uitkomstmaat: samengesteld eindpunt (o.a. mortaliteit) na 6 maanden. Voor IE o.b.v. streptokokken: 9.6% in iv groep versus 8.7% in switch groep = non-inferiority. iv-orale switch na minstens 10 dagen iv.	Hoge kwaliteit. Alleen bewijs voor dubbeltherapie. RCT, n=400 met linkszijdige IE (met/zonder kunstklep) waarvan 199 iv en 201 iv-oral switch. -199 iv groep: 104 streptokokken. -201 switch: 92 streptokokken.
Mourad (2024)	Nee, alleen stafylokokken.	n.v.t. systematic review + meta-analyse: S. aureus bacteremie en endocarditis.
Mzabi (2016)	Ja, 91 (vd 171, 43%) patienten met streptokokken endocarditis met orale therapie behandeling. Standaard 4 weken behandeling. Median switch na 14 dagen switch naar oraal. (range 7-42). Behandeling 92% amoxicilline, 4% met amoxi-clinda, 3% amoxi-rifa. (niet verder uitgesplitst) No recurrence in de oral group (streptococci), geen verschil in mortality na median opvolging van 33 (1-2823) dagen. Na correctie in de hele groep voor leeftijd, DM I, immunosuppressie, shock, kunstklep en S aureus – switch naar oraal is niet geassocieerd met een verhoogde mortaliteit.	Retrospective, tijdspannen 2000-2013, minimaal 1 week IV, met goede kliniek en dalend CRP. Dukes Definite endocarditis en possible. Patienten in oral route hadden zelfde leeftijd, sexe, of aangeboren afwijkingen. De groepen verschilden in comobiditeit en waren bij presentatie minder ziek. (en S aureus was minder vaak het pathogeen).
Parker (1980)	Nee (alleen staphylokokken)	n.v.t.
Pries Heje (2023)	Ja. Overall all cause mortality lower in PO group. POETry 106 PO versus 126 IV voor streptokokken.	Guideline implementation study, tijdspanne 1-5-2019 en 12-2020 1017 patienten geincludeerd Retrospectief observationale studie met de gebruikelijke caveats.
Rezar (2020)	Nee, meta analyse – niet gesplitst op verwekker	Meta analysis 1848 studies gescreend, 4 studies geïncludeerd.

Spellberg (2020)	Nee, narrative review (sterk in favor of partial oral treatment)	n.v.t.
Stamboulian (1991)	Primaire uitkomstmaat cure (negatieve bloedkweek na 6 maanden). 100% in beide armen. In subgroep van ongecompliceerde natieve klep IE is iv-orale switch even veilig als iv.	Redelijke kwaliteit, RCT maar kleine aantallen. RCT 30 NVIE (15 viridans, 15 bovis). Linkszijdige IE zonder complicaties. iv: 4 weken ceftriaxon (kon ook IM!). switch: 2 weken ceftriaxon+2 weken amoxi per os. 100% cure. Toxicity niet genoemd.
Svanbom (1979)	Nee (anecdotal)	n.v.t.
Wildenthal (2023)	Nee (S. aureus)	n.v.t.

PICO 3b: Orale uitbehandeling van endocarditis door staphylokokken

Patients: Patiënten met endocarditis door staphylokokken

Intervention: Orale therapie voor minimaal de laatste twee weken van de behandelduur (zowel mono als dubbeltherapie)

Control: IV therapie gedurende de hele behandelduur

Outcome: Mortaliteit (primaire uitkomst), composiet van mortaliteit & embolism en ongeplande cardiale chirurgie (conform eindpunt POET trial)

Onderzochte literatuur met opmerkingen van de richtlijncommissie:

Artikel (auteur, jaar)	**Geeft artikel antwoord op de PICO, zo ja, beschrijf kort hoe**	**Indien antwoord op de PICO:** **Opmerkingen over kwaliteit van artikelen (vermeld iig studie design en aantal patiënten)**
Al Omari (2014)	Colli: Op uitkomst cure met linezolid goede uitkomstmaat (100%). Iv-orale switch na 5 (+/-3) dagen (Colli)	Lage kwaliteit, kleine aantallen, MRSA. Systematic review (11 studies, waarvan 3 met staphylokokken endocarditis) -Colli (2007): retrospectief, n=8 MRSA, vanco+linezolid. 100% cure. -Dworkin (1989): prospectief, n=13 S. aureus, rechtszijdig IE met IVDU, cipro+rifamp. 77% cure. -Philips (1977): retrospectief, n=3 staph. Kinderen. Oraal (flu)clox. 100% cure

Bock (2023), substudie POET.	Geen antwoord op PICO, wel op target levels orale antibiotica voor (o.a.) staph. Amoxi 4x1000mg: PTA 100%. Diclox 4x100mg: PTA 9-17%. Linezolid 2x600mg: PTA 90-100% (MIC), 67-94% (BP). Moxi 1x400mg: PTA 100% (MIC), 83% (BP). Rifamp 2x600mg: PTA 100% (MIC), 66% (BP).	Hoge kwaliteit studie. n=236 patienten, maar onduidelijk hoeveel S. aureus. PTA (probability of target attainment)
Brown (2020)	'pharmacological data offer theoretical reassurance for the safety of oral therapy. This is coupled with a growing evidence base for non-inferiority of oral antimicrobials compared with prolonged parenteral therapy in practice.'	Geen meerwaarde. review van papers die ook in deze tabel zijn opgenomen (één extra toegevoegd: Tissot-Dupont et al. (2019).)
El Dalati (2024)	Samengesteld eindpunt 90-dagen mortaliteit/recidief: n=2. Mediane iv duur: 18 dagen Mediane orale duur: 18 dagen	Lage kwaliteit. retrospectief, 32 patienten met IE (veel IVDU) die oraal uitbehandeld werden. n-12 S. aureus (11x MSSA, 1x MRSA). Veelal dubbeltherapie: linezolid + cefalosporine/dicloxacilline/rifampicine.
Freling (2023)	Primaire uitkomstmaat: clinical succes dag 90. Geen verschil in uitkomsten tussen beide groepen.	Lage kwaliteit. multicenter, retrospectief. 257 pt met IE: -211 iv only (52% S. aureus), -46 iv-orale switch (63% S. aureus) Veel MRSA (20% en 35%). Veel dubbeltherapie (suppl).
Heldman (1996)	Primaire uitkomstmaat: treatment failure (uitgebreide definitie, incl mortaliteit). 1 in orale groep, 3 in iv groep (niet sign). Meer toxiciteit in IV groep: 62% versus 3% oraal.	Redelijke kwaliteit, wel lage aantallen, specifieke groep patienten (rechtszijdig IE, IVDU) prospectief, RCT. rechtszijdige IE o.b.v. Staph (S. aureus 93,5%) bij IVDU. IV versus oraal (cipro/rifamp). n= 44: 25 IV en 19 oraal.
Iversen (2019) RCT, n=400 met linkszijdige IE (met/zonder kunstklep) waarvan 199 iv en 201 iv-oral switch. -199 iv groep: 40 S. aureus en 10 CNS. -201 switch: 47 S. aureus, 13 CNS.	Primaire uitkomstmaat: samengesteld eindpunt (o.a. mortaliteit) na 6 maanden. 12,1% in iv groep versus 9% in switch groep = non-inferiority. iv-orale switch na minstens 10 dagen iv.	Hoge kwaliteit. Alleen bewijs voor dubbeltherapie. S. aureus in switch groep met kunstklep: n=7...
Mourad (2024)	Primaire uitkomstmaat: treatment failure. 11.3% in beide groepen. Geen verschil in AE tussen beide groepen, maar CI was wijd (0.07-5.94) en erg heterogene resultaten tussen studies.	Redelijke kwaliteit. Erg heterogene studies (IE links, IE rechts, ongecompliceerde SAB) systematic review + meta-analyse: S. aureus bacteremie en endocarditis. n = 4 RCTs Heldman, Iversen (met endocarditis) en Schrenzel (S. aureus bacteriemie,

		Kaasch (ongecompliceerde SAB). n = 204 switch, n = 186 iv. Geen subgroep analyses (MSSA, MRSA, IE)
Mzabi (2016)	Na correctie in de hele groep voor leeftijd, DM I, immunosuppressie, shock, kunstklep en S aureus – switch naar oraal is niet geassocieerd met een verhoogde mortaliteit. Maar omdat in SAB meer overlijden (overall groep) geeft deze paper geen duidelijk antwoord op deze PICO.	Retrospective, tijdspannen 2000-2013, minimaal 1 week IV, met goede kliniek en dalend CRP. Dukes Definite endocarditis en possible. De groepen verschilden in comobiditeit en waren bij presentatie minder ziek. Bij S. aureus werd vaker IV uitbehandeld. Staph: n=129 (S. aureus n=81 waarvan MSSA n= 67 en MRSA n= 14, CNS n=48)
Parker (1980)	100% cure	Lage kwaliteit studie. 35 cases met S. aureus IE (1969-1979). IV-orale switch nadat bloedkweken negatief, geen koorts meer, na mediaan 16,4 dagen (4-33d).
Pries Heje (2023)	Ja. Overall all cause mortality lower in PO group. S. aureus IE werd minder vaak geswitcht naar oraal.	Guideline implementation study, tijdspanne 1-5-2019 en 12-2020 1017 patienten geincludeerd, 562 pt waren mogelijke switch kandidaten, 240 pt (43%) zijn daadwerkelijk geswitcht. Retrospectief observationele studie met de gebruikelijke beperkingen.
Rezar (2020)	Nee, meta analyse – niet gesplitst op verwekker	Meta analyse. 1848 studies gescreend, 4 studies geïncludeerd. Deze 4 studies zijn ook opgenomen in deze tabel.
Spellberg (2020)	Nee, narrative review (sterk in favor of partial oral treatment)	n.v.t.
Svanbom (1979)	Nee (anecdotal)	n.v.t.
Tissot-Dupont (2019)	Uitkomstmaten: in-hospital mortaliteit, 30 dagen mortaliteit, 90-dagen mortaliteit, oorzaak overlijden. 30-dagen mortaliteit: 7% (switch) versus 14% (iv), p = 0,05. mortaliteit laatste follow-up (166 dagen): 19% (switch) versus 30%, p = 0,02.	Lage kwaliteit, design studie is opvallend. Before-and-after interventie studie. 2001-2011: n=170 S. aureus IE 6 wkn iv (oxa of vanco). 2012-2019: n=171 S. aureus IE 1 week cotrim/clinda iv en nadien 5 weken cotrim oraal (hoge dosis: 960/4800mg per dag).
Wildenthal (2023)	Primaire uitkomstmaat: microbiologisch falen dag 90. Geen verschil in strategie A (IV) en C (PO), maar IE werd minder vaak geswitcht.	Lage kwaliteit. Retrospectief (2016-2021). S. aureus bacteriemie (MSSA en MRSA, niet perse IE) bij patienten met IVDU. n= 238 strategie A (totaal IV): n=122. strategie B (incompleet behandeld,

		alleen IV): n=36 strategie C (iv-oral switch): n=69.

PICO 3c: Orale uitbehandeling van endocarditis door enterokokken

Patients: Patiënten met endocarditis door enterokokken

Intervention: Orale therapie voor minimaal de laatste twee weken van de behandelduur (zowel mono als dubbeltherapie)

Control: IV therapie gedurende de hele behandelduur

Outcome: Mortaliteit (primaire uitkomst), composiet van mortaliteit & embolism en ongeplande cardiale chirurgie (conform eindpunt POET trial)

Onderzochte literatuur met opmerkingen van de richtlijncommissie:

Artikel (auteur, jaar)	**Geeft artikel antwoord op de PICO, zo ja, beschrijf kort hoe**	**Indien antwoord op de PICO:** **Opmerkingen over kwaliteit van artikelen (vermeld iig studie design en aantal patiënten)**
Al-Omari, 2014	Nee. Systematic review tot 1 juni 2013. 3 studies waarbij enterokokken worden meegenomen: Coli,retrospectief cohort n = 14, 10% (?!) enterokokken, uitbehandled met linezolid. → onvoldoende kwaliteit om iets van te zeggen Philips, retospectief bij kinderen, n = 13, 15% (1…) enterokok. → onvoldoende om iets van te zeggen Campeau, retrospectief cohort, n = 10, 30% enterkokken → onvoldoende om iets van te zeggen	Eigenlijk geen studies naar enterkokken endocarditis, dus beantwoordt de pico niet.
Bock, 2024	Nee, spiegels en geen klinsiche uitkomsten als uitkomst	

Brown, 2020	Nee, sys review met zelfde studies als Al-Omari 2014	
El-Dalati, 2024	**Deels** Retrospectieve studie uit Kentucky naar pten met IE die oraal uitbehandeld waren (n = 32) over periode van 1 jaar**. N = 7 met E. faecalis.** AB niet gespecificeerd, maar vermoedelijk amoxicilline en/of linezolid. Over hele studie (niet enterokok specifiek) 2 dood/relapse, onbekend welke verwekkers. Geen vergelijkende data, maar dus worst case	Door kleine N, geen detailering van AB en specificering van uitkomsten zeer lage kwaliteit tot niet te interpreteren.
Freling 2023	**Ja** Retrospectief cohort naar aanleiding van beleidsaanpassing na POET trial uit de VS**. In totaal 33 pt'en met enterokokken endocarditis. 29 IV, 4 oraal**. Minimaal 1 therapie falen (onder amoxi/moxiflox). Overige 3 kregen linezolid monotherapie, therapiefalen niet gerapporteerd. (NB: getallen stonden in supplement)	Door kleine N (**maar 4 enterokokkken oraal behandeld**) zeer lage kwaliteit.
Heldman, 1996	Nee, staph IE	
Iversen, 2019	Ja RCT uit denemarken naar IV vs oraal uitbehandelen. Enterokokken n = 97 (46 iv, 51 oraal) Composiet eindpunt numeriek vaker in de IV groep (7/46 vs 4/51), geen significant verschil. 21 patiënten met E. faecalis kunstklep endocarditis die orale therapie kregen (en 18 IV) NB: altijd dubbel therapie, vnl amoxi + moxiflox (47%) en amoxi + linezolid (25%)	Hoge kwaliteit studie, ook qua aantallen voor enterokokken best redelijk (**N = 96**) met redelijke vertegenwoordiging kunstkleppen.
Mourad 2024	Nee, aureus	
Mzabi 2016	Ja Retrospectieve studie uit frankrijk naar oraal uitbehandelde IE. Vergelijkend met	Niet gerandomiseerde studie dus moderate kwaliteit. Enterokok specifieke

	IV door. Totale N = 426, **n = 49 voor e. faecalis.** Mediane tijd tot over op oraal voor enterokok 28 dagen. Oraal 23 pt'en, IV 26. 21/23 kregen amoxi monotherapie.	uitkomsten niet los gerapporeerd, **dus downgraden naar laag.** Desondanks redelijke N voor enterokokken en lage prevalentie van primaire uitkomst (dood/relapse) overall
Parker, 1980	Nee, staph	
Pries-Heje, 2023	Ja Retrospectieve studie uit Denemarken na wijzigen richtlijnen na de POET trial. **94 patiënten met enterokokken endocarditis, 45 oraal, 49 IV.** HR voor composiet uitkomst 0.79 (0.24-2.06).	**Moderate kwaliteit** (niet gerandomiseerd), wel enterokok specifieke uitkomsten gerapporteerd. Redelijke N voor enterokokken
Rezar, 2020	Nee, Sys rew en meta analyse van eerder besproken studies, geen enterokok specifieke analyse gedaan	
Spellberg 2020	Nee, Narrative review, niets enterokok specifieks	
Svanbornl 1980	Nee, geen enterokokken oral behandeld	
Wildenthal 2023	Nee, s. aureus	

PICO 4: Orale uitbehandeling van endocarditis, mono versus dubbel orale therapie

Patients: Patiënten met endocarditis

Intervention: Orale therapie voor minimaal de laatste twee weken van de behandelduur **met één middel**

Control: Orale therapie voor minimaal de laatste twee weken van de behandelduur **met twee middelen**

Outcome: Mortaliteit (primaire uitkomst), composiet van mortaliteit & embolism en ongeplande cardiale chirurgie (conform eindpunt POET trial)

Onderzochte literatuur met opmerkingen van de richtlijncommissie:

Artikel (auteur, jaar)	**Geeft artikel antwoord op de PICO, zo ja, beschrijf kort hoe**	**Indien antwoord op de PICO:** **Opmerkingen over kwaliteit van artikelen (vermeld iig studie design en aantal patiënten)**
Bock 2023	Nee, correleert data niet aan klinische uitkomst. Geeft wel inzicht in target attainment van orale therapie. (zie commentaar hiernaast) In 100% van stafylokokken en streptokokken werd met amoxicilline (1000mg 4 dd) target attainment behaald mbt clinical breakpoints op dag 1 en 5. Voor enterokokken was dat 75 en 85% resp. Tevens 100% (97 voor enterokokken dag 1) bij amoxicilline gerelateerd aan MIC. PK/PD analyses die gebruik maken van de MIC bereiken hogere PTA's dan tov BP A total of 236 patients were included in this substudy, of whom 175 patients had 2 oral antibiotics, 35 patients received an oral antibiotic adjunctive to intravenous treatment, and 26 patients received intravenous antibiotics alone.	Poet substudy analyse Commentaar in studie: Although the POET trial was not designed or powered to evaluate outcome in subgroups of patients, and the collected PK/PD data are not sufficient to analyze the correlation to outcome, the data allow for general analyses of target attainment with prespecified PK/PD targets. PK data was available in 392/261 treatments at day 1/ day 5
Brown 2020	Nee Artikel is een clinical review van bestaande literatuur, daarnaast: "comparing published serum antimicrobial levels after oral and IV administration, we conclude that safe	Artikel bevat theoretische verhandeling en samenvatting van 3 RCT's (POET, Heldman et al 1996 en Stamboulin 1991) en 8 observationele publicaties.

	levels of commonly used antibiotics can be achieved orally."	
El dalati 2024	Nee, wel wat handige data Amerikaanse studie. 32 patients with infectious endocarditis switched to oral treatment after MDO – vraag in artikel: clinical success? In 75% behandeling met per os dubbeltherapie, 25% single (8 pat). Quote: "Additionally, 25% of patients were treated with a single agent, suggesting that a subset of patients may not require dual antimicrobial therapy to effectively eradicate their infection."	Beschrijving van ervaring met patiënten die na MDO overgingen op per os behandeling. Geen data waarin single versus multiple AB per os wordt vergeleken. Geen rationale waarom voor single of multiple AB werd gekozen. Data betreffende single drug therapy: Eight patients (25%) were treated with a single oral agent. Of these, 2 patients were transitioned to oral doxycycline after receiving >5 weeks of IV therapy. Both of these individuals discharged rapidly BMA and before prior authorizations could be obtained for the protocol's oral antibiotics. Two patients were initially discharged receiving IV dalbavancin and developed side effects requiring a transition to oral linezolid. One patient, the only case of culture-negative IE, was treated with both IV dalbavancin and oral levofloxacin. One patient with *Candida* IE was transitioned to monotherapy with isavuconazole. One patient with MSSA tricuspid valve endocarditis was treated with linezolid alone after 3 weeks of IV therapy.
Freling 2023	Nee (één tabel met directe vergelijking van linezolid mono versus plus rifam – geen verschil in clinical outcome n=26 mono versus 4 met rifampicin). Doseringen: linezolid 2 dd 600 (evt plus rifampicine 1 dd 600 mg of 3dd 300 mg) Andere doseringen mono: amoxicilline 4 dd 500 mg of 3dd 1 gram, penicilline V 3dd 1 ram, levofloxa 4dd 750 mg, cotrim 3dd 8-12 mg/kg "We identified 257 patients with IE treated with IV-only (n = 211) or oral transitional (n = 46) therapy who met study inclusion criteria. → Criteria, the patient was clinically stable with no immediate indication for cardiac surgical intervention; the initial course of IV therapy cleared the patient's bacteremia; there were no concerns	Amerikaanse, multicenter (3), retrospectieve (extractie uit bloedkweekregistratie SEH database), Cohort Study Monotherapie verder werd gegeven voor 1 S agalactiae, 1 peni gevoelige S aureus (amoxi), 1 S gallolyticus (peni V), 1 MRSA (Levo), 3 E faecalis, 1 VRE en 5 S aureus, 10 MRSA, 1 S capitis,1 S anginosus, 1 S gallolyticus, 1 S bovis, 1 S viridans groep, 1 S pneumoniae (linezolid), 1 MRSA (cotrim), de andere micro-organismen in de per os groep werden met dubbeltherapie (wisselende regimes) behandeld.

	regarding absorption of oral therapy from the gastrointestinal tract; there were no psychosocial concerns that would cause IV therapy to be preferred for compliance or level of care concerns; and an oral antibiotic regimen was available to which the etiologic organism was susceptible in vitro, and had published clinical data. There was no significant difference between the groups in clinical success at 90 days or last follow-up. There was no difference in recurrence of bacteremia or readmission rates. However, patients treated with oral therapy had significantly fewer adverse events. Multivariable regression adjustments did not find significant associations between any selected variables and clinical success across treatment groups". Therapieduur (totaal) was gelijk aan de geijkte IV duur.	
Extra gereviewed: Heldman et al.	Nee, want alleen ri-sided endocarditis (44, 19 per os, 25 IV voor 28 dagen) – alleen dubbeltherapie in per os arm. Oral (ciprofloxacin and rifampicin) or IV (oxacillin or vancomycin plus 5 days of gentamicin) antimicrobials prior to blood culture results	Geen extra info
Mzabi, 2016	Nee, want retrospectief en niet gecontroleerd. Studie laat zien dat Relapse & re-infecties vergelijkbaar zijn in iv en iv 7 dgn/po groep In de iv groep ernstigere patenten, vaker Staph.aur, cerebrale embolien & co morbiditeit Studie laat wel zien dat er de bekeken micro-organismen meestal met monotherapie werd behandeld. Voor streptokokken (niet gespecificeerd) bij 84 van 91 patiënten oraal met amoxicilline per os mono-therapie. Bij enterkokken bij 21 van 23 met amoxi en bij staphylokken van 15 van de 54 met verschillende (monotherapie, 4 patienten mono met cipro, amoxi en clinda). Onduidelijk of mono-therapie geassocieerd was met slechtere	Retrospectief, tijdspanne 2000-2013, minimaal 1 week IV, met goede kliniek en dalend CRP. Aantal patienten: 426 Dukes Definite endocarditis en possible. Patienten in per os groep hadden zelfde leeftijd, sexe, of aangeboren afwijkingen.

	uitkomst – wsch ook veel te kleine getallen om dit na te gaan. Dosering wordt nergens genoemd	
Parker (1980)	Nee, geen vergelijk gemaakt. S aureus endocarditis (25 cases in 33 patient) en oraal behandeld met diclox, clinda of penicilline V. (voor clinda en peni geen doseringen genoemd) Insituut houdt 'nu' protcol aan: Patienten werden oraal met mono-therapie dicloxacilline 4 dd 1 gram per os behandeld waarna minimum serum lethal dilutions worden bepaald en dosering evt aangepast..	Patiënten (alle IV drugs gebruikers) gevolgd tussen 1969 en 1979. Retrospectief verzameld, all cured (6 maanden follow-up) Extra *in vitro*: "efficacy of both intravenous and oral antimicrobial therapy was monitored by in-vitro determination of serum antibacterial activity. Serum bactericidal titers using the blood culture isolates showed similar activity with both intravenous and oral drugs."
Pries-Heje (2023)	Nee Volgens de POET principes behandeld: 2 middelen. Artikel rapporteert niet welke middelen er gebruikt zijn, alleen of er oraal is behandeld.	Retrospectieve observationele cohort analyse na POET publicatie, patiënten tussen May 2019 and December 2020 Aantal patiënten: 562 - All cause mortaliteit belangrijkste verschil tussen iv vs po groep - Mediane switch na 16 dgn - Mediane opnameduur 24(17-36) vs 43 (32-51) dgn Resultaat ondersteunt POET criteria voor switch naar po
Wildenthal 2023	Nee, want gaat over complicated S aureus bacteriemie en niet alleen over endocarditis – wel hebben 154 patiënten in de studie van de 238 een endocarditis (64%) Geen data over welke antibiotica en in welke dosering werden gebruikt. "Although not powered to assess individual regimens, our data suggest that several oral antibiotic regimens with twice-daily dosing including doxycycline, linezolid, cefadroxil, and trimethoprim-sulfamethoxazole may be potential options for patients in whom pill burden and medication nonadherence is a significant concern." Zeggen wel iets over slagingskans van dubbel versus monotherapie op gecompliceerde S aureus bacteriemie an sich maar dus niet over endocarditis (tabel 4): Failure in single agent 13% (7/52 patienten) en 19% in dual agent (4/21).	Retrospectief cohort analyse. Aantal patiënten: 293 Patiënten zijn IV drugs gebruikers: antibiotica keuze beïnvloed door therapietrouw & doseringen ivm interactie co-medicatie Minimum 10 dagen IV antibiotica minimaal
Extra: Stamboulian 1991	Nee 30 patiënten met penicilline gevoelige Streptokokken (MIC <0.25 ug/mL voor peni, MIC <0.25 voor ceftriaxon, 50% S bovis). In twee groepen 15 pat 4 weken	Argentinie, RCT, single center. Kleine aantallen maar wel enige RCT met IV versus IV waarin monotherapie ingezet is.

	IV ceftriaxon, 15 pat 2 weken ceftriaxon gevolgd door 2 weken amoxicilline. Baseline karakterisieken waren niet sign verschillend. 100% cure rate in beide groepen. Geen orale therapie indien: hartfalen, ernstige aortaklep insuf, geleidingsstoornissen, thrombo-embolische complicaties, kunstklep of overgevoeligheid voor penicillines dan wel ceftriaxon)	Dosering amoxicilline 4 dd 1 gram per os. Ceftriaxon 1 dd 2 gram. Aorta en mitralisklep en combinatie. NB ceftriaxon werd ook im gegeven! Kunstkleppen ge-excludeerd.

PICO 5: Endocarditis profylaxe voor niet-tandheelkundige ingrepen

Werkgroepleden: Edwin Boel, Wilco Tanis, Nelianne Verkaik, Marlous Toren-Wielema

Patients: Patiënten met een hoog risico op endocarditis die een niet-tandheelkundige ingreep (bijv ERCP, bronchoscopie) ondergaan

Intervention: Antibiotica proylaxe

Control: Geen antibiotica profylaxe

Outcome: Incidentie van endocarditis (primaire uitkomst), mortaliteit, optreden van adverse drug events

Onderzochte literatuur met opmerkingen van de richtlijncommissie:

Artikel (auteur, jaar)	**Geeft artikel antwoord op de PICO, zo ja, beschrijf kort hoe**	**Indien antwoord op de PICO:** **Opmerkingen over kwaliteit van artikelen (vermeld iig studie design en aantal patiënten)**
Larry M. Baddour Circulation. 2023;148:1529–1541. DOI: 10.1161/CIR.000000000000118	Nee Review	In summary, we propose that there is sufficient evidence associating certain NDIPs with the subsequent occurrence of IE, in particular, in those at high IE risk, to warrant a reevaluation of IE prevention advice.
Briana Goddard, MD Urol Clin N Am 51 (2024) 467–474	Nee Opsomming van beperkte data	Best practice statements by the AUA and AHA do not recommend administering antibiotic prophylaxis for patients with artificial valves undergoing a GU

		procedure for the sole purpose of preventing infectious endocarditis.
Imre Janszky JACC VOL. 71, NO. 24, 2018	Nee Geen RCT All patients >20 years of age with a primary discharge diagnosis with International Classification of Diseases-10th Revision codes I33, I38, or I39 occurring between January 1, 1998, and December 31, 2011, in Sweden were included.	several invasive nondental medical procedures are associated with a markedly increased risk for infective endocarditis. Health care professionals performing particularly risk-prone procedures should consider every possible preventive measure to decrease the excess risk.
Tejs Ehlers Klug Journal of Cardiovascular Pharmacology and Therapeutics 17(3) 298-302	Nee aim of the present study was to explore the incidence of bacteremia during elective and quinsy tonsillectomy in order to evaluate the antibiotic prophylaxis recommendations to patients at high risk of infective endocarditis who are undergoing tonsillectomy.	In all, 59% and 42% of electively and acutely tonsillectomized patients, respectively, had bacteremia with microorganisms that are predominant in bacterial endocarditis. These results challenge the distinction made by the European Society of Cardiology between elective and quinsy tonsillectomy, namely that antibiotic prophylaxis is the only recommendation to patients undergoing procedures to treat an established infection. Based on our findings, we advocate the use of amoxicillin with clavulanic acid in patients at high risk of developing infective endocarditis.
Amar R. Mohee BJU Int 2014; 114: 118–124	Nee The objectives of the present study were to assess if there was an association between urological procedures and thedevelopment of IE. A retrospective, case-control design was used to compare four distinct groups of patients with IE: (1) enterococcal IE, (2) CoNS IE, (3) *Streptococcus bovis*-group IE, (4) oral streptococcal IE.	The association between enterococcal IE and urological procedures raises questions about the pathogenesis of enterococcal IE. Can enterococcal IE result from bacteraemia caused by the procedure? Or, are patients who undergo urological procedures more likely to have an underlying urological pathology that causes repeated undetected bacteraemias in the period preceding the procedures? Both mechanisms may lead to the bacterial seeding of cardiac valves, but would warrant different approaches to prophylaxis
Mia M. Pries-Heje1,2 Current Cardiology Reports (2023) 25:1873–1881	Nee The aim of this review is to compare similarities and differences in current recommendations for antibiotic prophylaxis for IE by the three largest international societies, with consideration of some of the recent published works.	The question of whether to recommend antibiotic prophylaxis or not in certain patient populations remains unanswered and remains largely based on expert consensus opinion
Swiss expert group on Infective Endocarditis Prevention, Sendi Parhamab	Nee The Swiss societies of Infectious Diseases, Pediatric Cardiology and Cardiology and the Pediatric Infectious	Gastrointestinal/genitourinary procedures – Antibiotic prophylaxis is not recommended for gastroscopy, colonoscopy, low-risk laparoscopic procedures on the biliary tract (see also

	Disease Group of Switzerland present the current update on infective endocarditis prophylaxis in a joint initiative.	recommendations for antimicrobial perioperative prophylaxis of Swissnoso 2015), cystoscopy, vaginal or caesarean delivery, or transoesophageal echocardiography. – In the case of an established infection, an empiric antibiotic regimen containing anti-enterococcal activity should be used.
YARDENA SIEGMAN-IGRA Scandinavian Journal of Infectious Diseases, 2010; 42: 208–21	Nee The purpose of this study was to explore the possible link between IE and GI and GU procedures and to examine the contribution of these procedures to the occurrence of IE in order to appreciate whether the removal of these procedures from the indications for IE prophylaxis was justified. In brief, data on all adults with culture-positive IE in a tertiary care university hospital in Tel Aviv were collected prospectively by reviewing all of the patients' medical records, with special attention to invasive procedures performed before the onset of IE symptoms. This database was currently reviewed and patients who had invasive procedures within the 3 months preceding the diagnosis of IE were the subject of the present study.	Hence, GI and GU procedures pose a non-negligible risk of acquisition of IE. Consequently, it is proposed here, that adults at high risk of IE who undergo surgical GI and GU procedures, receive prophylaxis that includes an anti-enterococcal agent In conclusion, GI and GU procedures pose a non-negligible risk of acquisition of IE, having been associated with 9% (20 of 212) of IE episodes,
Martin H. Thornhill JACC VOL. 71, NO. 24, 2018	No EDITORIAL COMMENT op het artikel van Janszky	If the breadth of procedures associated with increased risk is confirmed by further studies, this will raise important questions for guideline committees about the benefits of recommending antibiotic prophylaxis prior to some of these procedures. However, broadening the scope of antibiotic prophylaxis to include all of these procedures is unlikely to be the solution. At least for those procedures where sterility should be easy to achieve and maintain, the solution is more likely to lay with improved sterile technique, infection control procedures and identifying systematic approaches for reducing health care–associated bacteremia rather than necessarily advocating antibiotic prophylaxis
Martin H Thornhill	Nee An admission was defined as a single continuous hospital stay (which could comprise several consultant episodes), where an International Classification of Diseases 10th Revision (ICD-10) primary or secondary diagnosis code I33.0, I33.9, I39.0, I39.1, I39.2, I39.3, I39.4 or I39.8, or a primary diagnosis	We report a significant association between implantation of CIEDs, upper and lower GI endoscopy, bronchoscopy, and dental extractions (including surgical tooth removal), and subsequent IE. These procedures resulted in an additional 14.3–49.5 IE cases/100000 procedures in those at high IE risk and an additional 1.1–3.9 IE cases/100000 procedures in those at moderate risk.

	code I38.X, was used for any consultant episode	These data support a reconsideration of the possible role of preprocedural AP for these procedures in those at high IE risk.
Presentatie van Bruno Hoen ISCVID 2024 (met toestemming, zie bijlage)	Nee	Geeft beschouwing over de gevonden associaties (mn vanwege verkeerd gebruik van icd codes). In Frankrijk is de aanbeveling geschrapt.

PICO 6: Suppressieve therapie

PICO 6:

Patients: Patiënten met endocarditis waarvoor operatie indicatie die geen operatie ondergaan

Intervention: Suppressieve therapie (3> maanden)

Control: Geen suppressieve therapie

Outcome: Mortaliteit (primaire uitkomst), relapse van endocarditis

Onderzochte literatuur met opmerkingen van de richtlijncommissie:

Artikel (auteur, jaar)	**Geeft artikel antwoord op de PICO, zo ja, beschrijf kort hoe**	**Indien antwoord op de PICO:** **Opmerkingen over kwaliteit van artikelen (vermeld iig studie design en aantal patiënten)**
Smego 2011	Deels Suppressieve therapie met fluconazol kan gegeven worden bij candida endocarditis, maar het lijkt er op dat een aanzienlijk deel van de patiënten ook genezen kan worden zonder levenslange suppressieve therapie	Systematic review over candida endocarditis en (suppressieve) therapie met fluconazol: Van 64 patiënten hadden 44 “cure”. 21 patiënten (onbekend of cure of failure) hadden >6 maanden therapie. Mediane duur van behandeling met fluconazol 60d.
Giuliano 2017	Deels Chronische suppressieve therapie lijkt kans op sterfte bij candida endocarditis te verminderen. Zeer lage kwaliteit evidence	Eigen database + systematic review van patiënten met candida endocarditis. N = 140. Pagina 6*: A reduced risk of death was demonstrated in patients with NVE or PVE who were administered chronic suppressive therapy (RR 0.30, 95% CI: 0.17–0.55)*.

		NB: natuurlijk wel enorme immortal time bias… Overall stuk van lage kwaliteit: retrospectieve data, statistische analyse matig. Wel effect te zien met minder sterfte, maar ik heb wel mijn vraagtekens
Vallejo Camazon, 2021	Nee, niet formeel aan de PICO, wel interessante overall informatie	Spaanse retrospectieve studie, wel multicenter, naar patiënten met endocarditis en een indicatie voor chirurgie maar die niet geopereerd zijn en in plaats daarvan verlengde antibiotica therapie kregen. Geen vergelijking met de patiënten met indicatie voor chirurgie zonder operatie die géén verlengde antibiotica therapie kregen. Verlengde therapie is in deze studie verlengde IV AB en/of suppressieve orale therapie. 24 patiënten kregen suppressieve therapie (wv 12 eerst ook al langer IV behandeld), met een relapse in 4 patiënten tijdens FU. Wel interessant: bij 9 patiënten werd na onbekende tijd een PET/CT verricht en AB gestopt als de PET/CT geen afwijkingen meer lieten zien. Hierbij traden dan geen relapses op. NB: ook een groep die enkel verlengde IV AB kreeg (9-34 wkn) waarna stop, ook met relatief goede uitkomsten na >1j (tabel 4, pagina 572)
Beaumont, 2024	Nee, niet formeel aan de PICO, wel interessante overall informatie	Franse single center retrospectieve cohort studie naar alle patiënten die op levenslange suppressieve antibiotica zijn gezet. 1jrs overleving was 84%, relapses kwamen voor in 12%, in 12% was sprake van drug adverse events. Indicaties voor suppressieve therapie waren voornamelijk niet kunnen verwijderen van kunstmateriaal (67%). Het ging voornamelijk om device IE (40 vd 42). AB voornamelijk amoxi (1gr 2dd of 3dd, voor enterokokken en streptokokken) en doxycycline (200mg 1dd, voor staph en enterokok)
Garofoli, 2024	Deels, Geen statistiek, maar bij enterokokken endocarditis met OK indicatie maar niet uitgevoerd zou suppressieve therapie relapse/dood kunnen voorkomen. Zeer lage kwaliteit evidence	Franse single center retrospectieve studie naar patiënten met specifiek E. *faecalis* endocarditis. N = 54, 15 (28%) kregen orale suppressieve therapie met amoxicilline, meestal 2000mg/dag, met als indicatie voor de helft chirurgie geïndiceerd maar niet uitgevoerd of grote kans op relapse volgens behandelaar. Relapses lijken numeriek minder vaak voor te komen in de suppressieve AB groep, maar gezien

		kleine aantallen geen statistiek op bedreven.
Lemmet, 2024	Nee, niet formeel aan de PICO, wel interessante overall informatie	Franse single center retrospectieve studie naar patiënten met endocarditis. N = 251, 22 (9%) kreeg suppressieve AB. Merendeel van deze patiënten had al eerder een endocarditis gehad door hetzelfde micro-organisme (15/22). 91% had wel een OK indicatie of indicatie voor CIED removal, geen onderging dit. Orale regimes varieerden van amoxicilline voor enterokokken (3dd1gr) tot cotrim of doxycycline voor staphylokokken. Suppressieve therapie leek goed in voorkomen van relapse, slechts 2/22 kregen dit tijdens FU. Bij 14% was sprake van tolerance issues. Geen vergelijking gedaan tussen de patiënten met zelfde risicoprofiel die geen SAT kregen

GEEN PICO: Vermijden van nefrotoxische combinaties

Werkwijze: de leden van de werkgroep zijn de richtlijn nagelopen op combinaties van nefrotoxische middelen, namelijk flucloxacilline, gentamicine, rifampicine en vancomycine, en hebben gekeken naar de onderbouwing voor deze combinaties en eventuele alternatieven.