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Guidelines

Antibiotic therapy and prophylaxis of infective endocarditis – A SPILF-AEPEI position statement on the ESC 2023 guidelines

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1. Introduction

The European Society of Cardiology has recently issued comprehensive guidelines on the management of infective endocarditis (IE) [1]. While some members of the *Association pour l'Étude et la Prévention de l'Endocardite Infectieuse* (AEPEI) have been involved in the conception and reviewing of these guidelines, both AEPEI and the *Société de Pathologie Infectieuse de Langue Française* (SPILF) considered that some sections of the guidelines dealing with antibiotic prophylaxis and treatment were imprecise or discrepant with the usual practices of infectious disease (ID) specialists in France. The two entities consequently mandated a group bringing together ID specialists and microbiologists to write the present position statement.

Clinical management of IE should always be multidisciplinary, and the chart of any IE patient should be discussed as frequently as needed with an endocarditis team, comprising at least a cardiologist and an ID specialist to adapt antibiotic treatment and discuss a possible need to refer the patient to a heart valve centre. All patients at risk of complicated clinical evolution should be presented to a reference endocarditis team comprising at least a cardiac surgeon and a microbiologist (Table 1). The involvement of addiction specialists and social workers is also needed in the increasingly frequent cases of IE occurring in people who inject drugs. In France, structuration of a network of endocarditis teams and reference endocarditis teams is in progress to ensure that each patient is offered the best treatment of this highly complex disease.

Of note, the total duration of antibiotic treatment is based on the first day of negative blood culture or on the day of surgery if valve culture is positive and blood cultures are already negative.

The antibiotic doses proposed below are intended for non-obese patients with normal renal function.

1.1. Use of β-lactam antibiotics in case of allergy

When patients have an antecedent of early severe allergy, i.e. anaphylaxis, to a cephalosporin or late severe allergy, i.e. DRESS-syndrome, to a penicillin or a cephalosporin, they should be considered as allergic to all β-lactams and these drugs should not be used until advice of an allergologist.

When patients have an antecedent of early (<24 h after initiation, regardless of severity) or late non-severe allergy to penicillin, cephalosporins (cefazolin, ceftriaxone, ceftaroline) may be used because their biochemical structure is different from that of penicillin.

2. Which antibiotic prophylaxis to prevent IE?

While the ESC was updating its recommendations for IE management, the Haute Autorité de Santé (French National Authority for Health) was drawing up good practice recommendations on "Oral management of patients at risk of infective endocarditis" [2]. The two recommendations are compared, and, in the event of a discrepancy, a choice is made and justified, with the aim of not recommending practices in France that contradict the HAS recommendations, to which the SPILF and AEPEI contributed.

2.1. Who are the patients at risk of IE requiring antibiotic prophylaxis?

The ESC 2023 and HAS 2024 recommendations are identical with regard to the definition of patients requiring antibiotic prophylaxis before invasive dental treatment.

2.2. What are the at-risk situations requiring an antibiotic prophylaxis?

Argumentation

Oral and dental procedures

The ESC 2023 and HAS 2024 recommendations are identical, although worded differently.

Invasive procedures other than oral care

The HAS 2024 recommendations do not address this issue. Breaking with the previous 2015 recommendations, the ESC 2023 recommendations reintroduce the possibility of prescribing antibiotic prophylaxis for non-dental procedures. The ESC 2023 recommendation reads: "Systemic

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Table 1
Patients at risk of complicated IE.

Cardiac and hemodynamic conditions
Unstable hemodynamic condition
Severe valvular regurgitation
Prosthetic valve or CIED-related IE
Peri-valvular complications (abscesses, fistula)
Stroke
Embolism
Infectious conditions
Positive blood cultures > 7 days under appropriate treatment
Aggressive or difficult to treat infectious agent (resistant streptococci or enterocci, *Staphylococcus aureus*, Gram negative bacilli, fungi)

Abbreviations: CIED: Cardiovascular Implanted Electronic Device; IE infective endocarditis.

Guidelines

Antibiotic prophylaxis must always be associated with optimized hygienic measures (tooth brushing, wound cleansing…).

Only patients at high risk of IE require antibiotic prophylaxis prior to situations entailing risk of bacteremia. These patients are the following:

- Patients with a history of IE.
- Patients with cardiac valve prostheses or prosthetic devices used for cardiac valve repair, whether implanted surgically or per/transcutaneously (TAVI, valve clip, etc.).
- Patients with congenital heart disease meeting one of the following criteria:
  - o Complex cyanogenic congenital heart disease (single ventricle, Eisenmenger syndrome, etc.)
  - o Complex congenital heart disease treated with a prosthetic device (systemic-pulmonary anastomosis, prosthetic tube or other prosthesis), placed surgically or transcutaneously, for up to six months after repair, or for life if a residual shunt remains.
- Patients with left ventricular assist devices.

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Oro-dental situations

While the European recommendations refer to oral procedures as "oral surgery and procedures involving manipulation of the gingival or periapical region of the teeth", the HAS recommendations provide dental surgeons with precise details, presenting them by type of procedure. We do not list these procedures in the present guidelines, and refer the reader to the HAS 2024 guidelines [2].

Other situations

Contrary to the ESC, the SPILF and AEPEI do not recommend antibiotic prophylaxis of IE in non-dental procedures.

antibiotic prophylaxis may be considered for high-risk patients undergoing invasive diagnostic or therapeutic respiratory, gastrointestinal, genitourinary, cutaneous or musculoskeletal procedures". These recommendations specify neither the antibiotics to be used, nor their conditions of use. In addition, the levels of strength (IIb) and evidence (C) of this recommendation are low and based on observational data following case-control design, in which bias control has not been perfected [3,4]. This probably explains why certain invasive procedures, such as bone marrow biopsy, blood transfusion and cataract surgery, have been identified as being at high risk of IE, even though they are not known to be so.

2.3. *Which antibiotic prophylaxis regimen should be given?*

Argumentation

In the absence of allergy to penicillin, the ESC 2023 and HAS 2024 recommendations are identical for regimens of antibiotic prophylaxis in dental procedures.

In cases of penicillin allergy, and due to the risk of *Clostridioides difficile* colitis, clindamycin has been abandoned in both recommendations. Having considered French data on the antibiotic susceptibility of oral streptococci, the risks of adverse effects and of drug-drug interactions and selection of resistant bacteria, in the absence of proven cephalosporin allergy the HAS 2024 recommendations have limited the choice to two antibiotics (azithromycin and pristinamycin) for oral administration, and to cefazolin for parenteral administration. While efficacy data in experimental models are most consistent for azithromycin, streptococcal resistance to the latter is frequent, while pristinamycin remains active on most strains. Considering these uncertainties, it is mandatory to have patients who will have frequent indications for antibiotic prophylaxis referred to an allergologist.

Guideline

Antibiotic prophylaxis regimens are listed in Table 2.

Antibiotics should be administered as a single dose administered in the hour preceding an oral procedure.

Table 2
Antibiotic prophylaxis regimens in patients at high risk of IE undergoing an at-risk dental procedure.

Situation	Antibiotic	Dose in adults	Dose in children
No allergy to penicillin	Amoxicillin IV or oral	2 g	50 mg/kg
Allergy to penicillin	Azithromycin*	500 mg	20 mg/kg
	Pristinamycin**	1000 mg	25 mg/kg*
	Cefazolin IV***	1 g	50 mg/kg

* Pristinamycin is contraindicated in children younger than 6 years.
** The paediatric dose of azithromycin has been adapted to the graduation system used for dispensing the product in children.
*** Contraindicated in case of allergy to cephalosporins or late severe allergy to penicillin; in this case, vancomycin may be used (15 mg/kg, 2 g maximum).

3. What should be the antibiotic prophylactic regimen for implantation of a Cardiovascular Implanted Electronic Device (CIED) or a transcatheter aortic valve (TAVI)?

Argumentation

The choice of antibiotic for prophylaxis when implanting a TAVI takes into consideration the presence of enterococci at the inguinal valve insertion site and, consequently, the high rate of IE, particularly early IE, caused by *Enterococcus faecalis* after TAVI [5]. The need to maintain coverage against staphylococci (methicillin-susceptible staphylococci) has led to the choice of amoxicillin-clavulanic acid.

We have chosen the doses of antibiotics recommended in the latest joint formalised expert recommendations of the French Society of Anaesthesiology and Reanimation (SFAR) and the SPILF [6].

Guideline

Cefazolin 2 g IV should be administered before implantation of a CIED.

Amoxicillin-clavulanate 2 g IV should be administered before implantation of a TAVI. In case of allergy to penicillin, antibiotic prophylaxis should be vancomycin 20 mg/kg or teicoplanin 12 mg/kg. This also applies to the following procedures: percutaneous atrial closure with device implantation, narrowing of the left atrioventricular orifice (MitraClip), closure of an atrial septal defect or patent foramen ovale.

4. What should be the antibiotic treatment of streptococcal IE?

Argumentation

Susceptibility of streptococci to β-lactam antibiotics

β-Hemolytic streptococci (*S. pyogenes* [group A *Streptococcus*], *S. agalactiae* [group B *Streptococcus*], *S. dysgalactiae* subsp. *equisimilis* [group C and G *Streptococci*]) and streptococci of the *S. anginosus* and *S. bovis* groups are usually susceptible to β-lactams. Oral streptococci (including *S. pneumoniae*) with reduced susceptibility (or susceptible, increased exposure) and resistance to β-lactams are on the rise and exceed 30–50 % of isolates for some species [7–10]. The critical concentrations defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are ≤0.5 mg/L for susceptibility to amoxicillin and ceftriaxone, >2 mg/L for resistance to amoxicillin and >0.5 mg/L for resistance to ceftriaxone. Since penicillin G is now rarely used, we chose to remove it from the present guidelines.

Guideline (see Fig. 1 and Table 3)

Susceptibility for the β-lactam chosen should be determined by its MIC measurement.

Antibiotic therapy is preferably based on monotherapy of either amoxicillin or ceftriaxone for 4–6 weeks when MIC is ≤0.5 mg/L.

Gentamicin should be associated for the first two weeks with high-dose amoxicillin when MIC is >0.5 mg/L and ≤2 mg/L.

Duration of antibiotic treatment should be four weeks in case of native valve IE (NVE) and six weeks in case of prosthetic valve IE (PVE).

In case of severe allergy to penicillin or resistance to both ceftriaxone (MIC > 0.5 mg/L) and amoxicillin (MIC > 2 mg/L), vancomycin should be used.

In the absence of high-level resistance, a combination of gentamicin with β-lactams or glycopeptides is synergistic. However, gentamicin is toxic and should be used only when there is no alternative, i.e. in association with amoxicillin when it is categorized as "susceptible, increased exposure". That is the reason why we chose not to recommend the short course of two-week association of a β-lactam and gentamicin proposed in the ESC 2023 guidelines.

Antibiotic therapy of IE due to streptococci that are "susceptible, increased exposure) or resistant to β-lactams

The ESC 2023 guidelines recommend a combination for two weeks of gentamicin with β-lactam therapy (penicillin G, amoxicillin or ceftriaxone). Considering the modality of administration of the drugs proposed and the preferential use of narrow-spectrum antibiotics, we believe that amoxicillin should be preferred when the strain is susceptible (MIC ≤ 0.5 mg/L), otherwise the β-lactam with the lowest MIC is to be proposed. However, the benefit of combining a β-lactam and gentamicin has not been clearly established [11]. Treatment with β-lactam monotherapy may consequently be considered if the strain is categorized as susceptible to the molecule chosen for treatment.

In cases of resistance to both penicillin and cephalosporins or allergy to all β-lactams, treatment with vancomycin should be preferred. Few studies have reported the use of daptomycin in this indication [12]. Its administration as monotherapy may lead to selection of tolerant or resistant mutants [13].

These guidelines also apply to *Abiotrophia*, *Granulicatella* and *Gemella*.

β-hemolytic streptococci, *S. anginosus* group streptococci and *S. pneumoniae*

Endocarditis due to β-hemolytic streptococci, *S. anginosus* group streptococci and *S. pneumoniae* is relatively rare, and particularly severe. However, addition of gentamicin does not seem to be necessary when β-lactams are fully active, as it is toxic and not necessary to ensure bactericidal activity.

5. What should be the antibiotic treatment for enterococcal IE? (Table 4)

5.1. What should be the antibiotic treatment for IE due to E. faecalis?

Argumentation

In France, enterococcal IE epidemiology is dominated by *E. faecalis*, which is always susceptible to amoxicillin.

The 2023 ESC guidelines take up the proposals of the 2015 ESC

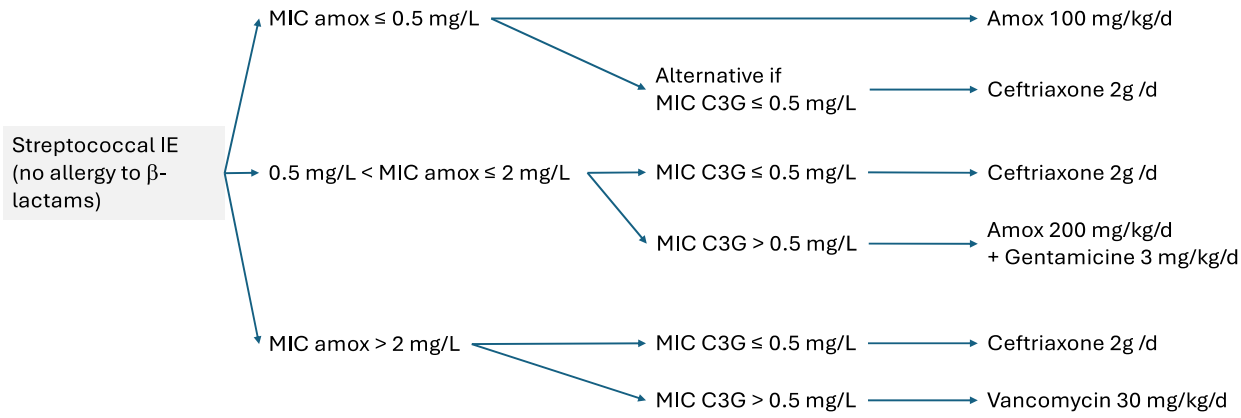

Fig. 1. Algorithm for the choice of antibiotic in streptococcal IE according to the MICs of amoxicillin and ceftriaxone. Abbreviations: MIC: minimal inhibitory concentration, C3G: ceftriaxone, amox: amoxicillin.

Table 3
Antibiotic dosages for antibiotics used in streptococcal IE.

Antibiotic	Dose
Amoxicillin	100 or 200 mg/kg/d (cf. Fig. 1), IV in 4–6 doses or continuously, not to exceed 12 g/d
Ceftriaxone	2 g/d, IV in 1 dose
Gentamicin	3 mg/kg/d, IV in 1 dose
Vancomycin	30 mg/kg/d, IV, in 2 doses or continuously

Guidelines

Antibiotic regimens are detailed in Table 4.

For strains susceptible to amoxicillin and regardless of the level of gentamicin resistance: amoxicillin + ceftriaxone for six weeks, whether on native or prosthetic valves. Particular attention should be paid to the nephrotoxicity (see § 4.3) and neurotoxicity of the combination.

In case of allergy to penicillin:

- daptomycin; there are currently insufficient data to recommend a combination with a β-lactam antibiotic for *E. faecalis* strains susceptible to daptomycin and vancomycin. In case of a combination, ceftaroline appears to be the most suitable companion.
- vancomycin (6 weeks) + gentamicin (non-HLAR strain) during the first two weeks of treatment. Particular attention should be paid to the nephrotoxicity of the combination.

guidelines by proposing the amoxicillin + ceftriaxone combination for amoxicillin-susceptible *E. faecalis* strains in patients who can tolerate β-lactam therapy, for a duration of six weeks for the two antibiotics. Due to high-quality epidemiological data, we endorse these recommendations, highlighting the potential nephrotoxicity and neurotoxicity of this combination, which is not nearly as frequent as the penicillin-gentamicin combination.

In patients unable to tolerate β-lactam therapy, the 2023 ESC guidelines suggest antibiotic therapy with vancomycin six weeks + gentamicin two weeks. The rationale for adding gentamicin is weak. This antibiotic regimen is highly nephrotoxic and requires close therapeutic drug monitoring of the two antibiotics (target of gentamicin residual plasma concentration ≤ 0.5 mg/L). The prescription of vancomycin for six weeks also requires the insertion of a central venous catheter. In case of nephrotoxicity, gentamicin must be stopped first.

Table 4
Recommendations for antibiotic treatment for IE due to enterococci (native and prosthetic valves).

Situation	Regimen	Duration	Comments
Enterococcus faecalis			
Without allergy to β-lactams	Amoxicillin	6 weeks	
	with ceftriaxone	6 weeks	
Allergy to penicillin	Daptomycin	6 weeks	Only if MIC ≤ 2 mg/L. Daptomycin may be prescribed in association with ceftaroline for the whole course of treatment
	or		
	Vancomycin with	6 weeks	
	Gentamicin	2 weeks	Not in case of HLAR
Non-HLAR *Enterococcus faecium*			
	Vancomycin	6 weeks	Even if susceptible to amoxicllin
	With Gentamicin	2 weeks	

Adult antibiotic dosage and route

Antibiotic	Daily dosage (normal kidney function)
Amoxicillin	200 mg/kg in 6 IV doses, not to exceed 12 g/d
Ceftriaxone	4 g in 2 IV doses
Gentamicin	3 mg/kg in 1 IV dose
Vancomycin	24 h-continuous infusion; serum drug level target around 20–25 mg/L
Daptomycin	12 mg/kg in 1 IV dose

HLAR: high-level aminoglycoside resistance.

As an alternative, we propose daptomycin at 12 mg/kg/day if MIC$_{daptomycin}$ ≤ 2 mg/L [14]. For MIC at 4 mg/L, PK/PD is very unfavorable, even at 12 mg/kg/day of daptomycin. An *in vitro* synergy between daptomycin and β-lactam antibiotics against vancomycin-resistant enterococci (VRE) and enterococci with reduced susceptibility to daptomycin is consequently very promising [15–17]. Antibiotics with high binding affinity to PBP5 (ceftaroline and ceftobiprole) appear to have greater synergy for enterococcal isolates with reduced susceptibility to daptomycin [16]. However, no relevant clinical data have appeared. Cephalosporins should not be used in the event of late severe allergy to penicillin.

Treatment with dalbavancin or oritavancin may also be considered, based on expert opinion.

High-dose teicoplanin has been used by some authors as switch after initial therapy. It may be an alternative when carrying out therapeutic drug monitoring. Efficacy in PVE seems limited [18].

5.2. What should be the antibiotic treatment of IE due to non-high-level aminoglycoside-resistant (HLAR) E. faecium?

Argumentation

In France, resistance to aminopenicillins in *Enterococcus faecium* approximates 78 % for strains isolated from blood cultures according to the SPARES network, a finding in line with data from the EARS-Net network. According to EARS-Net data, in 2019, 32 % of *E. faecium* strains isolated from blood cultures are highly resistant to gentamicin and fewer than 1 % are resistant to vancomycin. Of note, the synergy between amoxicillin and ceftriaxone observed with *E. faecalis* is not observed with *E. faecium*.

Given this epidemiology, we will limit ourselves to treatment of non-HLAR amoxicillin-susceptible or resistant *E. faecium* IE. For other situations, we suggest seeking advice from an ID expert. The dalbavancin or oritavancin options for vancomycin-susceptible *E. faecium* isolates can be considered in consultation with microbiologists.

Approximately 20–25 % of *E. faecium* isolates are classified as susceptible to amoxicillin, but as these isolates may become resistant through acquired mutations in PBP-5, the vancomycin + gentamicin combination should be preferred.

The 2023 ESC guidelines suggest amoxicillin/clavulanic acid for *E. faecium* IE if the mechanism of resistance to amoxicillin is production of a β-lactamase. We do not agree with this proposal. In fact, no β-lactamase is produced in *E. faecium*. More than 80 % of *E. faecium* strains are highly resistant to amoxicillin due to qualitative and/or quantitative changes in PBP-5, and this mechanism is not compensated by clavulanic acid.

5.3. How to prevent crystalluria due to amoxicillin in IE treatment?

Argumentation

Amoxicillin crystalluria is a frequent cause of acute kidney injury (AKI) in patients with IE.

Factors favoring amoxicillin crystalluria are high dose of amoxicillin, low urinary pH, and concomitant administration of nephrotoxic drugs or agents [19,20].

6. What should be the antibiotic treatment of staphylococcal IE?

In all cases of staphylococcal IE, follow-up blood culture should be performed until negativity is obtained. Because of the occurrence of intermittent positivity in some patients ("skip phenomenon") [21], it is advisable to document bacterial clearance in two consecutive blood cultures drawn at least one day apart. We consider *Staphylococcus aureus* and coagulase-negative staphylococci conjointly.

6.1. What should be the antibiotic treatment of native valve staphylococcal IE? (Table 5)

6.1.1. What should be the antibiotic treatment of native valve IE (NVE) due to methicillin-susceptible Staphylococcus spp.?

Guidelines

Regardless of susceptibility to amoxicillin, vancomycin (6 weeks) + gentamicin (2 weeks) in native or prosthetic IE is to be preferred (Table 4). Particular attention should be paid to the nephrotoxicity of the combination.

Guidelines

When using high-dose amoxicillin in IE, it is essential to:

- comply with amoxicillin administration procedures: maximum dose of 200 mg/kg/day, not to exceed 12 g/day, maximum of 2 g per infusion in a volume of 100 mL, minimum infusion time of 20 min, ideally 1 h or continuously with an infusion pump.
- keep the patient well-hydrated,
- alkalinize urine (target urinary pH > 7 using dipsticks).
- monitor renal function and diuresis.

If available, monitoring of crystalluria may be useful; when occurring, it predicts acute kidney injury and may necessitate change of therapy, i.e. switch to a cephalosporin in streptococcal IE.

Occurrence of crystalluria does not contraindicate subsequent use of amoxicillin, particularly as antibiotic prophylaxis.

Argumentation

The ESC 2023 guidelines suggest (cl)oxacillin or cefazolin. The combination with gentamicin has not been recommended since the 2015 ESC guidelines.

Cefazolin may be preferred as first-line treatment insofar as this antibiotic appears to be less nephrotoxic and as effective as anti-staphylococcal penicillin [22,23]. Results of two comparative trials, Cloceba and SNAP, are pending. Cefazolin should also be preferred in cases of meningeal infection associated with IE [24].

One concern with cefazolin is that some strains have an "inoculum effect" that may be associated with clinical failure [25]. However, a recent retrospective study showed that an inoculum effect can also be observed with oxacillin and that this effect is a risk factor for one-month mortality in IE [26]. There is currently no method of assessing inoculum effect. in routine clinical microbiology practice In case of suspected failure, it may be prudent to switch to the alternative.

In case of presumed late severe allergy to penicillin, we suggest using daptomycin combined with fosfomycin to prevent selection of resistance. There is nonetheless only one retrospective study describing outcomes for this combination in methicillin-susceptible *S. aureus* bacteremia [27].

Intravenous administration of fosfomycin is associated with a high sodium intake, which could be a limitation in patients with heart or renal failure. Other adverse events include hypokalemia, nausea, neutropenia, hypereosinophilia and local phlebitis.

6.1.2. What should be the antibiotic treatment of NVE due to methicillin-resistant Staphylococcus spp.?

Argumentation

Guidelines (see Table 5)

These guidelines are susceptible to change after availability of the results of the CLOCEBA trial.

- IV (Cl)oxacillin and IV cefazolin should be used in monotherapy.
- IV cefazolin may be preferred, with dosage adapted to renal function.
- In case of meningitis associated with IE, prefer IV cefazolin.

Table 5
Recommendations for antibiotic treatment for staphylococcal NVE.

Situation	Regimen	Comments	Duration
Methicillin-susceptible staphylococci			
Without allergy to β-lactams	Cefazolin or(Cl)oxacillin	Preferred option in case of meningitis.	
Early or non-severe late allergy to penicillin	Cefazolin		Left-sided NVE 4-week treatment if i) apyrexia obtained during the first few days of treatment and ii) blood cultures negative by day 3 6 weeks in other cases Right-sided NVE 2-week treatment if i) apyrexia obtained during the first few days of treatment and ii) blood cultures negative by day 3 4 weeks in other cases
Late severe allergy to penicillin	Daptomycin with fosfomycin		
Methicillin-resistant staphylococci			
Without allergy to β-lactams	Daptomycin with ceftaroline or Daptomycin with fosfomycin	Duration of the combination therapy: as long as the bacteremia lasts and for a maximum of 7 days from the 1st negative blood culture.	Left-sided NVE 4-week treatment if i) apyrexia obtained in the first few days of treatment and ii) blood cultures negative by day 3 6 weeks in other cases Right-sided NVE 2-week treatment if i) apyrexia obtained in the first few days of treatment and ii) blood cultures negative by day 3 4 weeks in other cases
Late severe allergy to penicillin or allergy to cephalosporins	Daptomycin with fosfomycin		
	or Vancomycin	If vancomycin MIC ≤ 1 mg/L.	

Adult antibiotic dosage and route

Antibiotic	Daily dosage (normal kidney function)
(Cl)oxacillin	12 g in 4–6 IV doses
Cefazolin	80–100 mg/kg in 3 IV doses Or, IV loading dose of 30 mg/kg over 1 h (max. 2g) immediately followed by IV maintenance dose of 80–100 mg/kg/24h (max. 10 g/24h) in 2 12-hour infusions
Ceftarolin	1800 mg/24h in 3 IV doses
Daptomycin	10 mg/kg/24h in 1 IV dose
Vancomycin	24 h-continuous infusion with loading dose; serum drug level target around 20–25 mg/L
Fosfomycin	8 g/24h hour in 4 IV doses

The main question is whether vancomycin or daptomycin combined with another antibiotic should be preferably used to treat methicillin-resistant staphylococcal NVE.

Daptomycin, at 10 mg/kg/day, in combination with a beta-lactam antibiotic (oxacillin or ceftaroline) or fosfomycin is listed in the 2023 ESC recommendations as an alternative to vancomycin in treatment for methicillin-resistant staphylococcal NVE. In the randomized controlled trial by Fowler *et al.* [28], daptomycin was non-inferior to standard treatment for bacteremia caused by methicillin-susceptible or resistant *S. aureus*. Retrospective studies have suggested the superiority of daptomycin in methicillin-resistant *S. aureus* (MRSA) bacteremia *versus* vancomycin in terms of mortality [29] or clinical failure [30], particularly with vancomycin MIC > 1 mg/L [31,32].

Case reports illustrate the emergence of resistance to daptomycin when used as monotherapy [33]. *In vitro* data support a more rapid and sustained bactericidal effect of dual therapies with daptomycin and a β-lactam antibiotic or fosfomycin *versus* daptomycin monotherapy on MRSA strains [34,35].

Clinical data pointing to increased efficacy of dual therapies with daptomycin still show a low level of evidence. The randomized open trial by Geriak *et al.* on MRSA bacteremia treated with daptomycin and ceftaroline (n = 17) vs. vancomycin (n = 21) or daptomycin (n = 2) was stopped prematurely due, despite a significant benefit of the combination on mortality, to its methodological flaws [36]. The only study to conclusively demonstrate a positive effect of dual therapy was the American retrospective bicentric observational study by Jorgensen *et al.* [37]. The authors compared the outcome of 72 patients who had received daptomycin + β-lactam therapy (cefepime or cefazolin) with 157 patients vs. daptomycin monotherapy. Dual therapy was associated with a 60 % reduction in 60-day mortality and/or recurrence.

The Spanish multicenter trial by Pujol *et al.* concluded that there was no difference in therapeutic success (resolution of clinical signs and sterile blood cultures) at week 6 between daptomycin and a combination

Guidelines (see Table 5):

- As a first-line treatment, a dual therapy: daptomycin with another antibiotic.
  - o Daptomycin should be prescribed at 10 mg/kg/day, with monitoring for toxicity (rhabdomyolysis, eosinophil pneumonia).
  - o The "best" companion to daptomycin appears to be ceftaroline. Fosfomycin may also be used.
  - o The duration of dual therapy is unknown, but we suggest at least as long as the bacteremia persists and for a maximum of 7 days from the first negative blood culture.
  - o In the event of persistent bacteremia on daptomycin, it is wise to monitor the daptomycin MIC (risk of daptomycin-resistant mutant selection).
- Although vancomycin is the oldest and most "validated" option, it should be considered essentially as an alternative, for example to the combination of daptomycin and ceftaroline in case of late severe allergy to penicillin, provided that vancomycin MIC is ≤ 1 mg/L. Serum drug levels and renal function must be monitored.

of daptomycin + fosfomycin. Time to negative blood cultures was shorter in the dual therapy arm, but at the cost of increased risk of adverse events [38].

The duration of the combination is not specified in the 2023 ESC recommendations. We suggest that in dual therapy with ceftaroline or fosfomycin, the companion drug to daptomycin should be maintained for seven days after the first negative blood culture.

Because of its toxicity and difficulties in everyday use, vancomycin should be an alternative only in treatment of methicillin-resistant staphylococcal NVE. As noted in the 2023 ESC recommendations, we propose to achieve vancomycin MIC on staphylococcal strains isolated in blood cultures. Indeed, with vancomycin MIC > 1 mg/L, the PK/PD targets of AUC/MIC of between 400 and 600 cannot be reached unless the vancomycin dosage is increased, thereby increasing nephrotoxicity. In addition, several studies have shown that the risk of failure is greater when vancomycin is used on *S. aureus* strains with MIC of 2 mg/L [31,32,39,40]. Due to the nephrotoxicity of vancomycin, it is important to monitor plasma concentrations and renal function. Moreover, prolonged treatment with vancomycin requires central venous access.

6.2. What should be the antibiotic treatment for prosthetic valve staphylococcal IE? (Fig. 2)

This section focuses exclusively on the antibiotic treatment of staphylococcal prosthetic valve endocarditis (PVE). It is important to remember that surgical discussion should take place as early as possible, so as to avoid overlooking or delaying an indication for surgery. Doses of antibiotics are displayed in Table 5 and in the text below for rifampicin and gentamicin.

6.2.1. Should rifampicin be systematically introduced in treatment for staphylococcal PVE?

Argumentation

Rifampicin is the antimicrobial agent that has demonstrated optimal activity on biofilm-embedded staphylococci and has been shown to reduce relapse rates in prosthetic joint infections [41]. Old and limited animal or clinical studies with a low level of evidence reported the benefit of multitherapy in the presence of PVE [42–44].

However, there are several arguments contesting the use of rifampicin in PVE: (i) A recent retrospective study on 180 patients in France found no benefit of adjunctive rifampicin in staphylococcal PVE [45], (ii) Tolerability of this treatment is particularly poor, with discontinuation of treatment in 31 % of cases being reported in the same study [44], (iii) Numerous drug interactions with rifampicin (oral anticoagulants, etc) have been found to occur (iv) When rifampicin is used early and the patient still has positive blood cultures, a 57 % risk of emergence of rifampicin-resistant mutants appeared in the study by Riedel *et al.* [46]). To avoid this risk, gentamicin is recommended in combination with rifampicin, but this strategy exposes the patient to an additional risk of AKI [47]. To conclude, a rifampicin-free strategy needs to be validated by means of a randomized controlled trial.

Guidelines (see Fig. 2)

- It is recommended to systematically add rifampicin in the absence of contraindication or drug interaction, at a dose of 900 mg per day IV or orally (600 mg if weight is <70 kg).
- If there is an indication of anticoagulation (e.g. mechanical valve), low-molecular weight heparin is impracticable. In associated treatments with complex interactions and definite benefit (tacrolimus, cancer chemotherapy, etc.), rifampicin may not be administered.
- Rifampicin should be introduced when the patient has sterile blood cultures for >48 h.

6.2.2. When and how should gentamicin be added to PVE treatment?

Argumentation

In the ESC 2023 guidelines, it is recommended to add aminoglycosides for a period of two weeks. This recommendation is based mainly on several retrospective studies concerning PVE patients [43,44] and on an animal study [42], which found that multitherapy was superior to monotherapy.

However:

1. In two retrospective studies and one *meta*-analysis [48–50], triple therapy does not appear to be superior to dual therapy.
2. The nephrotoxicity of aminoglycosides is well-known, and AKI is a risk factor for mortality in IE.
3. In a survey of AEPEI members, all of the experts declared that they systematically added an aminoglycoside treatment to the initial phase of treatment, but only 54 % systematically continued this treatment for a period of two weeks. A second international survey indicated that only 66 % of the practitioners questioned included

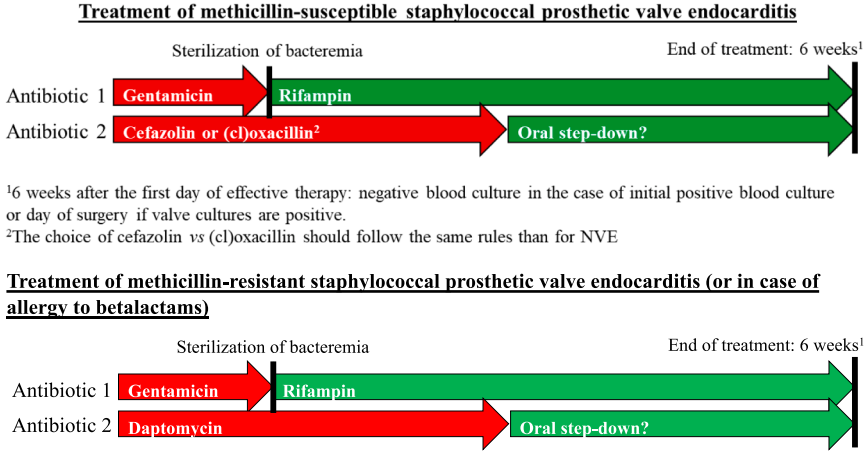

Fig. 2. Treatment of staphylococcal prosthetic valve IE.

Guidelines (see Fig. 2)

- Gentamicin remains recommended in methicillin-susceptible staphylococcal PVE treated with a β-lactam.
- It is recommended to use gentamicin in the initial phase of management until blood cultures are sterile when daptomycin is used.
- As soon as blood cultures are sterile, replace gentamicin with rifampicin (see paragraph on rifampicin for indications and administration).
- Gentamicin should be administered once daily at a dose of 3 mg/kg/day, with close monitoring of renal function and gentamicin residuals.

aminoglycosides in their initial treatment, while 21 % discontinued the treatment before the recommended two weeks of aminoglycosides [51].

4. Finally, it has recently been proposed to individualize the duration of treatment with aminoglycosides for staphylococcal PVE and suggested that their use be limited to either the pre-operative period, or until the blood cultures have been sterilized [47].

6.2.3. How to treat staphylococcal PVE in cases of resistance to methicillin or severe allergy to penicillin?

Argumentation

The reasons to prefer daptomycin over vancomycin have been detailed in § 5.1.2. In PVE, the systematic addition of gentamicin renders vancomycin very hazardous.

In the case of PVE, it is recommended that gentamicin be used until sterilization of blood cultures, followed by rifampicin (once blood cultures are sterile). The main limitation of daptomycin is its use as a monotherapy, which entails a risk of resistant mutant selection. In PVE, the consecutive combination of daptomycin with these two molecules will limit this risk.

The main adverse events to be monitored in patients treated with daptomycin are rhabdomyolysis (regular monitoring of CPK is required) and eosinophilic pneumonia.

7. What should be the indication and timing of oral antibiotic therapy?

In the 2023 ESC guidelines, it is now suggested that antibiotic therapy may be continued orally after the acute phase of IE. This recommendation does not concern most IE involving intracellular bacteria, for which oral antibiotic therapy is the rule.

This new recommendation relies mainly on data from the POET (Partial Oral Treatment for Endocarditis) trial. This multicentre randomized controlled trial conducted in Denmark from 2011 to 2017 demonstrated the non-inferiority of switch to oral antibiotic therapy in left-heart IE in 400 patients. The authors used a composite criterion combining all-cause mortality, unscheduled cardiac surgery, embolic event or relapse within 6 months (12.1 % *versus* 9 %, difference between groups 3.1 %, 95 % CI −3.4–9.6, p = 0.40) [52]. Similar results were found at five years in a retrospective real-life cohort [53–55]. These results are consistent with other clinical trials, retrospective cohorts, and with a recent meta-analysis [56–60].

7.1. Which patients can benefit from oral antibiotic therapy?

Argumentation

Studies demonstrating the efficacy of oral treatment have been focused on streptococcal, staphylococcal and enterococcal IE [52,55–59]. Caution is advised in staphylococcal IE as the main treatment regimen used in the POET trial, dicloxacillin, is not available in France. Care must also be taken for enterococcal IE, given a higher risk of recurrence. Awaiting the results of the French multicentre RODEO trial is advised [61]. Oral switch is applicable to IE involving prostheses or after surgical management. A new TEE before initiating oral therapy may not be required if high-quality recent TEE is available.

Psychosocial criteria guaranteeing good compliance should not be overlooked. The American Heart Association considers that oral treatment remains a viable option for people who inject drugs [62]. Careful follow-up with regular appointments is mandatory during oral antibiotic treatment to monitor adherence and tolerance, and to ensure early detection of possible relapse.

When oral treatment is deemed unfeasible, the same stability criteria may also be used to decide on the continuation of antibiotics as outpatient parenteral treatment.

Given the rarity of GNB IE, there exist few data on the efficacy of oral antibiotic therapy, and the ESC 2023 guidelines do not recommend this strategy. However, in cases of stabilized infection, and given the risks inherent to prolonged intravenous administration, oral fluoroquinolone therapy may be considered by the endocarditis team.

Guidelines (see Fig. 2)

- The recommended first-line treatment is daptomycin (10 mg/kg/d) combined with gentamicin (3 mg/kg/d) until blood cultures are sterilized, and then combined with rifampicin (900 mg/d) until the end of treatment.
- Vancomycin is a second-line alternative and should not be used when vancomycin MIC > 1 mg/L.
- If daptomycin is used, renal function, CPK and eosinophils should be monitored weekly.

7.2. When should intravenous antibiotic therapy be switched to oral treatment?

Argumentation

The median time to oral switch observed in the POET trial was 17 days (IQR 12–24 days), similar to that reported in cohorts (median 15.5 to 21 days) [52,55,57,59]. In the Freling et al. cohort, time to oral treatment was not associated with clinical outcome [59]. In the Vroon et al. cohort, stability criteria were reached at 10 days in 47 % of patients, 14 days in 68 %, 21 days in 92 %, and 28 days in all patients [63].

7.3. Which oral antibiotic regimen should be used? (Table 6)

Argumentation

As suggested in the ESC 2023 guidelines, it seems reasonable to use the drugs proposed in the POET trial, particularly those with better oral bioavailability [52]. Despite lower bioavailability, oral administration of amoxicillin achieves effective concentrations [64,65]. Due to its poor oral bioavailability, Dicloxacillin is not recommended [64].

In the POET trial, only dual therapy was used. In the literature, however, oral monotherapy was also reported [55–59]. Of note, in a French cohort amoxicillin was used as monotherapy in 92 % of cases for streptococcal IE and in 91 % for enterococcal IE [57]. It is nonetheless preferable to await the results of the RODEO trial, which will provide comparative data on oral amoxicillin monotherapy in streptococcal and enterococcal IE [61]. In case of dual therapy with a fluoroquinolone, moxifloxacin may be preferred, given its use in the POET trial and its bactericidal effect in gram-positive cocci infections [66]. In cases of

Guidelines

Oral antibiotic therapy may be used for patients with streptococcal IE meeting stability criteria as defined in the POET trial (apyrexia for at least 2 days, C-reactive protein < 25 % of its maximum value or < 20 mg/L, and leukocytes < 15 x10^9/L). In addition, recent transoesophageal echocardiography (TEE) must show no remaining criteria for surgical management (especially no abscess), and the patient should have no risk factor for oral antibiotic underdosing (BMI ≤ 40 kg/m^2 and no digestive malabsorption) and no psychosocial criteria entailing risk of poor adherence.

Caution is advised concerning enterococcal and staphylococcal IE. Awaiting the results of the RODEO trial seems reasonable.

Oral treatment may be feasible for patients with Gram-Negative Bacilli (GNB) IE (HACEK, *Enterobacterales* or *Pseudomonas aeruginosa*).

Guideline

Oral switch may be offered after at least 10 days of effective IV antibiotic therapy and at least seven days after valve surgery in stable patients.

Table 6
Oral antibiotic regimen according to IE bacteria.

	First-line oral antibiotic regimen	Alternative oral antibiotic regimen
Streptococcus spp.	Amoxicillin + rifampicin *or* Amoxicillin + moxifloxacin	*Awaiting results of the RODEO trial* Amoxicillin
Enterococcus faecalis	Amoxicillin + moxifloxacin	*Awaiting results of the RODEO trial* Amoxicillin
Staphylococcus spp.	*Awaiting results of the RODEO trial* Rifampicin + levofloxacin	Cotrimoxazole
GNB	Ciprofloxacin	

Adult antibiotic dosage and route		
Oral antibiotic	Dosage if patient ≤ 70 kg	Dosage if patient > 70 kg
Amoxicillin	1.5 g tid	2 g tid
Rifampicin	600 mg qd	900 mg qd
Moxifloxacin	400 mg qd	400 mg qd
Levofloxacin	500 mg qd	750 mg qd
Cotrimoxazole	320/1600 mg tid*	320/1600 mg tid*
Ciprofloxacin	750 mg bid	750 mg bid

*Lower doses of oral cotrimoxazole (160/800 mg bid) have been used in uncomplicated *S. aureus* bacteraemia.

staphylococcal IE, antibiotic regimens not including dicloxacillin were rarely used in the POET trial. Rifampicin-based dual therapy may be preferable, but it also seems reasonable to wait the results of the RODEO trial [61]. Data from a French cohort suggest that when rifampicin cannot be used, cotrimoxazole monotherapy might be a reliable alternative [58]. The dose of cotrimoxazole used in this cohort was quite high. Much lower doses (160/800 mg bid) were shown to be efficient as an oral relay in uncomplicated *S. aureus* bacteremia in the SABATO trial [67]. In case of streptococcal or enterococcal IE and contra-indication to amoxicillin, oral therapy should not be used. In fact, the number of patients treated with alternative antibiotics in the POET trial was very low.

8. What should be the empirical antibiotic treatment of IE?

8.1. What are the indications for empirical antibiotic treatment?

Argumentation

The early start of appropriate antimicrobial treatment is a strong prognostic factor in patients with sepsis.

The risk of symptomatic embolism is highest when vegetations are mobile and larger than 10 mm and decreases rapidly after the start of appropriate antimicrobial treatment in patients with IE.

Acute IE with rapid progression of symptoms is associated with increased risk of *S. aureus* IE. *S. aureus* IE is associated with increased risk of sepsis, central nervous system complications, and death.

8.2. What are the modalities of empirical antibiotic treatment?

Argumentation

The yield of blood cultures is optimal when 60 mL of blood are sampled before the start of any antimicrobial treatment. As shown in the UniENDO study, sampling of all three blood cultures at the same time does not impact the diagnostic performance in case of IE [68].

The main pathogens responsible for native valve IE and late-onset prosthetic valve IE are methicillin-susceptible staphylococci (35 %), streptococci (35 %) and enterococci (10 %).

In methicillin-susceptible *S. aureus* bloodstream infections, early treatment with cefazolin or an anti-staphylococcal penicillin (e.g., cloxacillin or oxacillin) have been associated in several large-scale observational studies with better survival.

The amoxicillin + cefazolin combination is bactericidal in vitro against > 95 % of the strains of *E. faecalis* responsible for IE [69].

The pathogens responsible for early-onset prosthetic valve IE may include methicillin-resistant staphylococci and Gram-negative bacilli.

Optimal treatment of methicillin-resistant staphylococci IE requires high-dose vancomycin (loading dose followed by continuous infusion) or daptomycin (10 mg/kg/d).

9. What is the antibiotic treatment of suspected IE with no microbiological documentation?

Argumentation

This situation most commonly reflects failure to sample appropriate volume of blood cultures before initiation of antimicrobial treatment.

A large proportion of suspected blood culture-negative IE is related

Guideline

Empirical antimicrobial treatment of suspected IE is recommended in each of the following situations:

- Acute onset with rapid progression of symptoms over the last week
- Large vegetation (>10 mm)
- Sepsis
- Before surgery when emergency valve surgery is indicated.

In all other situations, antibiotic treatment may be deferred until the results of blood cultures are available.

Guidelines

Empirical treatment of suspected IE must be started only after three pairs of blood culture bottles have been drawn (from a single or separate venipunctures), with a total volume of 60 mL, as well as any other suspected infection site with easy access (e.g., urine culture, joint aspiration, abscess drainage).

Empirical treatment should always include a combination of high-dose intravenous antibiotics.

For native valve IE and late-onset prosthetic valve IE (i.e., symptoms onset > 1 year post-valve implantation), preferred empirical treatment may be.

- amoxicillin (200 mg/kg/day) + cefazolin (100 mg/kg/day)
- combined with gentamicin (5 mg/kg/day) only in patients with sepsis

or (if allergy to β-lactams).

- vancomycin (30 mg/kg/day, continuous infusion after a loading dose).

For early-onset prosthetic valve IE (i.e., symptoms onset < 1 year post-valve implantation), preferred empirical treatment may be.

- daptomycin (12 mg/kg/day), or vancomycin (30 mg/kg/day, continuous infusion after a loading dose)
- combined with cefepime (2 g IV/8h)
- combined with gentamicin (5 mg/kg/day) only in patients with sepsis

Empirical treatment must be adapted as soon as reliable microbiological documentation is obtained.

Guideline

A typical situation is that of a patient with high suspicion of IE and no microbiological documentation three days after blood cultures sampling.

These cases must be comprehensively discussed with the Endocarditis Team.

Investigations must include prolonged incubation for at least 14 days of blood cultures, serological tests for *Coxiella burnetii* and *Bartonella* spp. and saliva, stool and blood PCR for *Tropheryma whipplei*.

Whenever the diagnosis of suspected IE remains likely, recommended empirical treatments are similar to those recommended for empirical treatment (see section 7). The addition of doxycycline may be considered, pending the results of tests for intracellular infections.

Although blood-culture negative IE is not an indication for valve surgery *per se*, valve surgery must be considered, after elimination of non-infectious causes of IE; failure to document the pathogens responsible for IE is associated with poor outcome. In case of surgery, additional investigations should be carried out on the valve (16S-RNA PCR, specific PCR or Next Generation Sequencing).

to atypical echocardiographic findings that possibly will not be confirmed as IE.

The pathogens most commonly responsible for blood-culture negative IE are the following:

- the usual pathogens responsible for IE (staphylococci, streptococci, and enterococci), blood cultures being negative due to previous antimicrobial treatment and/or inappropriate sampling of blood cultures before antimicrobial treatment is started;
- fastidious organisms that may require prolonged incubation of blood cultures (i.e. *Cutibacterium acnes, Gemella* sp., *Abiotrophia sp*., *Candida* sp., HACEK bacteria);
- "non-cultivable" organisms (*Coxiella burnettii*, *Bartonella* sp., *Tropheryma whipplei*) whose diagnosis requires serologic and/or nucleic amplification techniques.

Author contributions

All authors contributed to the intellectual content and the drafting of the manuscript. VLM, CS and EB supervised the final version, which was approved by all authors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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