Medical treatment of prosthetic vascular graft infections: review of the literature and proposals of a Working Group

M. Revest, F. Camou, E. Senneville, J. Caillon, Frédéric Laurent, Brigitte Calvet, P. Feugier, M. Batt, Christian Chidiac

Highlights

- A literature review dealing with medical treatment of vascular prosthesis infections was performed.
- The microbiological epidemiology of vascular prosthesis infections was highlighted.
- Indications and modalities of empirical antibiotherapy are proposed.
- Documented antibiotherapy of vascular prosthesis infections is described.

Medical treatment of prosthetic vascular graft infections: review of the literature and proposals of a Working Group

M. Revest [a,b], F. Camou [c], E. Senneville [d], J. Caillon [e], F. Laurent [f], B. Calvet [g], P. Feugier [h], M. Batt [i], C. Chidiac [j,*]; Groupe de Réflexion sur les Infections de Prothèses vasculaires (GRIP)

[a] *Infectious Diseases and Intensive Care Unit, Pontchaillou University Hospital, Rennes, France*

[b] *CIC Inserm 1414, Rennes 1 University, Rennes, France*

[c] *Intensive Care Unit, Saint-André University Hospital, Bordeaux, France*

[d] *Infectious Diseases Department, Gustave Dron Hospital, Tourcoing, Lille 2 University, France*

[e] *Bacteriology Department, EA 3826 Nantes University, Hôtel Dieu University Hospital, Nantes, France*

[f] *Bacteriology Department, International Center for Infectiology Research (CIRI)– INSERM U1111, CNRS UMR5308, Lyon 1 University, ENS de Lyon, Hospices Civils de Lyon, Lyon, France*

[g] *Anesthesiology Department, Beziers, France*

[h] *Department of Vascular Surgery, University Claude Bernard Lyon 1, Hospices Civils de Lyon, Lyon, France*

[i] *Department of Vascular Surgery, University of Nice-Sophia Antipolis, Nice, France*

[j] *Infectious Diseases Department, University Claude Bernard Lyon 1, Hospices Civils de Lyon, Inserm U1111, Lyon 1 University, Lyon, France*

ARTICLE INFO

Article history:

Received 19 January 2015

Accepted 21 April 2015

Keywords:

Vascular prosthesis infection

Antibiotic therapy

Staphylococcus

Rifampicin

* Corresponding author. Present address: Infectious Diseases Department, University Hospital of Lyon, Inserm U1111, University of Lyon 1, Hôpital de la Croix Rousse, 103 Grande rue de la Croix Rousse, 69004 Lyon, France. Tel.: +33 4 72 07 11 07; fax: + 33 4 72 07 17 50.

E-mail address: christian.chidiac@chu-lyon.fr (C. Chidiac).

ABSTRACT

More than 400 000 vascular grafts are inserted annually in the USA. Graft insertion is complicated by infection in 0.5–4% of cases. Vascular graft infections (VGIs) are becoming one of the most frequent prosthesis-related infections and are associated with considerable mortality, ranging from 10–25% within 30 days following the diagnosis. Treatment of VGI is based on urgent surgical removal of the infected graft followed by prolonged antibiotherapy. Data regarding the best antibiotherapy to use are lacking since no well designed trial to study antimicrobial treatment of VGI exists. Moreover, since VGIs demonstrate very specific pathophysiology, guidelines on other material-related infections or infective endocarditis treatment cannot be entirely applied to VGI. A French multidisciplinary group gathering infectious diseases specialists, anaesthesiologists, intensivists, microbiologists, radiologists and vascular surgeons was created to review the literature dealing with VGI and to make some proposals regarding empirical and documented antibiotic therapy for these infections. This article reveals these proposals.

1. Introduction

Due to advances in surgical techniques and increased possibilities for interventional radiology, the number of patients with vascular implants is constantly on the rise [1]. Prosthetic vascular graft infections (PVGIs) are among the most serious complications associated with these procedures. Their frequency, ranging from 1–5% of patients, varies depending on the anatomical implantation site, the biomaterial used and the patient's co-morbidities. The mortality rate is estimated to be 10–25% within 30 days after the diagnosis and almost 50% after 1 year, and the risk of amputation is estimated at 4–14% [2]. However, there are very few validated data on the best medical treatments for these infections. A focus group composed of French vascular surgeons, anaesthesiologists, microbiologists, intensivists, radiologists and infectious diseases specialists was conducted to review the literature on the subject and to formulate proposals for anti-infective therapies for PVGIs.

2. Methodology

This study relates to aortic (chest and abdominal) and peripheral PVGIs, including prosthetic arteriovenous fistula infections and axillofemoral bypass graft infections. Venous or arterial catheter infections, endovascular stimulation material infections and autologous graft infections were excluded.

A French and English literature search was conducted through PubMed for the period 1 January 1991 to 1 March 2013 using a selection of keywords from the

Medical Subject Heading (MeSH) database as well as other unreferenced keywords. From the 9188 references thus selected, the following were excluded: series with less than 10 cases; in vitro studies; and incomplete or insufficiently documented series. Some animal studies were retained for the analysis when they were considered to be sufficiently informative. Series on arteriovenous fistula infections carried out on bovine carotid grafts were also excluded. The bibliographic references for all publications selected were reviewed. All of the studies that were retained were reviewed using the grid proposed by the Society for Vascular Surgery [3]. The recommendations are graded in accordance with the Haute Autorité de Santé (French Health Authority) methodology sheet from December 2010 (Table 1) [4]. In the absence of data, they correspond to recommendations based on a professional consensus (expert opinion) within the Working Group. Forty-six clinical studies were thus selected for analysis [5–50]. There were 43 cohort studies, with the number of patients ranging from 11 [8,19,21] to 187 [32] (mean, 49; median, 32) and a case–control study involving 51 cases, for a total of 102 controls [34]. Four animal studies were also retained for analysis [51–54].

3. Empirical antibiotic therapy

3.1. Rationale

3.1.1. Microbiological information

The microbiological epidemiology of PVGIs is broken down as follows: *Staphylococcus aureus*, 20–53%; Enterobacteriaceae, 14–41%; coagulase-negative staphylococci (CoNS), 15%; *Pseudomonas aeruginosa*, *Streptococcus* sp. and

Enterococcus sp., 10–15%; polymicrobial infection, 20%; obligate anaerobic bacteria (always associated with other bacteria), 5%; and yeast, 1–2%.

3.1.2. Indication

In the study by Legout et al. [33], the proportion of intra-operative samples with positive culture did not differ between patients who did or did not receive antibiotics before revision surgery, i.e. 38/43 vs. 40/42, respectively (P = 0.4). However, patients who received antibiotherapy prior to surgery were operated within the first 48 h of treatment, and these results do not rule out the possible loss of microbiological information for patients treated >48 h prior to surgery, nor do they allow for the recommendation of empirical antibiotic therapy for all PVGI situations.

The issue of non-prescriptive empirical antibiotic therapy arises only when the patient has not received antibiotics prior to admission and when the expected time between diagnosis or suspicion and the revision surgery is short. No data are available to define the acceptable length of the expected timeframe for revision surgery beyond which empirical antibiotic therapy should be initiated. Ideally, this should be decided on a case-by-case basis as part of a multidisciplinary consultation.

3.1.3. Choice of antibiotics

3.1.3.1. Impact of the biofilm

Biofilm developed on the vascular prosthesis plays a particular role in the difficulties encountered in treating PVGIs. Biofilm is formed by surface-associated communities

of micro-organisms embedded in an extracellular matrix that acts as both a barrier against antibiotic penetration and protection against host defences [55]. Moreover, bacteria express a distinct metabolic pathway within the biofilm [56]. Whilst planktonic bacteria found outside the biofilm or in the very top layers of it display active metabolism and are therefore fully sensitive to antibiotics that mainly impair bacterial mechanisms of replication, bacteria embedded deeply in a mature biofilm demonstrate very slowed-down metabolic pathways and a decreased efficacy of antibiotics [56,57]. In this context, curing PVGIs with antibiotics alone without removal of the infected device therefore seems elusive.

There are very few data, if any, regarding the efficacy of antibiotics on infected vascular graft biofilm. An in vitro study evaluated the impact of various antimicrobial agents on staphylococcal adherence on Dacron© or polytetrafluoroethylene (PTFE). In this model, daptomycin and rifampicin were the two best agents to eradicate staphylococcal biofilm, whereas vancomycin and ceftriaxone failed to sterilise it [58]. Other authors investigated the capabilities of various antibiotics to penetrate biofilm formed on other medical devices. Rifampicin is probably the antimicrobial agent that demonstrated the best activity on staphylococcal biofilm [54,59–63]. When in combination, fosfomycin has been found to enhance the antimicrobial activities of many antibiotics in meticillin-resistant *S. aureus* (MRSA) biofilm [64]. Daptomycin has also demonstrated interesting capacities in biofilm penetration [65], and some studies revealed a higher activity against stationary phase staphylococci than vancomycin [66]. However, the clinical relevance of all these in vitro data is still lacking and the therapeutic choice of the antimicrobial chemotherapy to use to treat

PVGIs cannot be only based on such biofilm penetration criteria, highlighting that clinical studies and data are required.

3.1.3.2. Gram-positive cocci

The prevalence of MRSA has steadily declined in Europe since 2001 but remains >20%. The situation is different for CoNS, with resistance to β-lactams [67], glycopeptides (including teicoplanin) [68] and, more recently, linezolid [69] steadily on the rise.

The risk factors associated with meticillin-resistant staphylococci (MRS) (*S. aureus* or CoNS) in PVGI were examined in a retrospective study [41], which determined that the proportion of PVGIs caused by MRSA was 16%. The only factor identified was the existence of hypertension, but this relationship could not be explained. Given the important role of staphylococci in PVGIs, the significant proportion of MRSA and the absence of clinical risk factors validated by the meticillin resistance, it is recommended that the spectrum of empirical antibiotic therapy for PVGIs should systematically cover MRSA.

Anti-Gram-positive antibiotics used in empirical antibiotic therapy for PVGIs should ideally be bactericidal against bacteria both in the stationary growth phase and when growing exponentially, and they should have a spectrum that covers MRS [including strains whose glycopeptide minimum inhibitory concentrations (MICs) are ≥1.5 mg/L], good tissue distribution (including biofilm), an anti-adhesion effect and a good safety profile (including a kidney safety profile) that is compatible with the characteristics of patients with PVGIs. Considering these elements, linezolid and

tigecycline are less than ideal due to their solely bacteriostatic action and their failure to demonstrate their benefits in bacteraemic patients and/or in patients with severe infection; the same applies for teicoplanin [67], the anti-CoNS spectrum of which no longer appears to be currently adapted to the empirical treatment of prosthetic infection [67]. Vancomycin poses the problem of its nephrotoxic potential [70]. Daptomycin has a profile that is adapted to all of these prerequisites, but it does not have an approval for this type of use [71].

3.1.3.3. Gram-negative bacilli

Bacterial ecology is highly variable from one health facility to another, and as such it is difficult to recommend a standardised anti-Gram-negative bacilli empirical antibiotic therapy. The empirical prescription of amoxicillin/clavulanic acid appears inadequate because of the increasing prevalence of resistant *Escherichia coli*, exceeding one-third of strains [72]. The combinations piperacillin/tazobactam and ticarcillin/clavulanic acid have an advantage over cephalosporins because they cover obligate anaerobes, including *Bacteroides fragilis*.

The increase in carbapenemase-producing bacteria in human pathology restricts the use of carbapenems to severe infections and/or when the patient has multidrug-resistant bacteria [73].

Aminoglycosides may be useful to intensify bactericidal activity and to rapidly reduce the bacterial inoculum, but they expose patients to the risk of nephrotoxicity, particularly patients with chronic renal failure or cirrhosis. The impact of their use on mortality varies: one study found no benefit of aminoglycosides on mortality rates

[41], whereas a separate study found that aminoglycosides might reduce mortality when used for patients in intensive care (59% vs. 27%; *P* = 0.07 in multivariate analysis) [42].

3.2. Recommendations

It is recommended that the use of empirical antibiotic therapy should be limited to suspected or known cases of PVGI for which it does not seem reasonable to wait for surgical microbiological sample results. Such situations include severe sepsis, septic shock, and instances in which the clinical and/or radiological signs indicate a mechanical complication of infectious origin, such as an aneurysmal rupture or anastomotic disunion (C-III). Two different sets of blood cultures should systematically be performed prior to empirical antibiotherapy.

Adaptation is necessary after receiving the microbiological results from blood cultures or surgical samples. Such 'de-escalation' should be performed as quickly as possible to limit the selection pressure for resistant strains that is induced by this broad-spectrum antibiotic therapy (B-III).

Table 2 presents proposals for empirical antibiotic therapy depending on the clinical situation (C-III).

The potential severity of PVGIs, their frequent association with bacteraemia, and the need for sufficient concentrations at the site of the infected material

interface/periprosthetic tissue are good arguments for parenteral administration and the use of high dosages (C-III).

4. Documented antibiotic therapy

The following proposals reflect the prerequisites outlined above (good diffusion in the biofilm, activity against slowly metabolising strains, high tolerance, need for bactericidal treatment) and result from an analysis of the PVGI literature and the most recent recommendations for the treatment of prosthetic valve endocarditis [34,74–76]. Although PVGIs cannot be entirely likened to infective endocarditis (IE), these two types of infection have many points in common, including infection of endovascular material with production of biofilm, patients with multiple co-morbidities, frequently impaired renal function, and similarity of causative micro-organisms, with the exception of Enterobacteriaceae and obligate anaerobic bacteria that are often encountered in cases of PVGI but are rare in IE.

Blood cultures and/or periprosthetic collection punctures can serve to document the infection prior to surgery. The following recommendations therefore distinguish two situations: pre-operative and post-operative antibiotic therapy. For the post-operative part, two situations are distinguished: optimal management (excision of the entire infected prosthesis and the surrounding infected tissue); and suboptimal surgery (all or part of the prosthesis left in place). In the absence of pre-operative documentation, the antibiotic therapy recommendations are outlined in Section 3.

There are no data regarding the impact of the surgical procedure performed on the antibiotherapy. It is not known whether the type of biomaterial used for the vascular reconstruction after infected graft removal (autogenous venous graft, cryopreserved arterial allograft, prosthetic graft) or the surgical procedure performed (extra-anatomical or in situ reconstruction) influence the choice or duration of antibiotic treatment. It is therefore recommended to apply the same medical treatment for all of the different surgical techniques (C-III).

It is also not known whether the anatomical site or the type of infected material impact the choice of antibiotherapy. In the literature, peripheral lower limb VGI and aortic VGI are often individualised but only for the surgical procedure and not for the medical treatment. Prosthetic dialysis arteriovenous graft infections have also been specifically studied but only in three studies [77–79], and data dealing with antibiotics are too scarce to propose specific medical treatment for these infections. Thus, it is recommended to adopt the same medical treatment for all the different types of PVGIs (C-III).

The dosages and modes of administration of the various compounds mentioned are provided in Table 3. Generally (B-III):

- In the event of reliable pre-operative documentation (deep sampling performed through healthy dermal route or positive blood culture), antibiotic therapy should target only the pathogen or pathogens found.
- Post-operative re-evaluation of this antibiotic therapy should be carried out in light of the intra-operative sampling results.

- Surgical treatment should be performed as quickly as possible because of the extreme severity of PVGIs in order to facilitate the efficacy of the anti-infective therapy. This is particularly important in cases of micro-organisms that are difficult to treat, such as multiresistant bacteria, enterococci, *P. aeruginosa* and yeasts.

4.1. Staphylococcal infections

4.1.1. Rationale

Although not new [80], data regarding the efficacy of meticillin derivatives are still valid [81] and the use of these derivatives remains highly recommended as the first-line treatment for severe meticillin-sensitive *S. aureus* infections [34,75,76,82]. In the case of penicillin allergy without allergy to cephalosporins, the choice will be between cefazolin, vancomycin and daptomycin. In the case of allergy to all β-lactams, the choice will be between vancomycin and daptomycin [34,81,83–90].

Treatment of MRSA infections is difficult. Vancomycin is established by usage as the compound of choice, although failures are reported, particularly in cases of high vancomycin MICs (≥1.5 mg/L) [91,92].

Given that PVGIs are severe infections on foreign materials, addition of an aminoglycoside, preferably gentamicin, is justified [59,93–95].

Addition of rifampicin is attractive because of its large diffusion capacity, anti-adhesion potency and preserved bactericidal activity despite the presence of a

biofilm [59,60,96]. Its use is also correlated with a better prognosis in osteoarticular staphylococcal infections [97]. Its prescription as monotherapy is strongly discouraged, as is its use in bacteraemic patients [98], owing to the rapid emergence of a resistant strain of bacteria. There are no data regarding the use of rifampicin in PVGIs, but the pharmacological, clinical and experimental data argue in favour of its use. Therefore, in the treatment of staphylococcal PVGIs, it is advisable to add rifampicin to the treatment after vascular surgery and certainty of negative blood cultures.

Daptomycin exhibits interesting bactericidal activity within the biofilm [58,99]. It is approved for bacteraemia and right-sided endocarditis caused by *S. aureus* at a dose of 6 mg/kg/day in a single injection [100]. However, there appears to be a possibility of decreased staphylococci susceptibility during treatment [101] and a greater number of microbiological failures compared with comparators [100], suggesting that the dose of 6 mg/kg/day may be insufficient. Some authors have also shown that higher doses (8–12 mg/kg/day) do not pose any particular tolerance problems [102,103], although it is not known whether this increase in dosage changes the prognosis of infections. However, no data are available regarding the use of daptomycin in the treatment of PVGIs, and the use of this compound as first-line therapy should be subject to a multidisciplinary approach when the staphylococcal strain is sensitive to meticillin and vancomycin (MICs < 1.5 mg/L). In staphylococcal infections caused by strains with vancomycin MICs ≥ 1.5 mg/L, the use of daptomycin is advised, at high doses, in combination with gentamicin for the first 3 days of treatment, followed by rifampicin. Daptomycin MICs for the isolated

strain should be documented. It has indeed been shown that sensitivity to daptomycin may decrease when the vancomycin MIC is elevated [104,105].

No scientifically valid data provide a basis for preferring one compound to another for PVGIs caused by glycopeptide-resistant staphylococci. However, daptomycin is the compound for which data related to use on foreign material [106] and IE [100] are the most documented. To improve efficacy and reduce the risk of emergence of strains with reduced susceptibility to daptomycin during treatment, it should be combined with another antibiotic, preferably gentamicin [107] or rifampicin [108].

For other antistaphylococcal agents, no data are available for this type of infection and their use should be considered only on a case-by-case basis, in combination, in the absence of an alternative and following a multidisciplinary opinion.

4.1.2. Recommendations

Therapeutic proposals for PVGIs caused by staphylococci (*S. aureus* or CoNS) are presented in Tables 4 and 5.

4.2. Streptococcal infections

4.2.1. Rationale

There is no study specific to the treatment of streptococcal PVGIs. Therefore, the following recommendations stem from extrapolations from comparable clinical

situations for which reliable data are available. Amoxicillin remains the antibiotic of choice for streptococcal infections [34,75,82,109–111].

The use of aminoglycosides for treating severe streptococcal infections is currently under debate because of their potential toxicity [112]. Analysis of the literature does not support any conclusion regarding their usefulness [113–116]. Their use in the first days of treatment to reduce bacterial inocula appears to be justified.

Post-operatively, this benefit is more questionable: the bacterial inoculum is reduced by surgery, and the remaining bacteria are located in the periphery of the prosthesis, in an extravascular position, an area in which the diffusion of aminoglycosides is very limited. If vancomycin is used, co-administration of gentamicin is not recommended because of the low level of evidence regarding its use in this context and the risk of renal toxicity associated with this combination. When used, gentamicin is given in a single daily dose [93].

The effectiveness of other antibiotics with antistreptococcal activity in PVGI treatment has not yet been established.

4.2.2. Recommendations

4.2.2.1. Pre-operative treatment

Determination of MICs of amoxicillin, cefotaxime and/or ceftriaxone, or even vancomycin, should be obtained, particularly in cases of *viridans* streptococci infection (B-III). Amoxicillin is the recommended treatment for streptococcal PVGIs

that are sensitive to this compound, with dosages ranging from 100 mg/kg/day (streptococci for which the amoxicillin MIC is <0.125 mg/L) to 200 mg/kg/day (MIC ≥ 0.125 mg/L) divided into four to six injections (B-III). Gentamicin can be added, for a maximum period of 3 days, at a dose of 3–8 mg/kg/day (C-III).

Vancomycin is the antibiotic of choice (B-III) when susceptibility to all β-lactam antibiotics is decreased or in the case of allergy to all members of this therapeutic class. Determination of the vancomycin MIC is therefore imperative. Combination with gentamicin is not systematic; it is only considered in the event of signs of severe sepsis or septic shock, and its use is then restricted to ≤3 days (C-III).

4.2.2.2. Post-operative treatment

4.2.2.2.1. For optimal surgical treatment

Post-operative treatment is the same as that recommended for pre-operative treatment (B-III). The duration of treatment is 6 weeks post-operatively, parenterally (C-III).

4.2.2.2.2. For suboptimal surgical treatment

Antibiotic treatment is the same as in the previous situation for 6 weeks post-operatively (B-III). Subsequently, switching to oral amoxicillin can be considered (C-III).

4.3. Enterococcal infections

4.3.1. Rationale

In the absence of high-level resistance to gentamicin, the combination of amoxicillin + gentamicin is synergistic and bactericidal [117,118]. Extrapolation of data regarding endocarditis would serve to restrict the duration of use of gentamicin [119]. Post-operatively, due to the decrease of inoculum, treatment with aminoglycoside is temporally shortened.

Experimental data have shown that the ampicillin + ceftriaxone combination may act synergistically when used in the treatment of experimental endocarditis caused by *Enterococcus faecalis* [120,121]. Human clinical data also appear to confirm this [122,123]. This combination could be an option in the case of significant toxicity of aminoglycosides or pre-existing renal insufficiency.

For PVGIs caused by vancomycin-resistant enterococci, there is not yet enough solid evidence to recommend one compound over another [124]. Linezolid has sometimes been used [125,126], most often in combination with other compounds, but its prolonged use is difficult because of its neurological and haematological toxicity and potential risk of relapse [127,128]. Some experimental studies [129] or clinical cases [130] also reported the efficacy of daptomycin in this indication, but the emergence of resistant strains [131,132] makes its use problematic. However, some in vitro data appear to indicate a real synergy between daptomycin and rifampicin or ampicillin against enterococci [133,134]. Monitoring of a cohort of 159 patients (90% bacteraemic) treated with daptomycin for enterococcal infection, 115 of whom were

resistant to vancomycin, showed a cure rate of 44% [135]. It is not possible to be categorical regarding the choice of the compound to be used in glycopeptide-resistant PVGIs caused by enterococci [136]. This choice must be made after multidisciplinary discussion.

4.3.2. Recommendations

4.3.2.1. Pre-operative treatment

Amoxicillin is the recommended treatment for PVGIs caused by susceptible enterococci. The dose is 200 mg/kg/day divided into four to six injections (B-III). Gentamicin is used, in a single daily dose, for 7 days at a dose of 3–8 mg/kg/day if surgery is not performed before treatment (B-III).

In the case of allergy or resistance to amoxicillin, teicoplanin or vancomycin alone is recommended (B-III). In the case of resistance to glycopeptides, the susceptibility of enterococcus to daptomycin and linezolid must be studied. The choice will be made following a multidisciplinary opinion (C-III).

4.3.2.2. Post-operative treatment

4.3.2.2.1. For optimal surgical treatment

Post-operative treatment is the same as that recommended for pre-operative treatment regarding amoxicillin or glycopeptides (B-III). Gentamicin is continued only for a maximum of 3 days (C-III). The duration of treatment is 6 weeks post-operatively, parenterally, at the same dosage (C-III).

4.3.2.2.2. For suboptimal surgical treatment

Antibiotic treatment is the same as in the previous situation for 6 weeks post-operatively (C-III). Subsequently, oral amoxicillin relay, for an extended period, can be considered (C-III).

4.4. Enterobacteriaceae infections

4.4.1. Rationale

The benefit of combination therapy in infections caused by enterobacteria is controversial [137]. The synergistic effect and prevention of resistance has not been demonstrated by clinical studies [137–144]. However, the severity of PVGIs and the risk of severe systemic impact justify the initial combination of an aminoglycoside with a β-lactam for a short period of time [93].

4.4.2. Recommendations

Therapeutic proposals for PVGIs caused by Enterobacteriaceae are presented in Table 6.

4.5. Pseudomonas infections

4.5.1. Rationale

On a compromised terrain and high inoculum, the slightest susceptibility to antibiotics and resistance make the treatment of PVGIs caused by *Pseudomonas* difficult. The benefit of combination therapy that has not been shown by discordant and heterogeneous clinical studies [145–148] remains established by usage prior to surgery and post-operatively.

4.5.2. Recommendations

4.5.2.1. Pre-operative treatment

Treatment is based on a β-lactam, and the choice is made according to the results of antibiotic susceptibility testing among ticarcillin, ceftazidime, piperacillin/tazobactam and a carbapenem (excluding ertapenem) (B-III). An aminoglycoside (amikacin or tobramycin) is combined with it for 3 days (C-III). The aminoglycoside is replaced by fosfomycin beyond these 3 days if the surgery has not yet been performed (C-III). Fluoroquinolones should be reserved for post-operative oral relay (B-III).

4.5.2.2. Post-operative treatment

4.5.2.2.1. For optimal surgical treatment

Combination therapy is continued, with the β-lactam selected pre-operatively being used in conjunction with ciprofloxacin or fosfomycin, depending on antibiotic susceptibility testing (C-III). This combination therapy is continued for ≥3 weeks, for a total of 6 weeks post-operatively (C-III).

4.5.2.2.2. For suboptimal surgical treatment

Multidisciplinary opinion (C-III).

4.6. Obligate anaerobic bacterial infections

4.6.1. Rationale

Metronidazole, which is consistently active against obligate anaerobes, particularly *B. fragilis*, is the compound of choice. Its absorption and exceptional diffusion allow its use as oral monotherapy [149]. *Propionibacterium acnes*, which is naturally resistant to imidazole, is susceptible to amoxicillin. Surgery is essential because relapse when the prosthetic material is left in place is virtually systematic [150]. Clindamycin, in addition to the risk of *Clostridium difficile* colitis, does not have a satisfactory anti-anaerobic spectrum, particularly against *B. fragili*s, which limits its empirical prescription in cases of PVGI [149].

4.6.2. Recommendations

4.6.2.1. Pre-operative treatment

Metronidazole is the first-line treatment for obligate anaerobic infections apart from *P. acnes*. It may be administered orally or intravenously (B-III). PVGIs caused by *P. acnes* are treated with intravenous amoxicillin (B-III). Monotherapy is sufficient (B-III).

4.6.2.2. Post-operative treatment

4.6.2.2.1. For optimal surgical treatment

The treatment is the same as pre-operative management (B-III). The total duration of treatment is 6 weeks (C-III).

4.6.2.2.2. For suboptimal surgical treatment

Suppressive oral amoxicillin treatment may be proposed for PVGIs caused by *P. acnes* and following a multidisciplinary opinion (C-III). For other obligate anaerobes such as *B. fragilis*, the possibility of suppressive treatment should be evaluated after multidisciplinary consultation (C-III).

4.7. Polymicrobial infections

Susceptibility testing should be performed for each of the isolated bacteria. Several compounds may sometimes be necessary to cover all of the bacteria considered pathogenic. A multidisciplinary opinion is necessary (B-III). The presence of obligate anaerobes does not require metronidazole if one of the combination antibiotics is already active on these bacteria (B-III).

5. Duration of treatment of bacterial prosthetic vascular graft infections and methods of administration

5.1. Rationale

Analysis of treatment duration from different studies is difficult to interpret because of: (i) the non-comparative nature of these studies; (ii) studies that do not include standardised durations or feature highly variable durations; and (iii) the use of a wide variety of compounds. In all of these studies, patients underwent surgery. The durations of antibiotic therapy are variable, ranging from 2 weeks after surgery [15,31] to 6 months [30], or even lifelong [22]. Many studies report durations of 6 weeks post-operatively [5,7,9,11–14,25,27,28,35,37] without the risk of relapse appearing greater than that encountered when the treatment period is longer. This 6-week duration is the same as that proposed in the treatment of prosthetic valve endocarditis [34,82].

5.2. Recommendations

The total duration of post-operative antibiotic therapy proposed for PVGIs is 6 weeks for optimal surgical treatment (C-III). It should be administered parenterally. When using compounds with good bioavailability (rifampicin, fluoroquinolones), oral administration is possible.

6. Methods of administration of anti-infective agents

These methods are presented for normal renal and hepatic function in Table 3. In patients with renal or hepatic impairment, an adjustment may be required.

7. Suppressive antibiotic therapy

7.1. Rationale

In the absence of surgery, or in cases of suboptimal surgery, suppressive antibiotic therapy is administered. Its aim is to inhibit bacterial growth around the prosthesis, or what is left of it. By analogy with infections on osteoarticular material [151], it is assumed that in the stationary growth phase, bacteria remain on the material that cannot be eliminated by intensive antibiotic therapy. Even with very high dosage and very long duration, antibiotherapy alone is not supposed to cure PVGIs [152]. For instance, a recent study dealing with aortic endograft infection demonstrated that all of the patients who did not undergo endograft removal died during follow-up [49].

Suppressive treatment is only conceivable in the case of documented infection. In cases of periprosthetic abscess, radiological drainage should be performed if possible to reduce the bacterial inoculum as much as possible. No formal studies currently serve to validate this approach.

7.2. Recommendations

Suppressive antibiotic therapy is administered in the absence of surgery or in the case of suboptimal surgery (C-III). This antibiotic therapy will follow a 6-week period

of intensive antibiotic therapy (B-III). It should therefore be easy to administer (orally), well tolerated and feasible as monotherapy. The choice of compound used should result from a multidisciplinary approach (B-III).

8. Specific case of fungal infection

8.1. Rationale

This essentially relates to yeast infections, such as *Candida*, in the context of bacterial co-infections. The therapeutic choice is made between amphotericin B derivatives (liposomal or lipid complex), azoles (mainly fluconazole) and echinocandins. The theoretical prerequisites are fungicidal treatment with activity preserved in the biofilm, anti-adhesion effect, proper dissemination to the infectious site and good tolerance. For this last reason, amphotericin B, which is nephrotoxic, is not recommended because of the frail nature of the patients.

Echinocandins have a good safety profile (including renal), in vitro fungicidal activity against yeasts, and good action in the case of existence of biofilm [153]. Their use is recommended by several scientific societies as a first-line treatment of moderate-to-severe infections [154]. One key disadvantage of using echinocandins is that they are available only for parenteral administration. There is a restriction on the use of micafungin (risk of liver tumours observed in a mouse model).

8.2. Recommendations

Isolation of the fungus and antifungal susceptibility testing are essential. An echinocandin (caspofungin, micafungin or anidulafungin, if available) is used as a first-line treatment for 10 days post-operatively and/or 10 days after the last positive blood culture for *Candida* (C-III). If the strain is susceptible, if blood cultures are negative for ≥10 days and if the clinical situation has stabilised, an oral relay treatment with fluconazole may be taken on Day 10: loading dose of 800 mg on the first day followed by a one-time dose of 400–800 mg/day (B-III). The duration of treatment is ≥6 weeks post-operatively and 3 months in cases involving a periprosthetic abscess (C-III).

9. Conclusions

PVGIs are infections burdened with heavy rates of morbidity and mortality, the frequency of which are rising because of surgical advances and endovascular techniques that make it possible to implant an increasing number of prostheses. No data currently provide solid evidence regarding the antimicrobial therapy to be administered to patients suffering from PGVIs. A comprehensive literature review was therefore conducted. We hope that the proposals resulting from this analysis will help practitioners with regard to the care of these patients. It is increasingly vital to validate these proposals by means of further research investigating this issue, and we hope that the results of such studies will soon be available.

Funding: This work was partly supported by a research grant from Novartis. Novartis had no role in the choice of the authors and had no access to the conclusions of the authors until the work was ended.

Competing interests: MR received research grant from Novartis, payment for lectures from MSD and Pfizer, and support for travel to international meetings from MSD; FC received research grant from Novartis, research investigator honoraria from Cubist, MSD, Sanofi and Trius Therapeutics, payment for lectures from Novartis, Pfizer and Sanofi, and support for travel to international meetings from Astellas, Janssen, MSD, Novartis, Pfizer and Sanofi. All other authors declare no competing interests.

Ethical approval: Not required.

References

[1] Darouiche RO. Treatment of infections associated with surgical implants. N Engl J Med 2004;350:1422–9.

[2] FitzGerald SF, Kelly C, Humphreys H. Diagnosis and treatment of prosthetic aortic graft infections: confusion and inconsistency in the absence of evidence or consensus. J Antimicrob Chemother 2005;56:996–9.

[3] Clagett GP. Clinical research and vascular surgery. The Society for Vascular Surgery Ad Hoc Committee on Clinical Research. J Vasc Surg 1992;15:867–8.

[4] Haute Autorité de Santé (HAS). *Elaboration de recommandations de bonne pratique. Méthode Recommandations par consensus formalisé*. HAS; 2010.

[5] Ehsan O, Gibbons CP. A 10-year experience of using femoro-popliteal vein for re-vascularisation in graft and arterial infections. Eur J Vasc Endovasc Surg 2009;38:172–9.

[6] Batt M, Jean-Baptiste E, O'Connor S, Bouillanne PJ, Haudebourg P, Hassen-Khodja R, et al. In-situ revascularisation for patients with aortic graft infection: a single centre experience with silver coated polyester grafts. Eur J Vasc Endovasc Surg 2008;36:182–8.

[7] Armstrong PA, Back MR, Bandyk DF, Johnson BL, Shames ML. Selective application of sartorius muscle flaps and aggressive staged surgical debridement can influence long-term outcomes of complex prosthetic graft infections. J Vasc Surg 2007;46:71–8.

[8] Mirzaie M, Schmitto JD, Tirilomis T, Fatehpur S, Liakopoulos OJ, Teucher N, et al. Surgical management of vascular graft infection in severely ill patients by partial resection of the infected prosthesis. Eur J Vasc Endovasc Surg 2007;33:610–3.

[9] Illuminati G, Calio FG, D'Urso A, Giacobbi D, Papaspyropoulos V, Ceccanei G. Infrascrotal, perineal, femorofemoral bypass for arterial graft infection at the groin. Arch Surg 2004;139:1314–9.

[10] Gabriel M, Pukacki F, Dzieciuchowicz L, Oszkinis G, Checinski P. Cryopreserved arterial allografts in the treatment of prosthetic graft infections. Eur J Vasc Endovasc Surg 2004;27:590–6.

[11] Kieffer E, Gomes D, Chiche L, Fléron MH, Koskas F, Bahnini A. Allograft replacement for infrarenal aortic graft infection: early and late results in 179 patients. J Vasc Surg 2004;39:1009–17.

[12] Batt M, Magne JL, Alric P, Muzj A, Ruotolo C, Ljungstrom KG, et al. In situ revascularization with silver-coated polyester grafts to treat aortic infection: early and midterm results. J Vasc Surg 2003;38:983–9.

[13] Arbatli H, DeGeest R, Demirsoy E, Wellens F, Degrieck I, VanPraet F, et al. Management of infected grafts and mycotic aneurysms of the aorta using cryopreserved homografts. Cardiovasc Surg 2003;11:257–63.

[14] Daenens K, Fourneau I, Nevelsteen A. Ten-year experience in autogenous reconstruction with the femoral vein in the treatment of aortofemoral prosthetic infection. Eur J Vasc Endovasc Surg 2003;25:240–5.

[15] Matsuura JH, Rosenthal D, Wellons ED, Castronovo CS, Fronk D. Hemodialysis graft infections treated with cryopreserved femoral vein. Cardiovasc Surg 2002;10:561–5.

[16] Vogt PR, Brunner-LaRocca HP, Lachat M, Ruef C, Turina MI. Technical details with the use of cryopreserved arterial allografts for aortic infection: influence on early and midterm mortality. J Vasc Surg 2002;35:80–6.

[17] Leseche G, Castier Y, Petit MD, Bertrand P, Kitzis M, Mussot S, et al. Long-term results of cryopreserved arterial allograft reconstruction in infected prosthetic grafts and mycotic aneurysms of the abdominal aorta. J Vasc Surg 2001;34:616–22.

[18] Bandyk DF, Novotney ML, Back MR, Johnson BL, Schmacht DC. Expanded application of in situ replacement for prosthetic graft infection. J Vasc Surg 2001;34:411–9; discussion 419–20.

[19] Kieffer E, Sabatier J, Plissonnier D, Knosalla C. Prosthetic graft infection after descending thoracic/ thoracoabdominal aortic aneurysmectomy: management with in situ arterial allografts. J Vasc Surg 2001;33:671–8.

[20] Seeger JM, Pretus HA, Welborn MB, Ozaki CK, Flynn TC, Huber TS. Long-term outcome after treatment of aortic graft infection with staged extra-anatomic bypass grafting and aortic graft removal. J Vasc Surg 2000;32:451–9; discussion 460–1.

[21] Hayes PD, Nasim A, London NJ, Sayers RD, Barrie WW, Bell PR, et al. In situ replacement of infected aortic grafts with rifampicin-bonded prostheses: the Leicester experience (1992 to 1998). J Vasc Surg 1999;30:92–8.

[22] Coselli JS, Koksoy C, LeMaire SA. Management of thoracic aortic graft infections. Ann Thorac Surg 1999;67:1990–3; discussion 1997–8.

[23] Vogt PR, Turina MI. Management of infected aortic grafts: development of less invasive surgery using cryopreserved homografts. Ann Thorac Surg 1999;67:1986–9; discussion 1997–8.

[24] Vogt PR, Brunner-La Rocca HP, Carrel T, von Segesser LK, Ruef C, Debatin J, et al. Cryopreserved arterial allografts in the treatment of major vascular infection: a comparison with conventional surgical techniques. J Thorac Cardiovasc Surg 1998;116:965–72.

[25] Nevelsteen A, Feryn T, Lacroix H, Suy R, Goffin Y. Experience with cryopreserved arterial allografts in the treatment of prosthetic graft infections. Cardiovasc Surg 1998;6:378–83.

[26] Fiorani P, Speziale F, Rizzo L, Taurino M, Giannoni MF, Lauri D. Long-term follow-up after in situ graft replacement in patients with aortofemoral graft infections. Eur J Vasc Endovasc Surg 1997;14(Suppl A):111–4.

[27] Sicard GA, Reilly JM, Doblas M, Orgaz A, Rubin BG, Flye MW, et al. Autologous vein reconstruction in prosthetic graft infections. Eur J Vasc Endovasc Surg 1997;14(Suppl A):93–8.

[28] Nevelsteen A, Lacroix H, Suy R. Infrarenal aortic graft infection: in situ aortoiliofemoral reconstruction with the lower extremity deep veins. Eur J Vasc Endovasc Surg 1997;14(Suppl A):88–92.

[29] Speziale F, Rizzo L, Sbarigia E, Giannoni MF, Massucci M, Maraglino C, et al. Bacterial and clinical criteria relating to the outcome of patients undergoing in situ replacement of infected abdominal aortic grafts. Eur J Vasc Endovasc Surg 1997;13:127–33.

[30] Darling RC 3rd, Resnikoff M, Kreienberg PB, Chang BB, Paty PS, Leather RP, et al. Alternative approach for management of infected aortic grafts. J Vasc Surg 1997;25:106–12.

[31] DiMuzio PJ, Reilly LM, Stoney RJ. Redo aortic grafting after treatment of aortic graft infection. J Vasc Surg 1996;24:328–35; discussion 336–7.

[32] Ali AT, Modrall JG, Hocking J, Valentine RJ, Spencer H, Eidt JF, et al. Long-term results of the treatment of aortic graft infection by in situ replacement with femoral popliteal vein grafts. J Vasc Surg 2009;50:30–9.

[33] Legout L, Sarraz-Bournet B, D'Elia PV, Devos P, Pasquet A, Caillaux M, et al. Characteristics and prognosis in patients with prosthetic vascular graft infection: a prospective observational cohort study. Clin Microbiol Infect 2012;18:352–8.

[34] Antonios VS, Noel AA, Steckelberg JM, Wilson WR, Mandrekar JN, Harmsen WS, et al. Prosthetic vascular graft infection: a risk factor analysis using a case–control study. J Infect 2006;53:49–55.

[35] Stone PA, Armstrong PA, Bandyk DF, Brumberg RS, Flaherty SK, Back MR, et al. Use of antibiotic-loaded polymethylmethacrylate beads for the treatment of extracavitary prosthetic vascular graft infections. J Vasc Surg 2006;44:757–61.

[36] Pinocy J, Albes JM, Wicke C, Ruck P, Ziemer G. Treatment of periprosthetic soft tissue infection of the groin following vascular surgical procedures by means of a polyvinyl alcohol-vacuum sponge system. Wound Repair Regen 2003;11:104–9.

[37] Jensen LP, Nielsen OM, Jorgensen L, Lorentzen JE. Conservative treatment of vascular graft infections in the groin. Eur J Vasc Endovasc Surg 1997;14(Suppl A):43–6.

[38] Oderich GS, Bower TC, Hofer J, Kalra M, Duncan AA, Wilson JW, et al. In situ rifampin-soaked grafts with omental coverage and antibiotic suppression are durable with low reinfection rates in patients with aortic graft enteric erosion or fistula. J Vasc Surg 2011;53:99–106, 107.e1–7; discussion 106–7.

[39] Roy D, Grove DI. Efficacy of long-term antibiotic suppressive therapy in proven or suspected infected abdominal aortic grafts. J Infect 2000;40:184–7.

[40] Young RM, Cherry KJ Jr, Davis PM, Gloviczki P, Bower TC, Panneton JM, et al. The results of in situ prosthetic replacement for infected aortic grafts. Am J Surg 1999;178:136–40.

[41] Legout L, D'Elia P, Devos P, Ettahar N, Sarraz-Bournet B, Haulon S, et al. Risk factors for methicillin-resistant staphylococcal vascular graft infection in an 11-year cohort study. J Infect 2012;64:441–4.

[42] Szczot M, Meybeck A, Legout L, Pasquet A, Van Grunderbeeck N, Langlois J, et al. Vascular graft infections in the intensive care unit: clinical spectrum and prognostic factors. J Infect 2011;62:204–11.

[43] Töpel I, Audebert F, Betz T, Steinbauer MG. Microbial spectrum and primary resistance to rifampicin in infectious complications in vascular surgery: limits to the use of rifampicin-bonded prosthetic grafts. Angiology 2010;61:423–6.

[44] Saleem BR, Meerwaldt R, Tielliu IF, Verhoeven EL, van den Dungen JJ, Zeebregts CJ. Conservative treatment of vascular prosthetic graft infection is associated with high mortality. Am J Surg 2010;200:47–52.

[45] Torsello G, Sandmann W. Use of antibiotic-bonded grafts in vascular graft infection. Eur J Vasc Endovasc Surg 1997;14(Suppl A):84–7.

[46] Holdsworth J. Treatment of infective and potentially infective complications of vascular bypass grafting using gentamicin with collagen sponge. Ann R Coll Surg Engl 1999;81:166–70.

[47] Gordon A, Conlon C, Collin J, Peto T, Gray D, Hands L, et al. An eight year experience of conservative management for aortic graft sepsis. Eur J Vasc Surg 1994;8:611–6.

[48] Fatima J, Duncan AA, de Grandis E, Oderich GS, Kalra M, Gloviczki P, et al. Treatment strategies and outcomes in patients with infected aortic endografts. J Vasc Surg 2013;58:371–9.

[49] Lyons OT, Patel AS, Saha P, Clough RE, Price N, Taylor PR. A 14-year experience with aortic endograft infection: management and results. Eur J Vasc Endovasc Surg 2013;46:306–13.

[50] Maze MJ, Laws P, Buckenham T, Pithie A, Gallagher K, Metcalf S, et al. Outcomes of infected abdominal aortic grafts managed with antimicrobial therapy and graft retention in an unselected cohort. Eur J Vasc Endovasc Surg 2013;45:373–80.

[51] Blaser J, Vergeres P, Widmer AF, Zimmerli W. In vivo verification of in vitro model of antibiotic treatment of device-related infection. Antimicrob Agents Chemother 1995;39:1134–9.

[52] Cirioni O, Mocchegiani F, Ghiselli R, Silvestri C, Gabrielli E, Marchionni E, et al. Daptomycin and rifampin alone and in combination prevent vascular graft biofilm formation and emergence of antibiotic resistance in a subcutaneous rat pouch model of staphylococcal infection. Eur J Vasc Endovasc Surg 2010;40:817–22.

[53] Gao H, Sandermann J, Prag J, Lund L, Lindholt JS. Rifampicin-soaked silver polyester versus expanded polytetrafluoro-ethylene grafts for in situ replacement of infected grafts in a porcine randomised controlled trial. Eur J Vasc Endovasc Surg 2012;43:582–7.

[54] Baldoni D, Haschke M, Rajacic Z, Zimmerli W, Trampuz A. Linezolid alone or combined with rifampin against methicillin-resistant *Staphylococcus aureus* in experimental foreign-body infection. Antimicrob Agents Chemother 2009;53:1142–8.

[55] Richards JJ, Melander C. Controlling bacterial biofilms. Chembiochem 2009;10:2287–94.

[56] Stewart PS, Franklin MJ. Physiological heterogeneity in biofilms. Nat Rev Microbiol 2008;6:199–210.

[57] Otto M. *Staphylococcus epidermidis*—the 'accidental' pathogen. Nat Rev Microbiol 2009;7:555–67.

[58] Edmiston CE Jr, Goheen MP, Seabrook GR, Johnson CP, Lewis BD, Brown KR, et al. Impact of selective antimicrobial agents on staphylococcal adherence to biomedical devices. Am J Surg 2006;192:344–54.

[59] Chuard C, Herrmann M, Vaudaux P, Waldvogel FA, Lew DP. Successful therapy of experimental chronic foreign-body infection due to

methicillin-resistant *Staphylococcus aureus* by antimicrobial combinations. Antimicrob Agents Chemother 1991;35:2611–6.

[60] Saginur R, Stdenis M, Ferris W, Aaron SD, Chan F, Lee C, et al. Multiple combination bactericidal testing of staphylococcal biofilms from implant-associated infections. Antimicrob Agents Chemother 2006;50:55–61.

[61] Zimmerli W, Frei R, Widmer AF, Rajacic Z. Microbiological tests to predict treatment outcome in experimental device-related infections due to *Staphylococcus aureus*. J Antimicrob Chemother 1994;33:959–67.

[62] Schwank S, Rajacic Z, Zimmerli W, Blaser J. Impact of bacterial biofilm formation on in vitro and in vivo activities of antibiotics. Antimicrob Agents Chemother 1998;42:895–8.

[63] Tang HJ, Chen CC, Cheng KC, Wu KY, Lin YC, Zhang CC, et al. In vitro efficacies and resistance profiles of rifampin-based combination regimens for biofilm-embedded methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 2013;57:5717–20.

[64] Tang HJ, Chen CC, Cheng KC, Toh HS, Su BA, Chiang SR, et al. In vitro efficacy of fosfomycin-containing regimens against methicillin-resistant *Staphylococcus aureus* in biofilms. J Antimicrob Chemother 2012;67:944–50.

[65] Stewart PS, Davison WM, Steenbergen JN. Daptomycin rapidly penetrates a *Staphylococcus epidermidis* biofilm. Antimicrob Agents Chemother 2009;53:3505–7.

[66] Murillo O, Garrigos C, Pachon ME, Euba G, Verdaguer R, Cabellos C, et al. Efficacy of high doses of daptomycin versus alternative therapies against experimental foreign-body infection by methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 2009;53:4252–7.

[67] Barbier F, Ruppe E, Hernandez D, Lebeaux D, Francois P, Felix B, et al. Methicillin-resistant coagulase-negative staphylococci in the community: high homology of SCC*mec* IVa between *Staphylococcus epidermidis* and major clones of methicillin-resistant *Staphylococcus aureus*. J Infect Dis 2010;202:270–81.

[68] Cremniter J, Slassi A, Quincampoix JC, Sivadon-Tardy V, Bauer T, Porcher R, et al. Decreased susceptibility to teicoplanin and vancomycin in coagulase-negative staphylococci isolated from orthopedic-device-associated infections. J Clin Microbiol 2010;48:1428–31.

[69] Liakopoulos A, Neocleous C, Klapsa D, Kanellopoulou M, Spiliopoulou I, Mathiopoulos KD, et al. A T2504A mutation in the 23S rRNA gene responsible for high-level resistance to linezolid of *Staphylococcus epidermidis*. J Antimicrob Chemother 2009;64:206–7.

[70] Lodise TP, Patel N, Lomaestro BM, Rodvold KA, Drusano GL. Relationship between initial vancomycin concentration–time profile and nephrotoxicity among hospitalized patients. Clin Infect Dis 2009;49:507–14.

[71] Gould IM, Cauda R, Esposito S, Gudiol F, Mazzei T, Garau J. Management of serious meticillin-resistant *Staphylococcus aureus* infections: what are the limits? Int J Antimicrob Agents 2011;37:202–9.

[72] ONERBA. *Annual report 2009–2010*. Vivactis Plus; 2011.

[73] Nordmann P, Naas T, Poirel L. Global spread of carbapenemase-producing Enterobacteriaceae. Emerg Infect Dis 2011;17:1791–8.

[74] Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention,

Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J 2009;30:2369–413.

[75] Gould FK, Denning DW, Elliott TS, Foweraker J, Perry JD, Prendergast BD, et al. Guidelines for the diagnosis and antibiotic treatment of endocarditis in adults: a report of the Working Party of the British Society for Antimicrobial Chemotherapy. J Antimicrob Chemother 2012;67:269–89.

[76] Baddour LM, Epstein AE, Erickson CC, Knight BP, Levison ME, Lockhart PB, et al. Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. Circulation 2010;121:458–77.

[77] Ryan SV, Calligaro KD, Scharff J, Dougherty MJ. Management of infected prosthetic dialysis arteriovenous grafts. J Vasc Surg 2004;39:73–8.

[78] Tokars JI, Miller ER, Stein G. New national surveillance system for hemodialysis-associated infections: initial results. Am J Infect Control 2002;30:288–95.

[79] Schutte WP, Helmer SD, Salazar L, Smith JL. Surgical treatment of infected prosthetic dialysis arteriovenous grafts: total versus partial graft excision. Am J Surg 2007;193:385–8; discussion 388.

[80] Korzeniowski O, Sande MA. Combination antimicrobial therapy for *Staphylococcus aureus* endocarditis in patients addicted to parenteral drugs and in nonaddicts: a prospective study. Ann Intern Med 1982;97:496–503.

[81] Chang FY, MacDonald BB, Peacock JE Jr, Musher DM, Triplett P, Mylotte JM, et al. A prospective multicenter study of *Staphylococcus aureus* bacteremia: incidence of endocarditis, risk factors for mortality, and clinical impact of methicillin resistance. Medicine (Baltimore) 2003;82:322–32.

[82] Chu VH, Miro JM, Hoen B, Cabell CH, Pappas PA, Jones P, et al.; International Collaboration on Endocarditis–Prospective Cohort Study Group. Coagulase-negative staphylococcal prosthetic valve endocarditis—a contemporary update based on the International Collaboration on Endocarditis: prospective cohort study. Heart 2009;95:570–6.

[83] Afssaps. *Recommandations pour l'antibiothérapie par voie générale en pratique courante dans les infections respiratoires hautes de l'adulte et de l'enfant*. 2005.

[84] Pichichero ME. A review of evidence supporting the American Academy of Pediatrics recommendation for prescribing cephalosporin antibiotics for penicillin-allergic patients. Pediatrics 2005;115:1048–57.

[85] Robinson JL, Hameed T, Carr S. Practical aspects of choosing an antibiotic for patients with a reported allergy to an antibiotic. Clin Infect Dis 2002;35:26–31.

[86] Fowler VG Jr, Kong LK, Corey GR, Gottlieb GS, McClelland RS, Sexton DJ, et al. Recurrent *Staphylococcus aureus* bacteremia: pulsed-field gel electrophoresis findings in 29 patients. J Infect Dis 1999;179:1157–61.

[87] Levine DP, Fromm BS, Reddy BR. Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant *Staphylococcus aureus* endocarditis. Ann Intern Med 1991;115:674–80.

[88] Stryjewski ME, Szczech LA, Benjamin DK Jr, Inrig JK, Kanafani ZA, Engemann JJ, et al. Use of vancomycin or first-generation cephalosporins for the treatment of hemodialysis-dependent patients with methicillin-susceptible *Staphylococcus aureus* bacteremia. Clin Infect Dis 2007;44:190–6.

[89] Nannini EC, Singh KV, Murray BE. Relapse of type A β-lactamase-producing *Staphylococcus aureus* native valve endocarditis during cefazolin therapy: revisiting the issue. Clin Infect Dis 2003;37:1194–8.

[90] Steckelberg JM, Rouse MS, Tallan BM, Osmon DR, Henry NK, Wilson WR. Relative efficacies of broad-spectrum cephalosporins for treatment of methicillin-susceptible *Staphylococcus aureus* experimental infective endocarditis. Antimicrob Agents Chemother 1993;37:554–8.

[91] Fridkin SK, Hageman J, McDougal LK, Mohammed J, Jarvis WR, Perl TM, et al. Epidemiological and microbiological characterization of infections caused by *Staphylococcus aureus* with reduced susceptibility to vancomycin, United States, 1997–2001. Clin Infect Dis 2003;36:429–39.

[92] Moore MR, Perdreau-Remington F, Chambers HF. Vancomycin treatment failure associated with heterogeneous vancomycin-intermediate *Staphylococcus aureus* in a patient with endocarditis and in the rabbit model of endocarditis. Antimicrob Agents Chemother 2003;47:1262–6.

[93] Afssaps. *Mise au point sur le bon usage des aminosides administrés par voie injectable: gentamicine, tobramycine, netilmicine, amikacine*. 2011.

[94] Cosgrove SE, Vigliani GA, Fowler VG Jr, Abrutyn E, Corey GR, Levine DP, et al. Initial low-dose gentamicin for *Staphylococcus aureus* bacteremia and endocarditis is nephrotoxic. Clin Infect Dis 2009;48:713–21.

[95] John MD, Hibberd PL, Karchmer AW, Sleeper LA, Calderwood SB. *Staphylococcus aureus* prosthetic valve endocarditis: optimal management and risk factors for death. Clin Infect Dis 1998;26:1302–9.

[96] Whitener C, Caputo GM, Weitekamp MR, Karchmer AW. Endocarditis due to coagulase-negative staphylococci. Microbiologic, epidemiologic, and clinical considerations. Infect Dis Clin North Am 1993;7:81–96.

[97] Senneville E, Joulie D, Legout L, Valette M, Dezeque H, Beltrand E, et al. Outcome and predictors of treatment failure in total hip/knee prosthetic joint infections due to *Staphylococcus aureus*. Clin Infect Dis 2011;53:334–40.

[98] Riedel DJ, Weekes E, Forrest GN. Addition of rifampin to standard therapy for treatment of native valve infective endocarditis caused by *Staphylococcus aureus*. Antimicrob Agents Chemother 2008;52:2463–7.

[99] Mascio CT, Alder JD, Silverman JA. Bactericidal action of daptomycin against stationary-phase and nondividing *Staphylococcus aureus* cells. Antimicrob Agents Chemother 2007;51:4255–60.

[100] Fowler VG Jr, Boucher HW, Corey GR, Abrutyn E, Karchmer AW, Rupp ME, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. N Engl J Med 2006;355:653–65.

[101] Marty FM, Yeh WW, Wennersten CB, Venkataraman L, Albano E, Alyea EP, et al. Emergence of a clinical daptomycin-resistant *Staphylococcus aureus* isolate during treatment of methicillin-resistant *Staphylococcus aureus* bacteremia and osteomyelitis. J Clin Microbiol 2006;44:595–7.

[102] Benvenuto M, Benziger DP, Yankelev S, Vigliani G. Pharmacokinetics and tolerability of daptomycin at doses up to 12 milligrams per kilogram of

body weight once daily in healthy volunteers. Antimicrob Agents Chemother 2006;50:3245–9.

[103] Figueroa DA, Mangini E, Amodio-Groton M, Vardianos B, Melchert A, Fana C, et al. Safety of high-dose intravenous daptomycin treatment: three-year cumulative experience in a clinical program. Clin Infect Dis 2009;49:177–80.

[104] Patel JB, Jevitt LA, Hageman J, McDonald LC, Tenover FC. An association between reduced susceptibility to daptomycin and reduced susceptibility to vancomycin in *Staphylococcus aureus*. Clin Infect Dis 2006;42:1652–3.

[105] Moise PA, Smyth DS, El-Fawal N, Robinson DA, Holden PN, Forrest A, et al. Microbiological effects of prior vancomycin use in patients with methicillin-resistant *Staphylococcus aureus* bacteraemia. J Antimicrob Chemother 2008;61:85–90.

[106] Durante-Mangoni E, Casillo R, Bernardo M, Caianiello C, Mattucci I, Pinto D, et al. High-dose daptomycin for cardiac implantable electronic device-related infective endocarditis. Clin Infect Dis 2012;54:347–54.

[107] Furustrand Tafin U, Majic I, Zalila Belkhodja C, Betrisey B, Corvec S, Zimmerli W, et al. Gentamicin improves the activities of daptomycin and vancomycin against *Enterococcus faecalis* in vitro and in an experimental foreign-body infection model. Antimicrob Agents Chemother 2011;55:4821–7.

[108] Saleh-Mghir A, Muller-Serieys C, Dinh A, Massias L, Cremieux AC. Adjunctive rifampin is crucial to optimizing daptomycin efficacy against rabbit prosthetic joint infection due to methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 2011;55:4589–93.

[109] Baddour LM. Infective endocarditis caused by β-hemolytic streptococci. The Infectious Diseases Society of America's Emerging Infections Network. Clin Infect Dis 1998;26:66–71.

[110] Lefort A, Lortholary O, Casassus P, Selton-Suty C, Guillevin L, Mainardi JL, et al. Comparison between adult endocarditis due to β-hemolytic streptococci (serogroups A, B, C, and G) and *Streptococcus milleri*: a multicenter study in France. Arch Intern Med 2002;162:2450–6.

[111] Sambola A, Miro JM, Tornos MP, Almirante B, Moreno-Torrico A, Gurgui M, et al. *Streptococcus agalactiae* infective endocarditis: analysis of 30 cases and review of the literature, 1962–1998. Clin Infect Dis 2002;34:1576–84.

[112] Buchholtz K, Larsen CT, Hassager C, Bruun NE. Severity of gentamicin's nephrotoxic effect on patients with infective endocarditis: a prospective observational cohort study of 373 patients. Clin Infect Dis 2009;48:65–71.

[113] Falagas ME, Matthaiou DK, Bliziotis IA. The role of aminoglycosides in combination with a β-lactam for the treatment of bacterial endocarditis: a meta-analysis of comparative trials. J Antimicrob Chemother 2006;57:639–47.

[114] Francioli P, Etienne J, Hoigne R, Thys JP, Gerber A. Treatment of streptococcal endocarditis with a single daily dose of ceftriaxone sodium for 4 weeks. Efficacy and outpatient treatment feasibility. JAMA 1992;267:264–7.

[115] Darras-Joly C, Bedos JP, Sauve C, Moine P, Vallee E, Carbon C, et al. Synergy between amoxicillin and gentamicin in combination against a highly

penicillin-resistant and -tolerant strain of *Streptococcus pneumoniae* in a mouse pneumonia model. Antimicrob Agents Chemother 1996;40:2147–51.

[116] Swingle HM, Bucciarelli RL, Ayoub EM. Synergy between penicillins and low concentrations of gentamicin in the killing of group B streptococci. J Infect Dis 1985;152:515–20.

[117] Dressel DC, Tornatore-Reuscher MA, Boschman CR, Stosor V, Zembower T, Postelnick MJ, et al. Synergistic effect of gentamicin plus ampicillin on enterococci with differing sensitivity to gentamicin: a phenotypic assessment of NCCLS guidelines. Diagn Microbiol Infect Dis 1999;35:219–25.

[118] Winstanley TG, Hastings JG. Synergy between penicillin and gentamicin against enterococci. J Antimicrob Chemother 1990;25:551–60.

[119] Olaison L, Schadewitz K; Swedish Society of Infectious Diseases Quality Assurance Study Group for Endocarditis. Enterococcal endocarditis in Sweden, 1995–1999: can shorter therapy with aminoglycosides be used? Clin Infect Dis 2002;34:159–66.

[120] Gavaldà J, Torres C, Tenorio C, López P, Zaragoza M, Capdevila JA, et al. Efficacy of ampicillin plus ceftriaxone in treatment of experimental endocarditis due to *Enterococcus faecalis* strains highly resistant to aminoglycosides. Antimicrob Agents Chemother 1999;43:639–46.

[121] Gavaldá J, Onrubia PL, Gómez MT, Gomis X, Ramírez JL, Len O, et al. Efficacy of ampicillin combined with ceftriaxone and gentamicin in the treatment of experimental endocarditis due to *Enterococcus faecalis* with no high-level resistance to aminoglycosides. J Antimicrob Chemother 2003;52:514–7.

[122] Gavaldà J, Len O, Miró JM, Muñoz P, Montejo M, Alarcón A, et al. Brief communication: treatment of *Enterococcus faecalis* endocarditis with ampicillin plus ceftriaxone. Ann Intern Med 2007;146:574–9.

[123] Fernández-Hidalgo N, Almirante B, Gavaldà J, Gurgui M, Peña C, de Alarcón A, et al. Ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin for treating *Enterococcus faecalis* infective endocarditis. Clin Infect Dis 2013;56:1261–8.

[124] Arias CA, Mendes RE, Stilwell MG, Jones RN, Murray BE. Unmet needs and prospects for oritavancin in the management of vancomycin-resistant enterococcal infections. Clin Infect Dis 2012;54(Suppl 3):S233–8.

[125] Wareham DW, Abbas H, Karcher AM, Das SS. Treatment of prosthetic valve infective endocarditis due to multi-resistant Gram-positive bacteria with linezolid. J Infect 2006;52:300–4.

[126] Archuleta S, Murphy B, Keller MJ. Successful treatment of vancomycin-resistant *Enterococcus faecium* endocarditis with linezolid in a renal transplant recipient with human immunodeficiency virus infection. Transpl Infect Dis 2004;6:117–9.

[127] Berdal JE, Eskesen A. Short-term success, but long-term treatment failure with linezolid for enterococcal endocarditis. Scand J Infect Dis 2008;40:765–6.

[128] Tsigrelis C, Singh KV, Coutinho TD, Murray BE, Baddour LM. Vancomycin-resistant *Enterococcus faecalis* endocarditis: linezolid failure and strain characterization of virulence factors. J Clin Microbiol 2007;45:631–5.

[129] Vouillamoz J, Moreillon P, Giddey M, Entenza JM. Efficacy of daptomycin in the treatment of experimental endocarditis due to susceptible

and multidrug-resistant enterococci. J Antimicrob Chemother 2006;58:1208–14.

[130] Cunha BA, Mickail N, Eisenstein L. *E. faecalis* vancomycin-sensitive enterococcal bacteremia unresponsive to a vancomycin tolerant strain successfully treated with high-dose daptomycin. Heart Lung 2007;36:456–61.

[131] Schwartz BS, Ngo PD, Guglielmo BJ. Daptomycin treatment failure for vancomycin-resistant *Enterococcus faecium* infective endocarditis: impact of protein binding? Ann Pharmacother 2008;42:289–90.

[132] Hidron AI, Schuetz AN, Nolte FS, Gould CV, Osborn MK. Daptomycin resistance in *Enterococcus faecalis* prosthetic valve endocarditis. J Antimicrob Chemother 2008;61:1394–6.

[133] Rand KH, Houck H. Daptomycin synergy with rifampicin and ampicillin against vancomycin-resistant enterococci. J Antimicrob Chemother 2004;53:530–2.

[134] Rand KH, Houck HJ, Silverman JA. Daptomycin-reversible rifampicin resistance in vancomycin-resistant *Enterococcus faecium*. J Antimicrob Chemother 2007;59:1017–20.

[135] Gallagher JC, Perez ME, Marino EA, LoCastro LG, Abrardo LA, MacDougall C. Daptomycin therapy for vancomycin-resistant enterococcal bacteremia: a retrospective case series of 30 patients. Pharmacotherapy 2009;29:792–9.

[136] Balli EP, Venetis CA, Miyakis S. Systematic review and meta-analysis of linezolid versus daptomycin for treatment of vancomycin-resistant enterococcal bacteremia. Antimicrob Agents Chemother 2014;58:734–9.

[137] Tamma PD, Cosgrove SE, Maragakis LL. Combination therapy for treatment of infections with Gram-negative bacteria. Clin Microbiol Rev 2012;25:450–70.

[138] Bliziotis IA, Michalopoulos A, Kasiakou SK, Samonis G, Christodoulou C, Chrysanthopoulou S, et al. Ciprofloxacin vs an aminoglycoside in combination with a β-lactam for the treatment of febrile neutropenia: a meta-analysis of randomized controlled trials. Mayo Clin Proc 2005;80:1146–56.

[139] Bliziotis IA, Samonis G, Vardakas KZ, Chrysanthopoulou S, Falagas ME. Effect of aminoglycoside and β-lactam combination therapy versus β-lactam monotherapy on the emergence of antimicrobial resistance: a meta-analysis of randomized, controlled trials. Clin Infect Dis 2005;41:149–58.

[140] Al-Hasan MN, Wilson JW, Lahr BD, Thomsen KM, Eckel-Passow JE, Vetter EA, et al. β-Lactam and fluoroquinolone combination antibiotic therapy for bacteremia caused by Gram-negative bacilli. Antimicrob Agents Chemother 2009;53:1386–94.

[141] Marcus R, Paul M, Elphick H, Leibovici L. Clinical implications of β-lactam–aminoglycoside synergism: systematic review of randomised trials. Int J Antimicrob Agents 2011;37:491–503.

[142] Paul M, Silbiger I, Grozinsky S, Soares-Weiser K, Leibovici L. β Lactam antibiotic monotherapy versus β lactam–aminoglycoside antibiotic combination therapy for sepsis. Cochrane Database Syst Rev 2006;(1):CD003344.

[143] Korvick JA, Bryan CS, Farber B, Beam TR Jr, Schenfeld L, Muder RR, et al. Prospective observational study of *Klebsiella* bacteremia in 230 patients:

outcome for antibiotic combinations versus monotherapy. Antimicrob Agents Chemother 1992;36:2639–44.

[144] Chow JW, Fine MJ, Shlaes DM, Quinn JP, Hooper DC, Johnson MP, et al. *Enterobacter* bacteremia: clinical features and emergence of antibiotic resistance during therapy. Ann Intern Med 1991;115:585–90.

[145] Bodey GP, Jadeja L, Elting L. *Pseudomonas* bacteremia. Retrospective analysis of 410 episodes. Arch Intern Med 1985;145:1621–9.

[146] Hilf M, Yu VL, Sharp J, Zuravleff JJ, Korvick JA, Muder RR. Antibiotic therapy for *Pseudomonas aeruginosa* bacteremia: outcome correlations in a prospective study of 200 patients. Am J Med 1989;87:540–6.

[147] Vidal F, Mensa J, Almela M, Martinez JA, Marco F, Casals C, et al. Epidemiology and outcome of *Pseudomonas aeruginosa* bacteremia, with special emphasis on the influence of antibiotic treatment. Analysis of 189 episodes. Arch Intern Med 1996;156:2121–6.

[148] Siegman-Igra Y, Ravona R, Primerman H, Giladi M. *Pseudomonas aeruginosa* bacteremia: an analysis of 123 episodes, with particular emphasis on the effect of antibiotic therapy. Int J Infect Dis 1998;2:211–5.

[149] Nagy E, Urbaán E, Nord CE; ESCMID Study Group on Antimicrobial Resistance in Anaerobic Bacteria. Antimicrobial susceptibility of *Bacteroides fragilis* group isolates in Europe: 20 years of experience. Clin Microbiol Infect 2011;17:371–9.

[150] Sohail MR, Gray AL, Baddour LM, Tleyjeh IM, Virk A. Infective endocarditis due to *Propionibacterium* species. Clin Microbiol Infect 2009;15:387–94.

[151] Segreti J, Nelson JA, Trenholme GM. Prolonged suppressive antibiotic therapy for infected orthopedic prostheses. Clin Infect Dis 1998;27:711–3.

[152] Moulakakis KG, Mylonas SN, Antonopoulos CN, Kakisis JD, Sfyroeras GS, Mantas G, et al. Comparison of treatment strategies for thoracic endograft infection. J Vasc Surg 2014;60:1061–71.

[153] Uppuluri P, Srinivasan A, Ramasubramanian A, Lopez-Ribot JL. Effects of fluconazole, amphotericin B, and caspofungin on *Candida albicans* biofilms under conditions of flow and on biofilm dispersion. Antimicrob Agents Chemother 2011;55:3591–3.

[154] Cornely OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, et al.; ESCMID Fungal Infection Study Group. ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect 2012;18(Suppl 7):19–37.

Table 1

Levels of evidence and grades of recommendations used

Level of evidence provided by the literature	Grade of recommendations
Level I	**A**
High-quality randomised controlled trials	Established scientific evidence
Meta-analysis of randomised controlled trials	
Decision analysis based on well conducted studies	
Level II	**B**
Low-quality randomised controlled trials	Scientific presumption
Non-randomised, well conducted comparative studies	
Cohort studies	
Level III	**C**
Case–control studies	Low level of evidence
Level IV	
Comparative studies with significant biases	
Retrospective studies	
Case series	

Table 2

Empirical antibiotic therapy for prosthetic vascular graft infections (PVGIs) depending on the clinical situation (C-III)

Clinical situation	In the absence of allergy to β-lactams	In the case of allergy to penicillin
PVGI with sepsis without signs of severity or known colonisation, no history of MDR bacterial infection	Piperacillin/tazobactam + vancomycin or daptomycin [a] ± gentamicin	Cefotaxime or ceftriaxone or cefepime or aztreonam + metronidazole + vancomycin or daptomycin [a] ± gentamicin
PVGI with sepsis, signs of severe sepsis and/or known colonisation or previous infection with ESBL-GNB [b]	Imipenem or meropenem or doripenem + vancomycin or daptomycin [a] ± gentamicin	Fosfomycin + metronidazole + vancomycin or daptomycin [a] ± gentamicin

MDR, multidrug-resistant; ESBL-GNB, extended-spectrum β-lactamase-producing Gram-negative bacillus.

[a] No approval for this indication.

[b] Resistant to third- or fourth-generation cephalosporins on antibiotic susceptibility testing.

Table 3

Dosage, route and rate of administration of anti-infectives in prosthetic vascular graft infections

Compound	Dosage	Route and rate of administration
Amikacin	15–30 mg/kg/day	One i.v. infusion over 30 min
Amoxicillin	100–200 mg/kg/day	Six i.v. infusions over 30 min or i.v. via infusion pump
Amoxicillin/clavulanic acid	100–200 mg/kg/day of amoxicillin	Six i.v. infusions over 30 min (2 g vials)
Caspofungin	70 mg the first day and then 50 mg/day (weight <80 kg) or 70 mg/day (weight ≥80 kg)	One i.v. infusion over 1 h
Cefazolin	60–80 mg/kg/day	Six i.v. infusions over 30 min or i.v. via infusion pump [a]
Cefotaxime	150 mg/kg/day	Six i.v. infusions over 30 min or i.v. via infusion pump [a]
Ceftazidime	100 mg/kg/day	Four i.v. infusions over 30 min or i.v. via infusion pump [a]
Ceftriaxone	50 mg/kg/day	One to two i.v. infusions over 30 min
Ciprofloxacin	1500–2000 mg/day (orally) or 800–1200 mg/day (i.v.)	Two to three oral doses [b] or two to three i.v. infusions over 30 min [b]

Cloxacillin or oxacillin	200 mg/kg/day	Six i.v. infusions over 30 min or i.v. via infusion pump on three syringes over 8 h [a]
Daptomycin	8–10 mg/kg/day	One i.v. infusion over 2–30 min
Doripenem	3 g/day	Three i.v. infusions over 4 h or i.v. via infusion pump (500 mg in 50 mL to 12 mL/h)
Fluconazole	800 mg on the first day and 400–800 mg/day	One oral dose or one i.v. infusion over 2 h [c]
Fosfomycin	150–200 mg/kg/day	Three to four i.v. infusions over 3–4 h
Gentamicin	3–8 mg/kg/day	One i.v. infusion over 30 min
Imipenem	3 g/day	Three i.v. injections over 30 min
Levofloxacin	500–1000 mg/day	One oral dose or one i.v. infusion over 30 min [b]
Meropenem	3–6 g/day	Three i.v. infusions over 30 min
Metronidazole	1500 mg/day	Three oral doses or three i.v. infusions over 30 min [c]
Micafungin	100 mg/day	One i.v. infusion over 1 h

Ofloxacin	400–600 mg/day	Two oral doses or two i.v. infusions over 30 min [b]
Piperacillin/tazobactam	150–200 mg/kg/day of piperacillin	Three infusions over 4 h
Rifampicin	10–20 mg/kg/day	Two oral doses (fasting) or two i.v. infusions over 30 min [c]
Teicoplanin [d]	8–12 mg/kg/12 h for 3 days and then 8–12 mg/kg/day	Slow i.v., i.m. or subcutaneous
Ticarcillin	250 mg/kg/day	Three i.v. infusions over 30 min or i.v. via infusion pump [a]
Vancomycin [d]	40–60 mg/kg/day	i.v. via infusion pump [a]

i.v., intravenous; i.m., intramuscular.

[a] Begin with a loading dose equal to one-quarter of the total daily dose, to be administered over 30 min via i.v. infusion, except for vancomycin for which the duration of administration of the loading dose is longer: 15 mg/kg loading dose to be infused over 1 h (1 g) or 1 h 30 min (1.5 g).

[b] The highest dosages of fluoroquinolones are to be considered when combined with rifampicin owing to the enzyme induction properties of the latter.

[c] Preference should be given to oral administration.

[d] Glycopeptide dosage: this will be done after 72 h for vancomycin and after the sixth infusion for teicoplanin (just before the infusion) and then once a week for the entire duration of the treatment.

Table 4

Antibiotic therapy for prosthetic vascular graft infections caused by meticillin-sensitive *Staphylococcus* sp.

	In the absence of allergy to β-lactams	In the case of allergy to penicillin	In the case of contraindication to β-lactams
Pre-operative treatment	Cloxacillin or oxacillin (B-III) + gentamicin [a] 3 days (B-III)	Cefazolin or vancomycin or daptomycin (B-III) + gentamicin [a] 3 days (B-III)	Vancomycin or daptomycin (B-III) + gentamicin [a] 3 days (B-III)

Post-operative treatment	Optimal	Cloxacillin or oxacillin (B-III) + gentamicin [a] 3 days (C-III) and then addition of rifampicin [b] in place of gentamicin (B-III) relay with oral rifampicin + fluoroquinolone at Day 15 post-operatively [c] (C-III) Duration of treatment, 6 weeks post-operatively (C-III)	Cefazolin or vancomycin or daptomycin (B-III) + gentamicin [a] 3 days (C-III) and then addition of rifampicin [b] in place of gentamicin (B-III) relay with oral rifampicin + fluoroquinolone at Day 15 post-operatively [c] (C-III) Duration of treatment, 6 weeks post-operatively (C-III)	Vancomycin or daptomycin (B-III) + gentamicin [a] 3 days (C-III) and then addition of rifampicin [b] in place of gentamicin (B-III) relay with oral rifampicin + fluoroquinolone at Day 15 post-operatively [c] (C-III) Duration of treatment, 6 weeks post-operatively (C-III)

	Suboptimal	Cloxacillin or oxacillin (B-III) + gentamicin 3 days (C-III) and then addition of rifampicin [b] in place of gentamicin (B-III) for 6 weeks post-operatively (C-III) and then suppressive treatment [d] (C-III)	Cefazolin or vancomycin or daptomycin (B-III) + gentamicin 3 days (C-III) and then addition of rifampicin [b] in place of gentamicin (B-III) for 6 weeks post-operatively (C-III) and then suppressive treatment [d] (C-III)	Vancomycin or daptomycin + gentamicin 3 days and then addition of rifampicin [b] in place of gentamicin (B-III) for 6 weeks post-operatively (C-III) and then suppressive treatment [d] (C-III)

[a] Dosage of 3–8 mg/kg/day in a single daily dose. In patients with severe infection with the risk of increased volume of distribution (severe sepsis or even septic shock, mechanical ventilation, presence of oedema, etc.), preference should be given to higher doses (5–8 mg/kg/day). The rate of administration and dosages are to be adapted to residual concentrations.

[b] After ascertaining that blood cultures are negative.

[c] Only in the case of good clinical evolution, if susceptible to fluoroquinolones and in the absence of post-operative bacteraemia. No other oral relay is recommended (C-III).

[d] To be determined based on susceptibility testing and following a multidisciplinary opinion.

Table 5

Antibiotic therapy for prosthetic vascular graft infections caused by meticillin-resistant *Staphylococcus* sp.

		Vancomycin MIC < 1.5 mg/L	Vancomycin MIC ≥ 1.5 mg/L
Pre-operative treatment		Vancomycin [a] (B-III) or daptomycin (C-III) + gentamicin 3 days (B-III)	Daptomycin (B-III) + gentamicin 3 days (C-III)
Post-operative treatment	Optimal	Vancomycin [a] (B-III) or daptomycin (C-III) + gentamicin 3 days (C-III) and then addition of rifampicin [b] in place of gentamicin (B-III) relay with oral rifampicin + fluoroquinolone at Day 15 post-operatively [c] (C-III) Duration of treatment, 6 weeks post-operatively (C-III)	Daptomycin (B-III) + gentamicin 3 days (C-III) and then addition of rifampicin [b] in place of gentamicin (B-III) relay with oral rifampicin + fluoroquinolone at Day 15 post-operatively [c] (C-III) Duration of treatment, 6 weeks post-operatively (C-III)

	Suboptimal	Vancomycin (B-III) or daptomycin (C-III) + gentamicin 3 days (C-III) and then addition of rifampicin in place of gentamicin (B-III) for 6 weeks post-operatively (C-III) and then suppressive treatment [d] (C-III)	Daptomycin (B-III) + gentamicin 3 days (C-III) and then addition of rifampicin in place of gentamicin (B-III) for 6 weeks post-operatively (C-III) and then suppressive treatment [d] (C-III)

MIC, minimum inhibitory concentration.

[a] Equilibrium concentrations of vancomycin, 20–30 mg/L. Teicoplanin can be considered, as a relay, after ascertaining the susceptibility of the bacterial strain and if the clinical condition has stabilised (C-III).

[b] After ascertaining that blood cultures are negative.

[c] Only in the case of good clinical evolution, if susceptible to fluoroquinolones and in the absence of post-operative bacteraemia.

[d] To be determined based on susceptibility testing and after multidisciplinary opinion.

Table 6

Antibiotic treatment of prosthetic vascular graft infections caused by Enterobacteriaceae

		In the absence of allergy to β-lactams	In the case of allergy to penicillin
Pre-operative treatment		Ceftriaxone or cefotaxime [a] (B-III) + gentamicin 3 days [b] (C-III)	Aztreonam (C-III) + gentamicin 3 days (C-III)
Post-operative treatment	Optimal	Ceftriaxone or cefotaxime [a] (B-III) and then relay with fluoroquinolones [c] (C-III) Duration of treatment, 6 weeks post-operatively (C-III)	Aztreonam (C-III) and then relay with fluoroquinolones [c] (C-III) Duration of treatment, 6 weeks post-operatively (C-III)
	Suboptimal	Ceftriaxone or cefotaxime [a] (B-III) and then relay with fluoroquinolones [c] (C-III) for 6 weeks post-operatively (C-III) and then suppressive treatment [d] (C-III)	Aztreonam (C-III) and then relay with fluoroquinolones [c] for 6 weeks post-operatively (C-III) and then suppressive treatment [d]

[a] Use of another narrower-spectrum β-lactam is possible based on the susceptibility testing data and following a specialist opinion.

[b] The dose of gentamicin is between 5 mg/kg/day and 8 mg/kg/day. Higher doses are preferable in the case of septic shock (B-III).

[c] The relay is done 15 days post-operatively in the case of good evolution. It can also be done earlier in the case of good evolution when aztreonam is used. If bacteria are resistant to fluoroquinolones and nalidixic acid, continue with β-lactam antibiotics for 6 weeks post-operatively (B-III).

[d] To be determined based on susceptibility testing and following a multidisciplinary opinion.

a.