STICHTING WERKGROEP ANTIBIOTICABELEID

SWAB guidelines for the antimicrobial treatment of infective endocarditis

June 2019

Typing errors that resulted in incorrect advice fixed February 2020 are highlighted in yellow

Typing errors that resulted in incorrect advice and corrected in January 2021 highlighted in green

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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/day in 6 doses + Ceftriaxone 4g/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) + Ceftriaxone 2g/day in 1 dose

Table 1.1.3. Empirical therapy, native valve, acute presentation

Situation	Recommendation
Native valve, acute presentation	Flucloxacillin 12g/day in 6 doses or by continuous infusion
Native valve, acute presentation *Non-severe penicillin allergy*	Cefazolin 6g/day in 6 doses or by continuous infusion
Native valve, acute presentation *Severe beta-lactam allergy*	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/day in 6 doses or by continuous infusion + 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/day in 6 doses or by continuous infusion + Vancomycin 2000-3000mg/day in 2-3 doses or by continuous infusion. Dose for trough levels of 15-20mg/l

Table 2.1.1 Viridans group streptococci including *S. gallolyticus*, penicillin MIC ≤0.125mg/l - 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/day in one dose for 4 weeks*

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Native valve *Severe beta-lactam allergy*	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*
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
Native valve – 2 week treatment (only in uncomplicated IE) *Non-severe penicillin allergy*	Ceftriaxone 2g/day in one dose for 2 weeks + Gentamicin 3mg/kg/day in 1 dose for 2 weeks

* Gentamicin not recommended

Table 2.1.2 Viridans group streptococci including *S. gallolyticus*, penicillin MIC ≤0.125mg/l - 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/day in one dose for 6 weeks*
Prosthetic valve *Severe beta-lactam allergy*	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

Table 2.2.1 Viridans group streptococci including *S. gallolyticus*, penicillin MIC 0.250 – 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
Native valve *Non-severe penicillin allergy*	Ceftriaxone 2g/day in one dose for 4 weeks + Gentamicin 3mg/kg/day in 1 dose for 2 weeks
Native valve *Severe beta-lactam allergy*	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 – 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

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Prosthetic valve *Non-severe penicillin allergy*	Ceftriaxone 2g/day in one dose for 6 weeks + Gentamicin 3mg/kg/day in 1 dose for 2 weeks
Prosthetic valve *Severe beta-lactam allergy*	Vancomycin 2000-3000mg/day in 2-3 doses or by continuous infusion for 6 weeks. Dose for trough levels of 15-20mg/m ¥

¥ Gentamicin not recommended if vancomycin is used

Table 2.3.1 *Streptococcus pneumoniae*

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

Situation	Recommendation
Native valve	Flucloxacillin 12g/day in 6 doses or by continuous infusion for 6 weeks*
Native valve *Non-severe beta-lactam allergy*	Cefazolin 6g/day in 3 doses or by continuous infusion for 6 weeks*
Native valve *Severe beta-lactam allergy*	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

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

Situation	Recommendation
Prosthetic valve	Flucloxacillin 12g/day in 6 doses or by continuous infusion for 6 weeks + Rifampicin1200mg day in 2 doses for 6 weeks + Gentamicin 3mg/kg/day in 1 dose for 2 weeks†
Prosthetic valve *Non-severe beta-lactam allergy*	Cefazolin 6g/day in 3 doses or by continuous infusion for 6 weeks + Rifampicin 1200mg day in 2 doses for 6 weeks + Gentamicin 3mg/kg/day in 1 dose for 2 weeks†

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Prosthetic valve *Severe beta-lactam allergy*	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 1200mg day in 2 doses for 6 weeks + Gentamicin 3mg/kg/day in 1 dose for 2 weeks†

† 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 2000-3000mg/day in 2-3 doses (trough levels 15-20mg/l) or by continuous infusion (plateau 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. 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 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 1200mg day in 2 doses for 6 weeks + Gentamicin 3mg/kg/day in 1 dose for 2 weeks†
Prosthetic valve	If vancomycin cannot be given, replacing vancomycin with daptomycin 10mg/kg/day in 1 dose might be an option if susceptible. 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 4.1.1 *Enterococcus* spp., amoxicillin susceptible, no high level aminoglycoside resistance (HLAR)

Situation	Recommendation
Native valve or Prosthetic valve	Amoxicillin 12g/day in 6 doses or by continuous infusion for 6 weeks + Ceftriaxone 4g/day in 2 doses for 6 weeks or by continuous infusion‡
Native valve or Prosthetic valve	Amoxicillin 12g/day in 4-6 doses or by continuous infusion for 6 weeks + Gentamicin 3mg/day in 1 dose for 6 weeks

‡ First choice regimen

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

Situation	Recommendation
Native valve or Prosthetic valve	Amoxicillin 12g/day in 6 doses or by continuous infusion for 6 weeks + Ceftriaxone 4g/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 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 3mg/day in 1 dose for 4-6 weeks

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

Situation	Recommendation
Native valve or Prosthetic valve	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

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

Situation	Recommendation
Native valve or Prosthetic valve	Decide the optimal treatment regimen in consultation with a medical microbiologist or infectious disease specialist or with an endocarditis team.

Table 5.1.1 HACEK spp. – native valve

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

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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/day in 2 doses for 6 weeks˚
Native valve or Prosthetic valve *Severe beta-lactam allergy*	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˚

˚ Consider adding rifampicin 1200mg/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/day in 6 doses for 6 weeks + Ceftriaxone 4g/day in 2 doses for 6 weeks + Doxycycline 200mg/day in 1 or 2 doses for 6 weeks Δ
Prosthetic valve	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 2g/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.: Q-fever, bartonellosis) are negative

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1. Introduction

Infective endocarditis (IE) 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. IE is a highly heterogenic disease that can be caused by a multitude of organisms with a myriad of signs, symptoms and complications. IE is also a rare disease, with an estimated annual incidence of 3 to 9 per 100.000 persons per year (1).

The rarity of the disease and the many treatment options warrant guidelines to support clinicians in the management of patients with IE. This guideline aims to provide clinicians guidance in choosing the best antibiotic strategy for patients with IE. The present text replaces the previous SWAB guideline on infective endocarditis which dates from 2003 (2).

2. Scope and validity of the guideline

The scope of this guideline encompasses the antimicrobial treatment of IE in adult patients, with the exception of pregnant women. The treatment of IE 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 rare 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) (3-5). 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.

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. 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.

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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 Association of Internal Medicine, the Netherlands Society of Cardiology and the Netherlands Society for Thoracic Surgery. 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 (6, 7). The guideline committee used the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for antimicrobial susceptibility.

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 (3, 4). 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(8, 9), 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 found in PubMed and indexed between January, 2015, and January, 2018. Wide search terms were used (see appendix B for details) and all articles were screened based on title and abstract for full text review. Full text review of selected articles was carried out by

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members of the guideline committee working in pairs of two, which led to a recommendation that was plenary 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 (10). 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(11). 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(10). 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 adapted as "strong" recommendations.

In cases where 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 in the results. The highest level of evidence in this guideline is thus scored as moderate quality evidence. In cases where 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.

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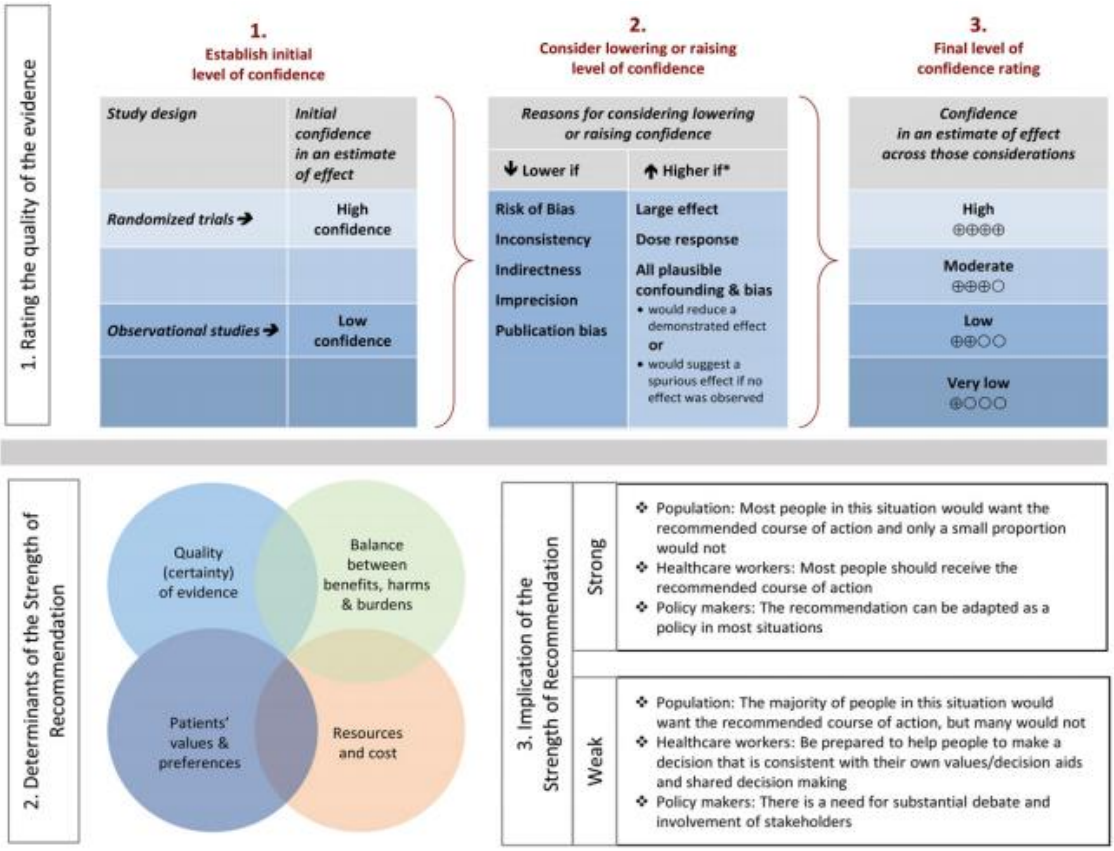


Figure 1 Approach and implications to rating the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology

Preparation of the guideline text was carried out by a 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 will be published through the SWAB website at (https://wwww.swab.nl/richtlijnen). The guideline committee will strive 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 (IGZ) and the Ministry of Health (VWS) since 2013. In each hospital, an Antimicrobial Stewardship

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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 in to 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 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 necessitates long term treatment with intravenous antibiotics. Treatment duration is 6 weeks in most patients, but can be longer or shorter in selected patients. Treatment duration is among others based on the causative micro-organism, the duration of bacteraemia and result of valve cultures if the patient underwent surgery. Bacteraemia in IE can last several days 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. In clinical practice, if follow-up cultures are missing or far in between, last day of 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 consist of multiple antimicrobial agents. The committee likes to emphasize that bioprosthetic valves contain metal susceptible to biofilm formation just like mechanical prosthetic valves. Hence, where the document says ‘prosthetic valves’, it refers to bio-valves and mechanical valves

Whether patients who underwent valve surgery for native valve IE 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. 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

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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 (12, 13). Additionally, continuous infusion allows for easier administration, creating an advantage for both health care providers and patients.

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 day of blood culture sterilisation and not day of surgery.	Strong	Very low

Recommendation 3	**Strength of recommendation**	**Quality of evidence**
If intra-operative cultures are positive, 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 IE who undergo valve surgery, postoperatively should receive 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 seems reasonable	Weak	Very low

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6. Allergies to first choice antibiotics and toxicity

The majority of patients with infective endocarditis are treated with a beta-lactam antibiotic. Up to 10% of patients report a penicillin or beta-lactam allergy, while 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 and 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 where a cephalosporin such as cefazolin or ceftriaxone may be given, while severe beta-lactam allergy is meant for patients in whom a cephalosporin is not an option. 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 thought to be more potent than the other classes of antibiotics (e.g.: vancomycin) and 2) the alternative antibiotics are often antimicrobials which are best held in reserve from an antimicrobial stewardship perspective.

7. Oral treatment of endocarditis

Shortly before the finalization of this guideline, a randomized controlled trial on the partial oral treatment of infective endocarditis was published (14) . 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 IE 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 late prosthetic valve IE share the common causative agents: streptococci, *S. aureus*, enterococci and HACEK (*Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella*) group bacteria, while early 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

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(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 IE and place of acquisition (hospital acquired versus community acquired, or health-care 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. 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.

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

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. In patients with a non-severe allergy to penicillin, a combination of vancomycin for enterococci and staphylococi and ceftriaxone for streptococci and HACEK bacteria covers the most microorganisms. In patients unable to tolerate cephalosporins, vancomycin monotherapy is an option, but consultation with a medical microbiologist 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 ouctome. A combination of vancomycin and flucloxacillin covers all 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.

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

Recommendation 6	**Strength of recommendation**	**Quality of evidence**
Amoxicillin 12g/day in 6 doses + 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) + Ceftriaxone 2g/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)	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 12g/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 6g/day in 3 doses or by continuous infusion	Weak	Very low

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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 or by continuous infusion. Dose for trough levels of 15-20mg/l	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) + Flucloxacillin 12g/day in 6 doses or by continuous infusion	Weak	Very low

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9. Treatment of endocarditis caused by streptococci

Streptococci are among the most common causative agents of IE. 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 IE 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 mostly susceptible to penicillin (Minimal Inhibitory Concentration [MIC] ≤0.125 mg/l) (15). Penicillin- intermediate resistant streptococci (MIC 0.250-2 mg/l) can still be treated with penicillin, but require a higher dose of penicillin and the addition of gentamicin. Penicillin resistant streptococci (MIC >2 mg/l)are rare in the Netherlands.

The ESC and AHA guidelines differ on a 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 extremely high doses, the guideline committee advises a maximum dose of 18 million units of penicillin per day where the ESC and AHA use a maximum penicillin dose of 24 million units per day

In general, native valve IE 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 (2, 16, 17):

1. MIC penicillin ≤0.125 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 thromboembolitic 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 necessitates 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. 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

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published since has not resulted in new information. As stated before, taking in to account the 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*.

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 IE in all cases. Literature on this subject is scarce, and the AHA recommendations appear mainly based on older case series(18, 19), one of which shows a survival benefit from combination therapy. Two more recent retrospective cohorts (30 and 49 patients) demonstrate no benefit from adding a aminoglycoside (20, 21). All studies in this field are severely limited by their retrospective designs and possible confounding by indication. The guideline committee concludes there is no data to support adding gentamicin to standard therapy in IE caused by β-haemolytic streptococci but no data to recommend against it either. 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.

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

Recommendation 13	**Strength of recommendation**	**Quality of evidence**
Penicillin 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 ≤0.125mg/l
Setting: native valve, non-severe penicillin allergy

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

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

Recommendation 15	**Strength of recommendation**	**Quality of evidence**
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	strong	moderate

Causative agent: Viridans group streptococci including *S. gallolyticus*, penicillin MIC ≤0.125mg/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 2g/day in one dose for 2 weeks + Gentamicin 3mg/kg/day in 1 dose for 2 weeks	strong	moderate

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

Recommendation 17	**Strength of recommendation**	**Quality of evidence**
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	low
Gentamicin not recommended if vancomycin is used	strong	low

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

Recommendation 18	**Strength of recommendation**	**Quality of evidence**
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	strong	moderate

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

Recommendation 19	**Strength of recommendation**	**Quality of evidence**
Ceftriaxone 2g/day in one dose for 4 weeks + Gentamicin 3mg/kg/day in 1 dose for 2 weeks	strong	moderate

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

Recommendation 20	**Strength of recommendation**	**Quality of evidence**
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 ≤0.125mg/l
Setting: prosthetic valve

Recommendation 21	**Strength of recommendation**	**Quality of evidence**
Penicillin 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 ≤0.125mg/l
Setting: prosthetic valve, non-severe penicillin allergy

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

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

Recommendation 23	**Strength of recommendation**	**Quality of evidence**
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 – 2 mg/l
Setting: prosthetic valve

Recommendation 24	**Strength of recommendation**	**Quality of evidence**
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	strong	moderate

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

Recommendation 25	**Strength of recommendation**	**Quality of evidence**
Ceftriaxone 2g/day in one dose for 6 weeks + Gentamicin 3mg/kg/day in 1 dose for 2 weeks	strong	moderate

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

Recommendation 26	**Strength of recommendation**	**Quality of evidence**
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

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Causative agent: Viridans group streptococci and *S. gallolyticus*, penicillin MIC >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*
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	moderate

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

Recommendation 29	**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 may be considered. Treatment should be discontinued if signs of toxicity occur.	weak	low

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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 by coagulase-negative staphylococci (CNS) mainly occurs on prosthetic material. In the Netherlands, *S. aureus* is generally methicillin susceptible, while methicillin resistance is frequent in CNS. Historically, gentamicin was added to *S. aureus* native valve endocarditis as a synergetic agent based on in vitro studies and reduction of bacteraemia duration. However, adjunctive gentamicin in native valve *S. aureus* IE does not result in better clinical outcomes but does lead to an increased incidence of kidney injury(22, 23). Therefore, routine administration of gentamicin in staphylococcal native valve endocarditis is no longer recommended.

The recommendations for treatment of staphylococcal IE differ slightly between the ESC and AHA guidelines. The ESC recommends 4 to 6 weeks of treatment for native valve IE 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.

The ESC guidelines advise an alternative, partially oral, regimen for staphylococcal IE using clindamycin and cotrimoxazole. This is recommendation based on one non-randomized study in 31 patients published in a letter to the editor (24). The guideline committee is of the opinion that this regimen lacks the required standard of evidence to be considered for this guideline. Cotrimoxazole has also been shown to be inferior to vancomycin in patients with MRSA bacteraemia (25).

Both guidelines recommend daptomycin as an alternative to vancomycin in patients with staphylococcal endocarditis. Daptomycin dosing differs between the guidelines, with the ESC guidelines advising 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. Experience with daptomycin is often limited, and treatment should happen in close coordination with a medical microbiologist or infectious disease specialist.

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(26) . The guideline committee has decided not to follow 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 plankton state, as seen in vegetations. The guideline committee recognizes that evidence for both rifampicin and gentamicin in staphylococcal prosthetic valve endocarditis is limited, but sees no reason 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 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(27, 28). 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

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guidelines recommend adding rifampicin only after a 3-5 days of therapy or after bacteraemia has been cleared.

The ESC advises to give gentamicin in a single dose, while the AHA recommends 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.

In staphylococci resistant to either gentamicin or rifampicin, adding this agent to the treatment regimen is unnecessary.

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

Recommendation 30	**Strength of recommendation**	**Quality of evidence**
Flucloxacillin 12g/day in 6 doses or by continuous infusion for 6 weeks	strong	moderate
Routinely adding gentamicin to the treatment of staphylococcal native valve IE is not advised	strong	low

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

Recommendation 31	**Strength of recommendation**	**Quality of evidence**
Cefazolin 6g/day in 3 doses or by continuous infusion for 6 weeks	strong	moderate
Routinely adding gentamicin to the treatment of staphylococcal native valve IE is not advised	strong	low

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

Recommendation 32	**Strength of recommendation**	**Quality of evidence**
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

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

Recommendation 33	**Strength of recommendation**	**Quality of evidence**
Flucloxacillin 12g/day in 6 doses or by continuous infusion for 6 weeks + Rifampicin1200mg day in 2 doses for 6 weeks$ + Gentamicin 3mg/kg/day in 1 dose for 2 weeks*	strong	moderate

$ 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 34	**Strength of recommendation**	**Quality of evidence**
Cefazolin 6g/day in 3 doses or by continuous infusion for 6 weeks + Rifampicin 1200mg day in 2 doses for 6 weeks$ + Gentamicin 3mg/kg/day in 1 dose for 2 weeks*	strong	moderate

$ 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 35	**Strength of recommendation**	**Quality of evidence**
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 1200mg day in 2 doses for 6 weeks$ + Gentamicin 3mg/kg/day in 1 dose for 2 weeks*	strong	moderate

$ 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 36	**Strength of recommendation**	**Quality of evidence**
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

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

Recommendation 37	**Strength of recommendation**	**Quality of evidence**
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 1200mg day in 2 doses for 6 weeks$ + Gentamicin 3mg/kg/day in 1 dose for 2 weeks*	strong	moderate

$ 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 38	**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. Decide the optimal treatment regimen in consultation with a medical microbiologist or infectious disease specialist or with an endocarditis team.	strong	low

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11. Treatment of endocarditis caused by enterococci

Enterococci are part of the normal digestive flora and the causative agent of IE in approximately 10% of all cases and more in the elderly (29). *E. faecalis* causes the majority of enterococcal IE, while *E. faecium* only rarely causes IE (30). 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 (31).

Traditionally, penicillin, amoxicillin or vancomycin together with an aminoglycoside has been used for the treatment of enterococcal endocarditis. This combination has in vitro and in vivo synergetic activity against enterococci, but suffers from the risks of aminoglycoside toxicity. A combination of amoxicillin and ceftriaxone is also 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 (32). Treatment of enterococcal IE 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. This is based on one single center retrospective study of low quality, and the guideline committee is of the opinion that 6 weeks of treatment is more appropriate for this severe and difficult to treat infection (33). 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 IE 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 (34, 35), while the AHA additionally cites several studies demonstrating the effectiveness of combination therapy versus beta-lactam monotherapy(30, 33), which do not answer the question of how long to dose gentamicin An additional search revealed no new studies examining the effectiveness of the different regimes. The guideline committee is of 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 4 gram per day, the guideline committee recommends following 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. 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.

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

Recommendation 39	**Strength of recommendation**	**Quality of evidence**
First choice: Amoxicillin 12g/day in 6 doses for 6 weeks + Ceftriaxone 4g/day in 2 doses for 6 weeks	strong	low
Alternative regimen Amoxicillin 12g/day in 6 doses for 6 weeks + Gentamicin 3mg/day in 1 dose for 4-6 weeks	strong	low
Amoxicillin + ceftriaxone is preferred over amoxicillin + gentamicin for enterococcal endocarditis	weak	low

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

Recommendation 40	**Strength of recommendation**	**Quality of evidence**
First choice: Amoxicillin 12g/day in 6 for 6 weeks + Ceftriaxone 4g/day in 2 doses for 6 weeks	strong	low
Alternative regimen: Amoxicillin 12g/day in 6 doses for 6 weeks + Gentamicin 3mg/day in 1 dose for 6 weeks	strong	low
Amoxicillin + ceftriaxone is preferred over amoxicillin + gentamicin for enterococcal endocarditis	weak	low

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

Recommendation 41	**Strength of recommendation**	**Quality of evidence**
Amoxicillin 12g/day in 6 doses for 6 weeks + Ceftriaxone 4g/day in 2 doses for 6 weeks	strong	low

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

Recommendation 42	**Strength of recommendation**	**Quality of evidence**
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 3mg/day in 1 dose for 6 weeks	strong	low

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

Recommendation 43	**Strength of recommendation**	**Quality of evidence**
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 44	**Strength of recommendation**	**Quality of evidence**
Decide the optimal treatment regimen in consultation with a medical microbiologist or infectious disease specialist or with an endocarditis team.	Strong	Not applicable

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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 IE cases is caused by HACEK bacteria(36). HACEK endocarditis often has a subacute presentation and identification of bacteria may take several days, as HACEK bacteria grow slowly. Both the ESC and AHA recommend ceftriaxone monotherapy as the preferred antimicrobial. When the bacteria are susceptible to amoxicillin, the ESC advises to add 2 weeks of gentamicin while the AHA recommends amoxicillin alone. After reviewing the literature there is little evidence for the use of gentamicin in HACEK endocarditis. The guideline committee advises to use amoxicillin in the case of confirmed susceptibility and not to add gentamicin.

If ceftriaxone cannot be given due to severe beta-lactam allergy, both the ESC and the AHA recommend ciprofloxacin. The guidelines differ slightly on ciprofloxacin dosing, with the ESC recommending high doses of ciprofloxacin and the AHA recommending a normal dose (2dd500mg oral or 2dd400mg IV). References reported for these recommendations provide no clinical outcomes on use of ciprofloxacin as treatment option for HACEK IE 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)(37), and normal dosing seems reasonable. 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 45	**Strength of recommendation**	**Quality of evidence**
Ceftriaxone 2g/day in 1 dose for 4 weeks	strong	low
Amoxicillin 12g/day in 6 doses for 4 weeks ◊	strong	low

◊ only if proven susceptible

Causative agent: HACEK spp.
Setting: prosthetic valve

Recommendation 46	**Strength of recommendation**	**Quality of evidence**
Ceftriaxone 2g/day in 1 dose for 6 weeks	strong	low
Amoxicillin 12g/day in 6 doses for 6 weeks ◊	strong	low

◊ only if proven susceptible

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

Recommendation 47	**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

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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(38). *Escherichia coli* and *Pseudomonas aeruginosa* cause the majority of cases. Both the ESC and AHA advice consultation with a medical microbiologist of 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 48	**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

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14. Right-sided endocarditis

Right-sided endocarditis is a separate entity distinctly different from the more common left-sided endocarditis. 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 metastastatic 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 (39)and a prospective cohort study (40) 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, determine optimal treatment in consultation with a medical microbiologist, infectious disease specialist or endocarditis team.

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

Recommendation 49	**Strength of recommendation**	**Quality of evidence**
Flucloxacillin 12g/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 50	**Strength of recommendation**	**Quality of evidence**
Ciprofloxacin 1500mg/day in 2 doses orally for 4 weeks + Rifampicin 600mg/dag in 2 doses orally for 4 weeks	weak	Very low

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

Recommendation 51	**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

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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 (41). *C. acnes* is the most important pathogen, but other species have been reported as well. Because of both the rarity and the novelty of *Cutibacterium* endocarditis, there is little evidence on the best treatment, and neither the ESC nor the AHA mentions 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 required surgery as part of treatment(41, 42), though cure through conservative treatment alone has also been described(41, 43).

In a cohort of 15 patients from the International Collaboration on Endocarditis (ICE) cohort most patients were treated with a beta-lactam agent with or without an aminoglycoside(43). In two retrospective cohort studies from the US with respectively 8 and 24 patients most patients were treated with vancomycin or a cephalosporin(44, 45). In contrast, a 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)(42).

There is no human data on the adjunctive use of rifampicin in treatment of *Cutibacterium* endocarditis. In vitro studies report rifampicin as the most active agent against *C. acnes* biofilm(46), 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. Vancomycin is the last line option. In selected patients (e.g.: inoperable, extensive paravalvular abscesses) rifampicin may be added.

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

Recommendation 52	**Strength of recommendation**	**Quality of evidence**
Penicillin 12-18 million units/day in 6 doses or by continuous infusion for 6 weeks	Strong	Low

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

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

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

Recommendation 54	**Strength of recommendation**	**Quality of evidence**
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 55	**Strength of recommendation**	**Quality of evidence**
Consider adding rifampicin 1200mg/day in 2 doses in selected cases	weak	Very low

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16. Culture negative endocarditis

In a 5 to 10% of the patients with endocarditis in the Netherlands blood cultures do not show growth(47, 48). Negative blood cultures may be the result of prior antibiotic use or inappropriate or insufficient blood culture collection. Or the result of fastidious or obligate intracellular growing microorganisms. It is important to distinguish between endocarditis caused by inappropriate blood culture collection or incubation and prior antibiotic use and endocarditis 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 days before blood cultures are reported positive (45), 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.

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 beyond the scope of this guideline.

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, but does not provide a recommendation for treatment when all additional tests are negative (4).

The moment of switching from empirical therapy to a regimen directed to culture negative endocarditis is another important factor. There are no studies investigating 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 endocarditis team, infectious disease specialist or medical microbiologist.

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

Causative agent: culture negative endocarditis

Recommendation 56	**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

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Causative agent: culture negative endocarditis

Recommendation 57	**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 58	**Strength of recommendation**	**Quality of evidence**
Amoxicillin 12g/day in 6 doses for 6 weeks + Ceftriaxone 4g/day in 2 doses for 6 weeks + Doxycycline 200mg/day in 1 or 2 doses for 6 weeks Consider stopping doxycycline if additional tests for intracellular microorganisms (e.g.: Q-fever, bartonellosis) are negative	Weak	Very low

Causative agent: culture negative endocarditis
Setting: Prosthetic valve

Recommendation 59	**Strength of recommendation**	**Quality of evidence**
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 2g/day in 1 dose for 6 weeks + Doxycycline 200mg/day in 1 or 2 doses for 6 weeks Consider stopping doxycycline if additional tests for intracellular microorganisms (e.g.: Q-fever, bartonellosis) are negative	Weak	Very low

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17. Treatment Cardiac Implantable Electronic Devices endocarditis.

Cardiac implantable electronic device endocarditis is a relatively new entity. It's incidence increases with the increasing number of cardiac implantable devices (49, 50). CIED infections cover a spectrum from infections limited to the device pocket infections to recurrent bacteraemia (8, 51, 52). The following chapter exclusively concerns CIED endocarditis: bloodstream infections due to an infected CIED. Isolated device pocket infections are not covered in this guideline.

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. 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 60

Situation	**Recommendation**	**Strength of recommend ation**	**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 explantation, two to four weeks if *S. aureus* is the causative agent. The BSAC guidelines also advise at least 2 weeks of post explantation 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(53, 54); (55). These were single center retrospective cohort studies, two of which used two week treatment after explantation with favourable results (54) (55). 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 explantation treatment and found no relapse in all 40 patients treated (53).

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

If there is involvement of other cardiac structures such as a 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 explantation treatment if blood cultures taken after explantation remain positive.

Recommendation 61

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 - No extra cardiac foci or involvement of cardiac structures other than the infected device	Treat for 14 days with IV antibiotics after removal of device	Weak	Very low

Recommendation 62

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	Weak	Very low

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Recommendation 63

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	Weak	Very low

Recommendation 64

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 65

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

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 provide no clear advise on this subject, while the UK 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 (55) or in combination with subsequent oral suppressive therapy (56). In summary, the cure for an infected CIED is 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

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salvage therapy fails, removal of the infected device should again be considered. In those patients with a relapse after salvage therapy and no possibility to remove the device, oral suppressive therapy may be attempted.

Recommendation 66

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 67

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 68

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 it is preferable to have a device-free interval before implantation of a new CIED. The AHA guidelines recommend at least 14 days of device free interval after the last positive blood culture in the 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 is these blood cultures are negative after 72 hours.

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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.

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

Recommendation 69

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 if possible	Weak	Very low

Recommendation 70

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 explantation if possible	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,

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albeit that the UK guidelines offer slightly different dosing regiments compared to the AHA an ESC guidelines(3, 4). For complicated CIED 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 weather 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 71

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

Recommendation 72

Situation	Recommendation	Strength of recommendation	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 73

Situation	Recommendation	Strength of recommendation	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

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18. 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

19. Funding and Conflict of Interest

For the development of this guideline, the SWAB was funded by the National Institute for Public Health and the Environment (RIVM-CIb), the Netherlands.

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:

Author	**Potential conflict of interest**
Drs. T.W. van der Vaart	None
Dr. A. Buiting	None
Prof. dr. J.W. Deckers	None
Dr. E.H. Natour	None
Dr. N.J. Verkaik	None
Dr. J.T.M. van der Meer	None

20. Topics for the next revision of the guideline

- More detailed recommendations for beta-lactam allergies
- Out-patient antibiotic treatment
- Oral treatment of endocarditis

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21. 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
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
IgE	Immunoglobulin E
MIC	Minimal Inhibitory Concentration
MSSA	Methicillin Susceptible Staphylococcus aureus
NVE	Native Valve Endocarditis
PBP	Penicillin Binding Protein
PCR	Polymerase Chain Reaction
PVE	Prosthetic Valve Endocarditis
Spp	Species (plural)
SWAB	Stichting Werkgroep Antibiotica Beleid

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Appendices

Appendix A – clustered differences between the ESC and AHA guidelines

Appendix B - SWAB richtlijn endocarditis - bespreking discrepanties en aanvullende searches

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Appendix A: clustered differences between the AHA and ESC guidelines and the solutions by the guideline committee

	Discrepancy	Solution
1	Netilmicin as an alternative for gentamicin	Resolved in committee: netilmicin is not available in the Netherlands so recommendation is not added to the SWAB guideline
2	Missing doses and missing beta-lactam agents for pneumococcal endocarditis in the AHA guideline	Resolved in committee: agreed to use the ESC dosing and agents
3	Duration of treatment for granulicatella and abiotrophia endocarditis	Resolved in committee: decided not to advise on treatment for abiotrophia and granulicatella IE due to the rarity of the condition
4	Amoxicillin treatment for granulicatella and abiotrophia endocarditis	Resolved in committee: decided not to advise on treatment for abiotrophia and granulicatella IE due to the rarity of the condition
5	Daptomycin dosing	Resolved in committee: use the ESC dosing of 10mg/kg
6	Rifampicin dosing	Resolved in committee: advise a high dose of 1200mg/day in 2 doses for all cases
7	Quinupristine / dalfopristin as an alternatative treatment for enterococci	Resolved in committee: Q/D is not available in the Netherlands, so recommendation is not added to the SWAB guideline
8	Penicillin susceptibility in streptococci AHA considers MICs of 0,5 as penicillin resistant and advises treatment as for enterococci in patients with streptococcal IE and penicillin MIC ≥0.5mg/l. ESC considers MICs between 0.25 and 2.0 as penicillin-less-susceptible and only advises treatment with an anti-enterococcal-regimen if MIC is ≥ mg/l.	Consultation with an external expert and discussed in full committee
9	Adding gentamicin to vancomycin for penicillin-less-susceptible or resistant streptococci	Literature review

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10	Penicillin dosing is generally higher in the AHA than in the ESC	Consultation with an external expert and discussed in full committee
11	Adding gentamicin to PVE by streptococci. Advised in the AHA, but not in the ESC	Literature review
12	AHA advises adding gentamicin to all group B, C or G beta-haemolytic streptococcal endocarditis. ESC only recommends this is patients with a high penicillin MIC or in PVE by group-B streptococci.	Literature review
13	Duration of treatment for uncomplicated native valve IE by S. aureus (AHA 6, ESC 4-6)	Resolved in committee: 6 weeks for all patients, following the AHA
14	Alternative regimen with cotrimoxazole/clindamycin S. aureus IE (not in AHA)	Resolved in committee: decided not to add advise to SWAB guideline due to insufficient evidence for the regimen
15	Vancomycin dosing and desired troughlevels for both staphylococi and enterococci.	Consultation with an external expert and discussed in full committee
16	Gentamicin dosing: once daily or thrice daily for Staphylococci	Resolved in committee: gentamicin is always dosed once daily in the Netherlands.
17	Adding ciprofloxacin in PVE by gentamicin resistant Staphylococci	Literature review
18	Duration of gentamicin in enterococcal IE (2-6 vs 4-6 weeks)	Literature review
19	Gentamicin dosing: once daily or thrice daily for enterococci	Resolved in committee: gentamicin is always dosed once daily in the Netherlands.
20	Preference and caveats of amoxicillin/ceftriaxone over amoxicillin/gentamicin in enterococcal IE	Resolved in committee: preference for amoxicillin/ceftriaxone
21	Adding a beta-lactam agent to daptomycin when treating enterooccal IE	Literature review
22	Duration of linezolid when treating enterocccal IE (6 vs 8 weeks)	Literature review
23	Adding gentamicin to amoxicillin in HACEK IE	Literature review

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24	Ciprofloxacin dosing in HACEK IE	Literature review
25	Culture negative IE is not mentioned in the AHA	Resolved in committee
26	Choice of empirical therapy	Resolved in committee

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Appendix B - Resterende vragen en discrepanties SWAB-richtlijn endocarditis

In dit document worden de vragen van de SWAB-richtlijn endocarditis wordt de zoekstrategie en de resultaten hiervan toegelicht.

Gezocht werd in Medline (PubMed). Er werden per search meerdere zoekcriteria uitgetest, waarbij de search die het meeste resultaten opleverde werd gebruikt. Er werd gezocht tussen 1 januari 2014 (een jaar voor het verschijnen van de ESC en AHA richtlijnen) en 1 januari 2018. Titel en abstracts werden gescreend op inclusiecriteria.

De inclusiecriteria waren:

Case series, retrospectieve en retrospectieve cohort studies waarin in titel of abstract wordt ingegaan op de vraag die beantwoord moet worden.

De resterende discrepanties en vragen die beantwoord moeten worden met een literatuursearch zijn:

1. Toevoegen gentamicine bij kunstklep endocarditis door streptokokken
2. Toevoegen van gentamicine aan vancomycine in het geval van penicilline-intermediaire streptokok.
3. Toevoegen gentamicine bij groep B, C of G streptokokken endocarditis
4. Toevoegen van ciprofloxacine ipv gentamicine bij genta-resistentie kunstklep staphylokokken endocarditis
5. Duur gentamicine bij enterokokken endocarditis (2-6 weken versus 4-6)
6. Duur van linezolid bij enterokokken endocarditis (6+ versus 8+ weken), en versus daptomycine
7. Gentamicine toevoegen aan amoxicilline bij HACEK endocarditis
8. Dosering ciprofloxacine bij HACEK endocarditis
9. Beste behandeling P. acnes endocarditis
10. Device endocarditis:
    a. Wat is de optimale behandelduur voor cardiac implantable electronic device endocarditis als het device wordt verwijderd?
    b. Wat is de optimale behandelduur voor cardiac implantable electronic device endocarditis als het device wordt NIET verwijderd?
    c. Wanneer is het beste moment om een geïnfecteerd cardiac implantable electronic device te verwijderen?
    d. Hoe lang dient gewacht te worden voor een nieuw cardiac implantable electronic device te implanteren?
    e. Welk antibiotische regimes dienen te worden aangehouden bij het behandelen van cardiac implantable electronic device endocarditis?

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1. Toevoegen gentamicine bij kunstklep endocarditis door streptokokken

Discrepantie: Toevoegen gentamicine bij kunstklep endocarditis door streptokokken
Toelichting: De AHA geeft het toevoegen van gentamicine als optie bij kunstklep endocarditis door streptokken, de ESC adviseert dit niet.

Bronnen ESC	**Bronnen AHA**
2005 AHA guidelines (Baddour et al. 2005)	(Francioli et al. 1992),
2009 ESC guidelines (Habib et al. 2009)	(Sexton et al. 1998)
2012 BSAC guidelines (Gould et al. 2012)	(Murray et al. 1986)
2007 Swedish guidelines (Westling et al. 2007)	(Francioli 1993) (een review)
(Francioli et al. 1992)	(Wilson 1992) (een editorial)
(Sexton et al. 1998)	*AHA noemt bij deze aanbeveling geen extra bronnen. De bronnen die worden gebruikt voor de adviezen over natieve klep endocarditis door streptokokken zijn:*

Search string:

Publication date: from 1 january 2014 to 1 january 2018
Search terms: ("endocarditis"[MeSH Terms] OR “endocarditis” [Title/Abstract]) AND streptococ*[Title/Abstract])

Aantal hits: **575**

Artikelen toegevoegd aan literatuur review na screening op titel en abstract: **2**

(Fayad et al. 2014)
(Sunnerhagen, Nilson, and Rasmussen 2015)

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2. Toevoegen van gentamicine aan vancomycine in het geval van penicilline-intermediaire streptokok.

Discrepantie: Toevoegen van gentamicine aan vancomycine in het geval van penicilline-intermediaire streptokok.
Toelichting: *De ESC richtlijn adviseert gentamicine toe te voegen aan vancomycine bij endocarditis door een penicilline intermediair-gevoelige streptokok, de AHA adviseert dit niet*

Bronnen ESC	**Bronnen AHA**
Geeft hier geen bronnen voor	*Geeft hier geen bronnen voor*

Search string (zelfde als voor vraag 1):

Publication date: from 1 january 2014 to 1 january 2018
Search terms: ("endocarditis"[MeSH Terms] OR “endocarditis” [Title/Abstract]) AND streptococ*[Title/Abstract])

Aantal hits: **575**

Artikelen toegevoegd aan literatuur review na screening op titel en abstract: **0**

In de literatuur zijn er geen artikelen die op deze vraag een antwoord geven.

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3. Toevoegen gentamicine bij groep B, C of G streptokokken endocarditis

Discrepantie: Toevoegen gentamicine bij groep B, C of G streptokokken endocarditis
Toelichting: AHA adviseert bij ALLE groep B, C of G (maar dus niet bij groep A) te overwegen 2 weken gentamicine toe te voegen, terwijl dit bij de ESC alleen hoeft bij penicilline MIC ≥0.25 of bij groep B kunstklep-endocarditis

Bronnen ESC	**Bronnen AHA**
(Lefort et al. 2002)	(Smyth, Pallett, and Davidson 1988)
(Sambola et al. 2002)	(Baddour 1998)
	(Lefort et al. 2002)
	(Sambola et al. 2002)

Search string (zelfde als voor vraag 1):

Publication date: from 1 january 2014 to 1 january 2018
Search terms: ("endocarditis"[MeSH Terms] OR “endocarditis” [Title/Abstract]) AND streptococ*[Title/Abstract])

Aantal hits: **575**

Artikelen toegevoegd aan literatuur review na screening op titel en abstract: **7**

(Fayad et al. 2014)
(El Rafei, DeSimone, DeSimone, et al. 2016)
(Chow et al. 2016)
(Lacave et al. 2016)
(Abdelghany and Schenfeld 2014)
(Aoyama et al. 2015)
(Pachirat et al. 2014)

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4. Toevoegen van ciprofloxacine in plaats van gentamicine bij kunstklep endocarditis door gentamicine resistente staphylokokken

Discrepantie: Toevoegen van ciprofloxacine in plaats van gentamicine bij kunstklep endocarditis door gentamicine resistente staphylokokken
Toelichting: AHA: als CNS resistent zijn tegen alle aminoglycosiden kan overwogen een fluorchinolon te geven (IIb, level C), ESC zegt hier niets over

Bronnen ESC	**Bronnen AHA**
Noemt dit advies niet en geeft dus ook geen bronnen	(Chuard et al. 1991)

Search string:

Publication date: from 1 january 2014 to 1 january 2018
Search terms: ("endocarditis"[MeSH Terms] OR "endocarditis" [Title/Abstract]) AND (ciprofloxacin[Title/Abstract])

Aantal hits: **24**

Artikelen toegevoegd aan literatuur review na screening op titel en abstract: **1**

(Al-Omari et al. 2014)

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5. Duur gentamicine bij enterokokken endocarditis (2-6 weken versus 4-6)

Discrepantie: Duur gentamicine bij enterokokken endocarditis (2-6 weken versus 4-6)
Toelichting: AHA adviseert 4-6 weken gentamicine naast de amoxicilline, in de ESC wordt 2-6 weken aanbevolen bij een enterokokken endocarditis.

Bronnen ESC	**Bronnen AHA**
(Dahl et al. 2013)	(Chirouze et al. 2013)
(Gould et al. 2012)	(Dahl et al. 2013)
(Habib et al. 2009)	(Gavalda et al. 2007)
(Miro et al. 2013)	(Miro et al. 2013)
(Olaison, Schadewitz, and Swedish Society of Infectious Diseases Quality Assurance Study Group for 2002)	(Olaison, Schadewitz, and Swedish Society of Infectious Diseases Quality Assurance Study Group for 2002)
(Westling et al. 2007)	(Wilson and Geraci 1983)
(Dahl et al. 2013)	(Wilson et al. 1984)

Search string:

Publication date: from 1 january 2014 to 1 january 2018
Search terms: (enterococcus[MeSH Terms] OR enterococc* [Title/Abstract]) AND (endocarditis[MeSH Terms] OR endocarditis [Title/Abstract])

Aantal hits: **236**

Artikelen toegevoegd aan literatuur review na screening op titel en abstract: **8**

(Yuh 2016)
(Fayad et al. 2014)
(Leone, Noviello, and Esposito 2016)
(Banzon et al. 2016)
(Pericas et al. 2014)
(Falcone, Russo, and Venditti 2015)
(Peterson, Lau, and Ensom 2017)
(Pericas et al. 2015)

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6. Duur van linezolid bij enterokokken endocarditis (6+ versus 8+ weken), en linezolid versus daptomycine

Discrepantie: Toevoegen B-lactam aan daptomycine bij enterokokken (alleen als hoge MIC of falen in AHA, altijd in ESC)
Toelichting: Daptomycine wordt in beide richtlijnen als alternatief regime aangeraden (bijv bij vancomycine allergie of vancomycine resistentie). De ESC richtlijnen adviseren als daptomycine wordt gestart dit altijd te combineren met een tweede middel, bij voorkeur een beta-lactam voor synergistische werking. De AHA adviseert dit alleen als er sprake is van een (relatief) hoge daptomycine MIC óf therapiefalen onder daptomycine monotherapie.

Discrepantie: Duur van linezolid bij enterokokken endocarditis (6+ versus 8+ weken)
Toelichting: Zowel de ESC als de AHA raden linezolid aan als alternatief regime bij enterokokken endocarditis. De ESC raadt echter behandeling van minimaal 8 weken aan, terwijl de AHA minimaal 6 weken adviseert.

Bronnen ESC	**Bronnen AHA**
Geeft hier geen bronnen voor	(Babcock et al. 2001)
	(Birmingham et al. 2003)
	(Casapao et al. 2013)
	(Falagas et al. 2006)
	(Hall et al. 2012)
	(Hidron et al. 2008)
(Dahl et al. 2013)	(Kainer et al. 2007)
	(Kanafani, Federspiel, and Fowler 2007)
	(Kullar et al. 2013)
	(Levine and Lamp 2007)
	(Mave et al. 2009)
	(Sakoulas et al. 2012)
	(Sakoulas et al. 2013)
	(Sakoulas et al. 2014)
	(Schutt and Bohm 2009)
	(Segreti, Crank, and Finney 2006)
	(Tsigrelis et al. 2007)
	(Wareham et al. 2006)

Search string (zelfde als voor vraag 5):

Publication date: from 1 january 2014 to 1 january 2018
Search terms: (enterococcus[MeSH Terms] OR enterococc* [Title/Abstract]) AND (endocarditis[MeSH Terms] OR endocarditis [Title/Abstract])

Aantal hits: **236**

Artikelen toegevoegd aan literatuur review na screening op titel en abstract: **8**

(Hall Snyder et al. 2015)
(Ceron et al. 2014)
(Marc et al. 2014)
(Leone, Noviello, and Esposito 2016)
(Pericas et al. 2017)
(Hall Snyder et al. 2014)
(Piszczek, Hutchinson, and Partlow 2015a)
(Piszczek, Hutchinson, and Partlow 2015b)

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7. Gentamicine toevoegen aan amoxicilline bij HACEK endocarditis

Discrepantie: Gentamicine toevoegen aan amoxicilline bij HACEK endocarditis
Toelichting: In zowel de ESC als de AHA is ceftriaxon de eerste keuze behandeling voor endocarditis door HACEK bacteriën. Als tweede optie wordt door beide amoxicilline genoemd, waarbij de ESC adviseert dan óók 4-6 weken gentamicine 3mg/kg toe te voegen. De AHA vindt alleen amoxicilline voldoende.

Bronnen ESC	**Bronnen AHA**
(Das et al. 1997)	(Chambers et al. 2013)
(Paturel et al. 2004)	(Coburn et al. 2013)

Search string:

Publication date: from 1 january 2014 to 1 january 2018
Search terms: ((HACEK[Title/Abstract]) OR (kingella[Title/Abstract]) OR (eikenella[Title/Abstract]) OR (cardiobacterium[Title/Abstract]) OR (Aggregatibacter[Title/Abstract]) OR (haemophilus[Title/Abstract]) AND (endocarditis[MeSH Terms]))

Aantal hits: **31**

Artikelen toegevoegd aan literatuur review na screening op titel en abstract: **3**

(Loubet et al. 2015)
(Sharara et al. 2016)
(Revest et al. 2016)

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8. Dosering ciprofloxacine bij HACEK endocarditis

Discrepantie: Dosering ciprofloxacine bij HACEK endocarditis
Toelichting: Zowel de ESC als de AHA geven ciprofloxacine als alternatief regime bij HACEK endocarditis (bijv bij beta-lactam allergie). De dosering verschilt echter: de ESC adviseert 1200mg/dag IV of 1500mg/dag oraal. De AHA adviseert lager te gaan zitten: 800mg/dag IV of 1000mg/dag oraal.

Bronnen ESC	**Bronnen AHA**
(Das et al. 1997)	(Chambers et al. 2013)
(Paturel et al. 2004)	(Coburn et al. 2013)

Search string:

Publication date: from 1 january 2014 to 1 january 2018
Search terms: ((HACEK[Title/Abstract]) OR (kingella[Title/Abstract]) OR (eikenella[Title/Abstract]) OR (cardiobacterium[Title/Abstract]) OR (Aggregatibacter[Title/Abstract]) OR (haemophilus[Title/Abstract]) AND (endocarditis[MeSH Terms]))

Aantal hits: **31**

Artikelen toegevoegd aan literatuur review na screening op titel en abstract: **3**

(Sharara et al. 2016)
(Revest et al. 2016)
(Cunha, Brahmbhatt, and Raza 2015)

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9. Beste behandeling *Propionibacterium (Cutibacterium) spp* endocarditis

Bronnen ESC	**Bronnen AHA**
Komt niet voor in de richtlijn, geen bronnen	*Komt niet voor in de richtlijn, geen bronnen*

Search string:

Publication date: from 1 january 2014 to 1 january 2018
Search terms: ("propionibacterium acnes"[MeSH Terms] OR ("propionibacterium"[All Fields] AND "acnes"[All Fields]) OR "propionibacterium"[All Fields]) AND ("endocarditis"[MeSH Terms] OR "endocarditis"[All Fields]))

Geselecteerde artikelen: Geselecteerde artikelen: case series > 2 patiënten en overzichtsartikelen van de eerdere case reports

Aantal hits: **107**

Artikelen toegevoegd aan literatuur review na screening op titel en abstract: **8**

(Lalani et al. 2007)
(Banzon et al. 2017)
(Clayton et al. 2006)
(van Valen et al. 2016)
(Park et al. 2011)
(Kestler et al. 2017)
(Sohail et al. 2009)
(Gunthard et al. 1994)

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10. Device endocarditis:

a) *Wat is de optimale behandelduur voor cardiac implantable electronic device endocarditis als het device wordt verwijderd?*
b) *Wat is de optimale behandelduur voor cardiac implantable electronic device endocarditis als het device wordt NIET verwijderd?*
c) *Wanneer is het beste moment om een geïnfecteerd cardiac implantable electronic device te verwijderen?*
d) *Hoe lang dient gewacht te worden voor een nieuw cardiac implantable electronic device te implanteren?*
e) *Welk antibiotische regimes dienen te worden aangehouden bij het behandelen van cardiac implantable electronic device endocarditis?*

Geraadpleegde richtlijnen:

BSAC: (Sandoe et al. 2015)

AHA: (Baddour et al. 2010)

Search string:

Publication date: from 1 january 2014 to 1 january 2018
Search terms: (("pacemaker, artificial"[MeSH Terms] OR ("pacemaker"[All Fields] AND "artificial"[All Fields]) OR "artificial pacemaker"[All Fields] OR "pacemaker"[All Fields]) OR ("defibrillators"[MeSH Terms] OR "defibrillators"[All Fields] OR "defibrillator"[All Fields]) OR (("electronics"[MeSH Terms] OR "electronics"[All Fields] OR "electronic"[All Fields]) AND ("heart"[MeSH Terms] OR "heart"[All Fields] OR "cardiac"[All Fields]) AND ("equipment and supplies"[MeSH Terms] OR ("equipment"[All Fields] AND "supplies"[All Fields]) OR "equipment and supplies"[All Fields] OR "device"[All Fields]))) AND (("infection"[MeSH Terms] OR "infection"[All Fields]) OR ("endocarditis"[MeSH Terms] OR "endocarditis"[All Fields]))

Aantal hits: **931**

Artikelen toegevoegd aan literatuur review na screening op titel en abstract: **31**

(Al-Ghamdi et al. 2016)
(Aydin et al. 2016)
(Aljabri et al. 2018)
(Bandyopadhyay et al. 2015)
(Carrasco et al. 2016)
(Chaudhry et al. 2016)
(Chrispin and Love 2018)
(DeSimone et al. 2017)
(DeSimone and Sohail 2016)
(Diemberger et al. 2017)
(Diemberger et al. 2018)
(El Rafei, Desimone, Sohail, et al. 2016)
(Fernandes et al. 2016)
(Ferrera et al. 2016)
(Gomes et al. 2017)
(Goya et al. 2016)
(Greenspon et al. 2018)
(Gutierrez Carretero et al. 2017)
(Harrison, Prendergast, and Sandoe 2015)
(Huang et al. 2016)
(Ihlemann et al. 2016)
(Jedrzejczyk-Patej et al. 2017)
(Kim et al. 2016)
(Nielsen, Gerdes, and Varma 2015)
(Perrin et al. 2017)
(Polewczyk, Janion, and Kutarski 2016)
(Polewczyk et al. 2017)

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(Salmeri et al. 2016)
(Sohail and Baddour 2016)
(Sridhar et al. 2017)
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