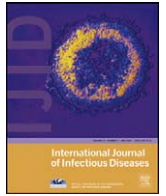




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Consensus document on controversial issues in the diagnosis and treatment of bloodstream infections and endocarditis

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SUMMARY

Background: The treatment of severe bloodstream infections (sepsis, endocarditis, and infections of vascular prostheses) caused by Gram-positive microorganisms is made even more difficult by the emergence of resistant strains. The introduction of new antibiotics with activity against these strains has created new opportunities, but many controversial issues remain.

Controversial issues: The aim of this GISIG (Gruppo Italiano di Studio sulle Infezioni Gravi) working group – a panel of multidisciplinary experts – was to define recommendations for some controversial issues using an evidence-based and analytical approach. The controversial issues concerned the duration of therapy and role of aminoglycosides and teicoplanin in the treatment of Gram-positive bacterial endocarditis, the optimal use of the new antibiotics in the treatment of bloodstream infections caused by resistant Gram-positive strains, and the use of microbiological techniques (i.e., bactericidal serum testing and synergy testing) and of pharmacokinetic data (e.g., monitoring of plasma levels of antibiotics) in the treatment of difficult-to-treat Gram-positive bloodstream infections.

Methods: A systematic literature search of randomized controlled trials and/or non-randomized studies was performed mainly using the MEDLINE database. A matrix was created to extract evidence from original studies using the CONSORT method to evaluate randomized clinical trials and the Newcastle–Ottawa Quality Assessment Scale for non-randomized studies. The GRADE method for grading the quality of evidence and strength of recommendation was applied.

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1. Introduction

Bloodstream infections are among the most serious and severe bacterial infections, with high mortality rates. The recent increase in antibiotic resistance among Gram-positive bacteria has changed the clinical scenario, making the treatment of these infections more difficult.

Infective endocarditis (IE), which is mainly caused by Gram-positive bacteria, has become more difficult to treat after the emergence of antibiotic resistance in its main etiological agents (streptococci, staphylococci and enterococci). Infection by methicillin-resistant *Staphylococcus aureus* (MRSA) has spread in an epidemic way, especially in some areas of the world, such as Spain, where more than 25% of hospital-isolated strains are reported to be resistant to methicillin.¹ Moreover, the problem of methicillin resistance in *S. aureus* is nowadays no longer restricted to hospital-acquired infections following the emergence of community-acquired MRSA in the USA.² Also alarming is the development of intermediate- and high-level resistance to vancomycin in strains of *S. aureus*.^{3,4} Vancomycin resistance is common in many nosocomial settings, and now also viridans streptococci, once a leading cause of subacute IE, are increasingly acquiring resistance to penicillin and other β -lactam antibiotics.^{5,6}

The treatment of IE has traditionally been based on consensus acquired during the years in which the majority of IE was due to penicillin-sensitive streptococci, and few randomized clinical studies have been conducted in the past. The appearance of *S. aureus* tricuspid valve endocarditis in intravenous drug users, again a relatively easy-to-treat condition in the absence of resistance to the very active anti-staphylococcal penicillins, has prompted a series of trials aimed at defining optimal treatment schedules. The appearance of Gram-positive resistant and multi-resistant microorganisms, together with the increasing number of patients with comorbidities, and of infection of prosthetic valves, has created new problems and the need for more evidence. Many questions remain unresolved: some, like the role of new antibiotics in the treatment of resistant infections, are new; others, like the optimal duration of treatment, the exact role of combination therapy with aminoglycosides and cell-wall active antibiotics, or the efficacy of glycopeptides in the treatment of IE are old but unresolved, in the absence of evidence from the literature. The role of traditional laboratory diagnostic techniques, like the determination of serum bactericidal activity and synergy tests, as well as the role of newer techniques like therapeutic drug monitoring of plasma levels of antibiotics widely used in the treatment of Gram-positive bloodstream infections, but with a narrow therapeutic window, or whose optimal dosage in critically ill patients is yet to be defined, are likewise uncertain and not supported by a great body of evidence.

The situation is also alarming in the setting of sepsis, one of the most common causes of death in the developed world⁷ with an estimated annual mortality rate of 30–50 deaths per 100 000 population.⁸ Therefore, the emergence of Gram-positive multi-resistant bacteria potentially causing sepsis is of serious concern to public health. Again, there is an urgent need to acquire sound evidence on the optimal treatment of sepsis in the setting of antibiotic resistance, and to evaluate the role of new drugs.

Finally, infections of vascular prostheses are severe infections involving vascular grafts, whose treatment is made extremely difficult by the need to remove the infected material, generally a life-sustaining implanted medical device, and for which very scarce evidence exist as to the optimal medical or surgical treatment.⁹ While some authors invoke the use of long-term suppressive antibiotic therapy for the treatment of these conditions,¹⁰ the introduction of new antibiotics active on resistant strains offers new treatment opportunities; however very few data are available on this issue.

2. Objective

The aim of this study was to review the literature on the optimal treatment of severe bloodstream infections (sepsis, endocarditis, and infections of vascular prostheses) caused by resistant Gram-positive strains, with a special focus on studies on new antibiotics against Gram-positive resistant microorganisms and new presentation of Gram-positive infections.

3. Materials and methods

3.1. Controversial issues

A group of experts in the field of bloodstream infections was identified and enrolled in a faculty. The faculty was in charge of defining controversial issues, developing a search strategy, and reviewing the retrieved literature in order to obtain data on controversial issues and to draw recommendations based on the best available evidence. After discussion with the faculty members, the following controversial issues were defined:

- Role of aminoglycosides and teicoplanin in the treatment of resistant Gram-positive bacterial endocarditis.
- Optimal duration of treatment of resistant Gram-positive bacterial endocarditis.
- Optimal use of the new antibiotics (quinupristin/dalfopristin, daptomycin, linezolid, tigecycline) in the treatment of bloodstream infections caused by resistant Gram-positive strains.
- Use of microbiological techniques (i.e., bactericidal serum testing and synergy testing) and of pharmacokinetic data (e.g., monitoring of plasma levels of antibiotics) in the treatment of difficult-to-treat Gram-positive bloodstream infections.

For each controversial issue, one or more structured new issues, in the form of a query, were created to obtain a series of unambiguous queries on the basis of which to create appropriate strings to optimize high quality literature searches. In other words, the strings were to be optimized to retrieve comparative studies on the topics of interest.

Firstly, the issues were divided in two distinct areas (therapeutic and diagnostic/laboratory monitoring).

For the therapeutic area, the following new queries were created:

1. In the treatment of infective endocarditis caused by Gram-positive microorganisms, is combination therapy with an aminoglycoside plus another antibiotic more effective than monotherapy?
2. In the treatment of infective endocarditis caused by Gram-positive microorganisms, is therapy with an aminoglycoside in a single daily dose more effective than therapy in three divided doses?
3. In the treatment of infective endocarditis caused by Gram-positive microorganisms, is therapy with teicoplanin as effective, and associated with fewer adverse events, than therapy with vancomycin?
4. In the treatment of infective endocarditis caused by Gram-positive microorganisms, what is the optimal duration of treatment?
5. In the treatment of infective endocarditis caused by multi-resistant Gram-positive microorganisms, is therapy with quinupristin/dalfopristin, linezolid, daptomycin, and tigecycline effective?
6. In the treatment of sepsis caused by multi-resistant Gram-positive microorganisms, is therapy with quinupristin/dalfopristin, linezolid, daptomycin, and tigecycline effective?

7. In the treatment of infections of vascular prostheses caused by multi-resistant Gram-positive microorganisms, is therapy with quinupristin/dalfopristin, linezolid, daptomycin, and tigecycline effective?

For the diagnostic/laboratory monitoring area the following new queries were created:

1. In the treatment of infective endocarditis caused by multi-resistant Gram-positive microorganisms, is monitoring of plasma levels of vancomycin, gentamicin, and teicoplanin effective in reducing adverse events and costs, and in increasing treatment efficacy?
2. In the treatment of infective endocarditis caused by multi-resistant Gram-positive microorganisms, is the use of serum bactericidal and synergy testing (along with traditional methods such as minimum inhibitory concentration (MIC) determination) effective in reducing adverse events and costs, and in increasing treatment efficacy?

3.2. Literature search and study selection

A series of inclusion criteria for the studies was then defined for each query: population studied, type of intervention, comparator or confrontation, type of outcome, and definition of the type of studies to be retrieved. In general it was decided to restrict the search to the adult population, to consider primary outcomes (such as cure or mortality), and to limit the search to randomized controlled studies or other comparative studies. Animal studies, as well as studies limited to pharmacokinetic/pharmacodynamic analysis, were excluded. No restrictions on year of publication or language were introduced. In some cases, however, the strategy was modified and made less restrictive because (as in the case of new antibiotics) very few randomized or comparative studies were obtained. As a rule, the use of MeSH terms was preferred; to delimit the search the 'limits' function of PubMed was used. For each query, different research strategies were tried, and the one considered more effective (maximum of high quality studies retrieved with minimum non-pertinent material) was eventually chosen. The research was mainly conducted on the PubMed (MEDLINE) database, and completed with hand searching of references of retrieved studies and of other material obtained from web sites of scientific societies such as the American Heart Association and the Infectious Diseases Society of America. For

each retrieved study a schematic report, based on a pre-defined form, was created.

After this phase, the obtained results were discussed with the group members. As for some issues the number of high quality studies obtained was too scarce, it was agreed to conduct a new literature search aimed at obtaining case reports, and to include cases from personal series of the faculty members. Minimum requirements for cases to be included in the evaluation were completeness and quality of exposition. Retrieved single case reports or case series were summarized on a pre-defined form. Case reports were searched for queries 5 and 7 in the therapeutic area (use of new antibiotics in the treatment of endocarditis and infections of vascular prostheses) using a new, unrestricted research strategy, which included only the MeSH term or generic name of the drug. The case reports to be included in the final collection were chosen after reading titles and abstracts. For query 7 (infections of vascular prostheses), only one case reporting treatment with the new antibiotics was retrieved; it was therefore decided to retrieve case reports describing modalities of treatment of infected vascular prostheses.

3.3. Classification and evaluation of selected evidence

The quality of the studies was then assessed. The methodological quality of randomized controlled trials and of non-randomized studies was assessed with the CONSORT method and Newcastle–Ottawa Quality Assessment Scale, respectively, while for case reports and case series the quality was assessed on the basis of a structured checklist.

Finally, the studies and case series/reports retrieved for each query were analyzed to draw draft recommendations, with the strength of each statement defined according to the GRADE score of the studies retrieved for that issue.¹¹ The results and the draft were then re-discussed with the faculty, and afterwards in an enlarged group that included a panel of experts in the field; as a result, those queries for which there were insufficient data or non-convincing evidence to draw a recommendation were eventually eliminated from the final recommendations. These recommendations were presented and voted for during a national conference in which physicians involved in the treatment of these conditions had convened.

The queries with the inclusion criteria, the search strings, and the flow charts with details of the results of the research for each query are presented in the Appendix. The results of each search,

Table 1
Quality evaluation of evidence according to the GRADE Working Group method

Study	Study design	Study limits	Consistency	Directness	Accuracy	Bias	Association evidence	Dose/response gradient	Confounder bias	Total quality score
Fowler (21)	4	–	–	–1	–1	–	–	–	–	2
Rehm (22)	4	–	–	–1	–1	–	–	–	–	2
Shorr (47)	3	–	–	–	–	–1	–	–	–	2
Stevens (48)	4	–1	–	–	–	–1	–	–	–	2
Wilcox (49)	4	–2	–	–	–1	–1	–	–	–	1
Wilcox (50)	4	–2	–	–	–1	–1	–	–	–	1
Cepeda (51)	4	–	–	–1	–	–	–	–	–	3
Adembri (52)	4	–1	–	–	–	–1	–	–	–	2
Linden (53)	2	–	–	–	–	–	–	–	–	2
Abrams (16)	4	–1	–1	–	–	–1	–	–	–	1
Sexton (19)	4	–1	–	–	–	–1	–	–	–	2
Ribera (15)	4	–1	–	–	–	–1	–	–	–	2
Cosgrove (20)	3	–	–	–	–	–1	–	1	–	3
Gilbert (17)	4	–	–	–	–	–1	–	–	–	3
Huang (18)	3	–	–	–	–	–1	–	–	–	2
Fortún (13)	4	–1	–	–	–	–1	–	–	–	2
Fortún (14)	4	–1	–	–	–	–1	–	–	–	2
Fernández de Gatta (55)	4	–1	–	–1	–	–	–	–	–	2
Welty (56)	2	–	–	–1	–	–	–	–	–	1

Note: the minimum score which can be assigned to each evidence is 1.

with the papers included and excluded for each query, the pre-defined forms for the collection of case reports, and a schematic form for each retrieved study and case report are available on request from the group coordinator. The quality evaluation of the evidence obtained from comparative studies according to the GRADE Working Group method is presented in Table 1. The details of the methodology are reported in this supplement.¹²

4. Results

4.1. Therapeutic area – queries 1–4

1. In the treatment of infective endocarditis caused by Gram-positive microorganisms, is combination therapy with an aminoglycoside plus another antibiotic more effective than monotherapy?
2. In the treatment of infective endocarditis caused by Gram-positive microorganisms, is therapy with an aminoglycoside in a single daily dose more effective than therapy in three divided doses?
3. In the treatment of infective endocarditis caused by Gram-positive microorganisms, is therapy with teicoplanin as effective, and associated with fewer adverse events, than therapy with vancomycin?
4. In the treatment of infective endocarditis caused by Gram-positive microorganisms, what is the optimal duration of treatment?

For these four queries a single research was conducted, i.e., a single, generic string was used for the MEDLINE search and the results were then refined manually.

4.1.1. Comparative studies

Eight comparative studies were retrieved. In one study by Fortún et al.,¹³ conducted on a small population of intravenous drug users, teicoplanin was compared to cloxacillin + gentamicin in right-sided endocarditis caused by methicillin-susceptible *S. aureus* (MSSA); the results in the teicoplanin arm (at a dosage of 10 mg/kg/12 h for the first 3 days, 6 mg/kg/12 h for the following 4 days, and then 7 mg/kg/24 h for 21 days) were significantly worse, with 7/8 (87.5%) cured in the cloxacillin + gentamicin group and only 2/6 (33%) in the teicoplanin group. In another study, again by Fortún et al.,¹⁴ the efficacy and safety of a short course of a combination of a glycopeptide (vancomycin or teicoplanin) and gentamicin compared with a combination of cloxacillin and gentamicin in the treatment of right-sided endocarditis caused by *S. aureus* was assessed. The results in both glycopeptide arms were inferior with respect to the cloxacillin + gentamicin arm (11/11, 100% success in the cloxacillin/gentamicin arm, vs. 6/10, 60% success in the vancomycin arm and 7/10, 70% in the teicoplanin arm); there were, however, no differences between teicoplanin (at a dosage of 12 mg/kg/day) and vancomycin.

Ribera et al.¹⁵ compared the efficacy of cloxacillin alone with that of cloxacillin + gentamicin in the 2-week treatment of right-sided *S. aureus* endocarditis in intravenous drug users. The results in the combination arm were no better than those of the single antibiotic arm (34/45, 76% success in the cloxacillin arm; 31/45, 69% in the combination arm). Abrams et al.¹⁶ compared single vs. combination (i.e., with aminoglycoside) drug therapy of *S. aureus* endocarditis in intravenous drug users; again, no differences were noted between the two groups (i.e., no advantage of the combination therapy).

Gilbert¹⁷ compared a higher teicoplanin dose, i.e., a 12 mg/kg loading dose followed by 6 mg/kg/day, with a standard dose of vancomycin of 30 mg/kg/day in the treatment of patients with documented bacteremia due to Gram-positive cocci. A small

subset of patients with infective endocarditis was present. Because of the observed high failure rate in the teicoplanin arm, enrolment was interrupted after 12 patients in order to conduct an interim analysis. Even with the small numbers, the failure rate of teicoplanin in patients with left-sided endocarditis almost achieved statistical significance ($p = 0.07$). The authors concluded that the drug was a failure at the dosage regimen employed.

Huang and Hsu¹⁸ retrospectively compared patients with MRSA endocarditis treated with teicoplanin (6–12 mg/kg) because of intolerance or contraindication to vancomycin, and vancomycin. There were no differences in the two groups. In the teicoplanin group, mortality was 7/15 (47%), embolization 3/15 (20%), and microbiological failure 6/15 (40%). while in the vancomycin group the corresponding figures were 15/36 (42%), 6/36 (17%), and 13/38 (34%), respectively.

Sexton et al.¹⁹ compared two regimens, one with ceftriaxone alone for 4 weeks, the other with a combination of ceftriaxone and gentamicin as a single dose in patients with penicillin-susceptible *Streptococcus* endocarditis. Both treatments were effective. Microbiological success was obtained in 22/23 (95.7%) patients in the ceftriaxone only arm and in 22/23 (95.7%) patients in the combination arm. Cure without surgery was obtained in 21/26 (80%) patients in the ceftriaxone only arm and in 15/25 (60%) patients in the combination arm.

Finally, in a recently published study by Cosgrove et al.²⁰ the safety data of a randomized, open trial comparing daptomycin and standard therapy (either anti-staphylococcal penicillin or vancomycin, plus initial gentamicin) in the treatment of bacteremia and endocarditis caused by *S. aureus* were analyzed. The aim of the study was to evaluate the clinical impact of initial low-dose gentamicin on renal function. The population analyzed was that of patients participating in the randomized trial comparing daptomycin and standard anti-staphylococcal therapy published by Fowler, presented in the next section. One-hundred twenty-two patients received gentamicin in association with other antibiotics, and were compared to a group of 100 not receiving gentamicin. A decrease in creatinine clearance was observed in 27 (22%) patients receiving gentamicin, as opposed to eight (8%) of those not receiving gentamicin. A sustained 50% decrease of creatinine clearance was observed in seven (6%) and no patients, respectively, and a sustained 25% decrease of creatinine clearance was observed in 26 (21%) and nine (9%) patients, respectively. At multivariate analysis, predictors of clinically significant decrease in creatinine clearance were age ≥ 65 years (odds ratio (OR) 3.56, confidence interval (CI) 1.66–7.65) and receipt of any dose of gentamicin, either as part of the study treatment or as an initial low dose before treatment (OR 3.39, CI 1.43–8.00). Though the study was not projected to assess this point, the results show that even small doses of gentamicin are associated with an increase in renal toxicity in this patient population.

4.2. Therapeutic area – query 5

In the treatment of infective endocarditis caused by multi-resistant Gram-positive microorganisms, is therapy with quinupristin/dalfopristin, linezolid, daptomycin, and tigecycline effective?

4.2.1. Comparative studies

Two comparative studies were retrieved, both referring to a randomized controlled trial that compared daptomycin vs. standard therapy in the treatment of bacteremia and endocarditis caused by *S. aureus*. The aim of this study was to test the non-inferiority of daptomycin as compared to standard treatment. In the study by Fowler et al.,²¹ 235 adult patients with one or more blood cultures positive for *S. aureus* infection were enrolled.

Patients were randomly assigned to daptomycin, 6 mg/kg/day (+ gentamicin for the first 4 days in left-sided endocarditis) or standard therapy (vancomycin or anti-staphylococcal penicillin + gentamicin for the first 4 days), in an unblinded fashion. The main outcome was the clinical success rate in each of the two treatment groups in the modified intention-to-treat population, assessed 42 days after the end of therapy. In the study population, 53/235 (22.5%) had infective endocarditis: of these, 9/28 (32%) in the daptomycin group and 9/25 (36%) in the standard treatment group were cured. Nineteen patients in the daptomycin group and 16 in the standard treatment group had right-sided endocarditis. The success rate for both groups was similar: 8/19 (42%) in the daptomycin group and 7/16 (43%) in the standard treatment group. Nine patients in the daptomycin group and nine in the standard treatment group had left-sided endocarditis. In this small subgroup, the failure rate was very high in both treatment arms: one patient in the daptomycin group (11%) and two in the standard treatment group (22%) were cured. Considering the entire population of patients (endocarditis plus bacteremia), daptomycin was associated with more microbiological failures, while standard treatment was associated with more failures due to adverse events, though the differences did not reach statistical significance.

In the study by Rehm et al.²² (a subset analysis of the Fowler study), patients with endocarditis caused by MRSA (13 in the daptomycin group and 10 in the standard treatment group) were analyzed in detail. Of the 13 patients with MRSA infective endocarditis in the daptomycin arm, 4/8 (50%) of those with right-sided endocarditis and 0/5 of those with left-sided endocarditis were cured; the same rates were obtained in the standard treatment arm, with 3/6 (50%) of those with right-sided endocarditis and 0/4 of those with left-sided endocarditis cured.

4.2.2. Case series

Falagas et al.²³ reported a series of 33 patients with 34 episodes of endocarditis treated with linezolid. Nineteen were male; the median age was 66 years (range 0.5–80 years); co-morbidities were present in the vast majority of cases (eight chronic renal failure, eight diabetes, six cancer, four treatment with steroids, one rheumatoid arthritis, one HIV infection). There were 27 episodes on native valves, and seven involved prosthetic valves. The isolates were vancomycin-intermediate *S. aureus* (VISA; 10 cases), MRSA (eight cases), vancomycin-resistant *Enterococcus spp* (VRE; eight cases), coagulase-negative staphylococci (CoNS; five cases), *Enterococcus faecalis* (two cases), and *Streptococcus mitis* and *Corynebacterium striatum* (one case each). Linezolid was administered for a median of 42 days, associated in one third of cases with other drugs (rifampin in five cases, gentamicin in four, fusidic acid in three, amikacin in one). Eight patients underwent surgery. The reported success rate was 63.6%, and the overall mortality 33%.

Muñoz et al.²⁴ reported a series of nine cases of infective endocarditis successfully treated with linezolid. They were six males and three females, aged 57–82 years, with serious co-morbidities (one cancer, three transplants). Five patients had a prosthetic valve infection (three aortic, two mitral) and four a native valve infection (two aortic, one mitral, one tricuspid). The isolates were MSSA (four cases), MRSA (two cases), and *E. faecalis*, *Streptococcus mutans*, and *C. striatum* in one case each. Patients received linezolid 600 mg every 12 h for 2–4 weeks after failure of previous antibiotic regimens. Four underwent surgery. The reported success rate was 100%, with no deaths after a follow-up of 7–31 months.

Falagas et al.²⁵ reported a series of 19 patients with endocarditis treated with daptomycin. Nine were male; the median age was 60.5 years (range 13–92 years); co-morbidities were present in two thirds of cases (three chronic renal failure, two diabetes, one cancer, two systemic lupus erythematosus (SLE), three bone

marrow transplantation). There were 17 episodes on native valves and two on prosthetic valves. The isolates were MRSA (eight cases), MSSA (five cases), VRE (three cases), and CoNS, *E. faecalis*, and *C. striatum* in one case each. Daptomycin was administered for a median of 28 days, associated in one half of cases with other drugs (rifampin in three cases, gentamicin in three, minocycline and linezolid, one case each). Data on surgery were not reported. The reported success rate was 57.8% and the overall mortality 38.9%.

Howden et al.²⁶ reported a series of patients with serious infections caused by MRSA with reduced susceptibility to vancomycin. Eight patients had infectious endocarditis. Median age was 72.5 years (range 66–80 years). The majority of patients had associated co-morbidities. Left-sided endocarditis was present in five patients (mitral valve in two and aortic valve in three; two were prosthetic aortic valves). The vancomycin MIC was 2 µg/ml for five isolates and 4 µg/ml for three isolates. Of these eight patients, seven were treated with linezolid, in different schemes, three of whom (42.8%) were cured.

4.2.3. Single case reports

Sgarabotto et al.²⁷ reported a case of successful treatment of an MRSA aortic valve endocarditis with the combination of vancomycin and quinupristin/dalfopristin. Arias et al.²⁸ adopted with success an unusual drug combination – daptomycin at 9 mg/kg + ampicillin + gentamicin for 6 weeks – after the failure of daptomycin monotherapy at the usual dosage for a mitral valve infective endocarditis caused by vancomycin-resistant *Enterococcus faecium*. The patient experienced mild dizziness, which was attributed to the prolonged exposure to the aminoglycoside, but no renal adverse events were reported.

Cunha et al.²⁹ reported clinical success with high-dose (12 mg/kg) daptomycin in a case of bacteremia and probable endocarditis caused by a vancomycin-tolerant *E. faecalis*. Cunha et al.³⁰ also reported an unusual case of a patient with Job's syndrome and MRSA meningitis who had failed a regimen of vancomycin + ceftriaxone + ampicillin. A diagnosis of mitral valve endocarditis was eventually made and the patient was successfully treated with a combination of high dose daptomycin (12 mg/kg) and linezolid. No adverse events were reported after an 8-week course.

Matsumura and Simor³¹ reported clinical success in a case of aortic valve endocarditis caused by a vancomycin-resistant *E. faecium* strain. The patient had failed a 2-week course of quinupristin/dalfopristin but responded to an association of quinupristin/dalfopristin + doxycycline + rifampin for 8 weeks. In this case, serum bactericidal testing showed the absence of activity of single drugs, while synergy testing showed that the association was synergistic.

Viale et al.³² reported a case of successful treatment of MRSA mitral valve endocarditis with quinupristin/dalfopristin followed by oral linezolid. Zinkernagel et al.³³ reported an unusual severe and destructive form of endocarditis due to *Staphylococcus epidermidis*. Clinical success was achieved with a combination of antibiotics (vancomycin, quinupristin/dalfopristin, levofloxacin) plus cardiac surgery. Konstantinov and Zehr³⁴ reported a case of aortic valve endocarditis caused by a vancomycin-resistant *E. faecium* treated with success with a combination of quinupristin/dalfopristin, rifampin, and doxycycline and aortic valve replacement. Mergenhagen and Pasko³⁵ described a case of successful treatment of left-sided endocarditis caused by community-acquired MRSA with the association daptomycin/rifampin and mitral repair; data on follow-up are, however, lacking.

Chesi et al.³⁶ reported clinical success with quinupristin/dalfopristin in a patient with MRSA tricuspid valve endocarditis complicated by septic pulmonary emboli, after failing sequential treatment with teicoplanin-co-trimoxazole and linezolid associated to vancomycin-rifampin-co-trimoxazole. Liu et al.³⁷ reported

a case of MRSA endocarditis of the tricuspid valve associated with the presence of a Hickman's catheter and defibrillator, in which treatment with daptomycin failed. The patient was successfully treated with linezolid/fusidic acid and then teicoplanin. In this case, the failure of daptomycin and the success of the combination regimen with linezolid was attributed to the appearance of pulmonary emboli during treatment with daptomycin.

Tenover et al.³⁸ reported the development of daptomycin resistance in an *S. aureus* isolate with hetero-resistance to vancomycin, during treatment for left-sided endocarditis. In this case, cure was achieved with linezolid. Babcock et al.³⁹ described a case of VRE infection of the tricuspid (and perhaps aortic) valve successfully treated with linezolid after failure of quinupristin/dalfopristin. The patient, a woman with Down syndrome and mental retardation, completed the 6-week course of treatment with oral linezolid.

Sakoulas et al.⁴⁰ reported a case of mitral valve endocarditis failing to respond to daptomycin because of acquisition of resistance during treatment. The patient was infected with an MSSA strain, but failed a standard regimen with gentamicin/nafcillin; a short course of treatment with vancomycin had also been administered before blood culture results. After switching to daptomycin, a progressive increase in the MIC (from 0.125 to 2 µg/ml) was noted. The patient was eventually cured with surgery and a combination of nafcillin and gentamicin.

Schwartz et al.⁴¹ reported a case of failure of sequential antibiotics in a mitral valve endocarditis caused by a vancomycin-resistant *E. faecium*. The patient was sequentially treated with linezolid, daptomycin 6 mg/kg, an association of daptomycin 8 mg/kg + gentamicin + doxycycline, and quinupristin/dalfopristin (which was associated with a transient negativity of blood cultures). Synergy tests showed the absence of synergy for any antibiotic combination. Serum bactericidal test showed the absence of bactericidal or bacteriostatic activity while on daptomycin 8 mg/kg.

Huang et al.⁴² described a patient who was admitted with fever and treated for MRSA bacteremia. A diagnosis of mitral valve endocarditis and septic thrombophlebitis was made 44 days after admission. The patient received several antibiotic courses (among which were vancomycin, teicoplanin, daptomycin, linezolid, and fusidic acid) without effect, and eventually died of a *Candida* sepsis. Several blood cultures were positive for MRSA, with the emergence of daptomycin resistance during treatment.

Lemaire et al.⁴³ reported a case of MRSA infection of the aortic valve, unsuccessfully treated with several courses of antibiotics (vancomycin, gentamicin, rifampin, daptomycin, linezolid, quinupristin/dalfopristin, trimethoprim) who was eventually cured after aortic valve replacement. An increased MIC for daptomycin (from 1 to 8) during treatment was reported. Chow et al.⁴⁴ reported a case of superinfection caused by *E. faecalis* during treatment with quinupristin/dalfopristin of an MRSA endocarditis.

Pistella et al.⁴⁵ reported a case of community-acquired MRSA sepsis with endocardial and cerebral metastatic seeding who developed coma with multiple cerebritis lesions under vancomycin plus amikacin therapy. The patient was eventually cured with the addition of linezolid to the initial antimicrobial regimen. Shah and Murillo⁴⁶ reported a case of *C. striatum* endocarditis that was treated successfully with daptomycin plus rifampin for 6 weeks following an unsuccessful attempt at vancomycin desensitization and failure of linezolid therapy.

4.3. Therapeutic area – query 6

In the treatment of sepsis caused by multi-resistant Gram-positive microorganisms, is therapy with quinupristin/dalfopristin, linezolid, daptomycin, and tigecycline effective?

4.3.1. Comparative studies

Seven comparative studies were retrieved. Shorr et al.⁴⁷ retrospectively analyzed the results of five randomized controlled studies comparing linezolid and vancomycin in the sponsor's database, in order to examine the outcomes in the subgroup of patients (144/3228) with *S. aureus* bacteremia. The patients were adults with pneumonia acquired within 48 h after hospital admission, or complicated skin and soft tissue infections, or MRSA infections, and the comparison was made between linezolid 600 mg twice daily and vancomycin 1 g twice daily. Linezolid was administered intravenously for at least 7 days and could then be changed to the oral formulation. Seventy-four patients (36 with MRSA) were treated with linezolid and 70 (28 with MRSA) were treated with vancomycin. Considered outcomes were cure of primary infection, microbiological eradication of *S. aureus* bacteremia, and overall survival. Clinical cure was obtained in 28/51 (54.9%) patients treated with linezolid and 25/48 (52%) patients treated with vancomycin (OR 1.12, 95% CI 0.51–2.47). Microbiological eradication was obtained in 41/59 (69.5%) patients treated with linezolid and in 41/56 (73.2%) of those treated with vancomycin (OR 1.00, 95% CI 0.47–2.12). Mortality was 19/74 (25.6%) in the linezolid arm and 18/70 (25.7%) in the comparator arm (OR 1.00, 95% CI 0.47–2.12).

In the study by Stevens et al.,⁴⁸ patients with presumed MRSA infections were randomly assigned to linezolid, 600 mg twice daily, or vancomycin, 1 g twice daily, both for at least 7 days, in an unblinded fashion. Both clinical and microbiological outcomes were considered. *S. aureus* bacteremia was present in 45/240 patients in the group randomized to linezolid and 40/220 in the group randomized to vancomycin. In the intention-to-treat analysis, cure was obtained in 17/33 (51.5%) bacteremic patients treated with linezolid and in 15/32 (46.9%) bacteremic patients treated with vancomycin.

Wilcox et al.⁴⁹ described the results of an open-label, randomized, multicenter study comparing the clinical efficacy, safety, and tolerance of linezolid with that of teicoplanin in patients with suspected or proven Gram-positive infections, including pneumonia, skin and soft tissue infections, right-sided endocarditis, and bacteremia. Linezolid was given at a dose of 600 mg twice daily, while the dosage of teicoplanin was at the discretion of the investigator. A clinical success (cure or improvement of clinical condition) was reported in 23/26 (88%) bacteremic patients treated with linezolid and in 17/30 (56%) bacteremic patients treated with vancomycin; the 31.8% treatment advantage was statistically significant ($p = 0.009$, 95% CI 10.2–53.4).

In the randomized, open trial study, again by Wilcox et al.,⁵⁰ linezolid 600 mg twice daily and vancomycin 1 g twice daily were compared in a group of patients with complicated skin and skin-structure infections and catheter-related bloodstream infections. In the subgroup of patients with catheter-related infections, catheter removal was required for enrolment. Considered outcomes were microbiological and clinical success. The results in the subgroup of patients with catheter-related bloodstream infections showed a microbiological success in 82/95 (86.3%) patients in the linezolid group and in 67/74 (90.5%) patients in the vancomycin group. Clinical success in the two arms was obtained in 70/93 (75.3%) and 59/73 (80.8%), respectively.

Cepeda et al.⁵¹ reported the results of a double-blind, double-dummy randomized trial comparing linezolid with teicoplanin in the treatment of suspected or proven Gram-positive infections in critically ill patients in two mixed medical-surgical, tertiary referral intensive care units (ICUs). Patients received either intravenous linezolid (600 mg/12 h) plus teicoplanin dummy (one dose/12 h for three doses then every 24 h intravenously) or teicoplanin (400 mg/12 h for three doses then 400 mg/24 h intravenously) plus linezolid dummy (one dose/12 h intravenously).

Table 2
Summary of extraction of comparative studies on new antibiotics in the treatment of multi-resistant Gram-positive sepsis

ID	Aim	Study design	Population	Intervention	Comparator	Outcomes	Num/Den (I)	Num/Den (C)	Quality	Notes
Shorr 2005 ⁴⁷	Compare LNZ and Vanco in SA bacteremia	Retrospective analysis of 5 RCT	144 pts from 5 studies	LNZ	Vanco	Cure; microbiological eradication	Cure: 28/51 Eradication: 41/59	Cure: 25/48 Eradication: 41/56	MRB	Small numbers with MRSA
Stevens 2002 ⁴⁸	Compare LNZ and Vanco in presumed MRSA infection	RCT open	85 pts with bacteremia from 104 sites	LNZ	Vanco	Cure; microbiological eradication	Cure: 17/33 (ITT)	Cure: 15/32 (ITT)	MRB	Small numbers with bacteremia
Wilcox 2009 ⁵⁰	Test non-inferiority of LNZ vs. Vanco in treating catheter-related infections	RCT open	180 pts with catheter-related infections from 100 sites	LNZ + catheter removal	Vanco + catheter removal	Microbiological eradication; cure	Eradication: 82/95 Cure: 70/93	Eradication: 67/74 Cure: 59/73	HRB	Different groups of pts (skin and soft tissue + catheter-associated infections) Difficult to analyze separately
Wilcox 2004 ⁴⁹	Compare clinical efficacy, safety and tolerance of LNZ with that of Teico	RCT open	56 pts (subgroup with bacteremia) from 50 sites	LNZ (600 mg q12h)	Teico (dose not specified)	Cure; microbiological eradication; safety	Cure: 23/26	Cure: 17/30	HRB	Weak comparator; definition of success vague; presentation of data confusing
Adembri 2008 ⁵²	Compare two different modalities of LNZ administration (intermittent vs. continuous infusion) in critically ill septic pts	RCT open	18 septic ICU pts	LNZ (600 mg q12h)	LNZ 300 mg i.v. loading dose + 900 continuous infusion on day 1, followed by continuous infusion of 1200 mg/daily	Cure; microbiological eradication; PK/PD parameters	Cure: 7/9 Eradication: 6/9	Cure: 7/9 Eradication: 7/9	MRB	Small number of pts
Cepeda 2004 ⁵¹	Compare LNZ with Teico in the treatment of suspected or proven Gram-pos infections in critically ill pts	RCT double-blind, double-dummy	202 pts in two mixed medical-surgical, tertiary referral ICUs	LNZ (600 mg/12 h) plus Teico dummy	Teico (400 mg/12 h for 3 doses then 400 mg/24 h i.v.) plus LNZ dummy	Microbiological eradication; cure	Clinical outcome: 71/100 success (EOT) 40/100 success (LTFU) Eradication: 49/70 (EOT)	Clinical outcome: 67/100 success (EOT) 35/102 success (LTFU) Eradication: 45/68 (EOT)	LRB	Good design of the study; no differences seen in the two groups
Linden 1997 ⁵³	Verify efficacy of Q/D in the treatment of VREF serious infections	Case-control	62 pts with VREF infection	Q/D	Other antibiotics (Vanco, β-lactams, ciprofloxacin, amino-glycosides)	Recurrent bacteremia; in-hospital mortality; VREF-associated mortality	Recurrent bacteremia 5/20 In-hospital mortality 13/20 VREF-associated mortality 5/20	Recurrent bacteremia 21/42 In-hospital mortality 22/42 VREF-associated mortality 17/42	LRB	Better microbiological results not associated with better survival

Num/Den (I), numerator/denominator for intervention group; Num/Den (C), numerator/denominator for control group; LNZ, linezolid; Vanco, vancomycin; Teico, teicoplanin; Q/D, quinopristin/dalfopristin; pts, patients; RCT, randomized controlled trial; LRB, low risk of bias; HRB, high risk of bias; MRB, medium risk of bias; MRSA, methicillin-resistant *Staphylococcus aureus*; SA, *Staphylococcus aureus*; VREF, vancomycin-resistant *Enterococcus faecium*; ITT, intention to treat; EOT, end of treatment; LTFU, long-term follow up; q12h, every 12 hours; ICU, intensive care unit; i.v., intravenous; PK/PD, pharmacokinetic/pharmacodynamic.

ly). At the end of treatment evaluation, clinical and microbiological success rates were 71/100 (71%) and 49/70 (70%), respectively, in the linezolid arm and 67/100 (67%) and 45/68 (66%) in the teicoplanin arm. In the long-term follow-up, a clinical success was reported in 40/100 (40%) of patients in the linezolid arm and in 35/102 (34%) in the teicoplanin arm.

Adembri et al.⁵² reported the results of a randomized, open-label study comparing two different modalities of linezolid administration (intermittent vs. continuous infusion) in critically ill septic patients (septic ICU patients with a microbiologically documented infection caused by either glycopeptide-resistant or glycopeptide-sensitive Gram-positive strains, but with no clinical improvement after 5 days of glycopeptide therapy). Patients were randomly assigned to receive linezolid 600 mg every 12 h as a 30-min intermittent infusion (standard), or as a continuous infusion of 1200 mg/day (after a first 300 mg loading dose administered as a 30-min infusion). Outcomes were clinical cure, microbiological eradication, and pharmacokinetic/pharmacodynamic (PK/PD) parameters. Nine patients were enrolled in each arm. Clinical cure was obtained in 7/9 (77%) patients in both arms. Microbiological eradication was obtained in 6/9 (66%) patients in the intermittent group and in 7/9 (77%) in the continuous infusion group.

Linden et al.⁵³ reported the results of a case-control study on the use of quinupristin/dalfopristin in adult patients with bacteremia caused by vancomycin-resistant *E. faecium* (vancomycin MIC 8 mg/l, teicoplanin MIC 8 mg/l, in vitro resistance to all other appropriate agents, and quinupristin/dalfopristin MIC 2 mg/l). All patients with vancomycin-resistant *E. faecium* bacteremia before the availability of quinupristin/dalfopristin (January 1991–December 1993) were considered the historical control cohort. The intervention group (20 patients) was treated with quinupristin/dalfopristin administered intravenously at 7.5 mg/kg every 8 h. The 42 patients in the control group received other antibiotics according to standard of care (vancomycin, β -lactams, ciprofloxacin, aminoglycosides). The main considered outcomes were recurrent bacteremia and in-hospital mortality. Recurrent bacteremia was lower in the intervention group (5/20, 25%) than in the comparator group (21/42, 50%; $p =$ not significant), but in-hospital mortality was similar (intervention group: 13/20, 65%; control group: 22/42, 52%).

A summary of these studies is reported in Table 2.

4.4. Therapeutic area – query 7

In the treatment of infections of vascular prostheses caused by multi-resistant Gram-positive microorganisms, is therapy with quinupristin/dalfopristin, linezolid, daptomycin, and tigecycline effective?

4.4.1. Comparative studies

Only one comparative study was retrieved, on a subset of patients from the study by Fowler et al. on daptomycin,⁵⁴ already presented in the results of query 1. The subset was composed of 38 patients with intravascular devices comprising both removable and non-removable catheters and vascular prostheses (pacemaker/defibrillators, coronary stents, tunneled catheters, abdominal aortic synthetic grafts, inferior vena cava filter, transjugular intrahepatic portosystemic shunt, intra-aortic balloon pump). As a group, no differences were noted in the two arms; 8/17 (47%) patients in the daptomycin arm and 9/21 (43%) in the standard treatment arm were defined as clinical success. Overall success was higher when antibiotic therapy was associated with removal of the device. In the case of pacemakers/defibrillators, a clinical success was obtained in 3/5 cases when the device was removed, as compared to 0/6 cases when the device was left in place. The

differences were less clear in the case of tunneled catheters (success in 4/8 following device removal and in 2/3 when the device was left in place). The numbers however were too small for definitive conclusions.

4.5. Diagnostic/laboratory monitoring area – query 1

In the treatment of infective endocarditis caused by multi-resistant Gram-positive microorganisms, is monitoring of plasma levels of vancomycin, gentamicin, and teicoplanin effective in reducing adverse events and costs, and in increasing treatment efficacy?

4.5.1. Comparative studies

Two comparative studies were retrieved. One study by Fernández de Gatta et al.⁵⁵ evaluated the cost-effectiveness of vancomycin serum concentration monitoring in patients with hematological malignancies. In this randomized, unblinded clinical trial, patients with hematological malignancies and Gram-positive infection requiring treatment with vancomycin were randomized to two groups; in one, treatment was modified according to therapeutic drug monitoring (TDM) of vancomycin with the active intervention of a clinical pharmacist, while in the other group TDM was not performed. Both clinical and economic outcomes were considered. A greater incidence of nephrotoxicity was observed in the group not receiving TDM. Logistic regression analysis confirmed that TDM independently reduced the incidence of nephrotoxicity in this patient population. On the basis of this reduced nephrotoxicity, an incremental cost of US\$ 435 per case of nephrotoxicity prevented was found for vancomycin serum concentration monitoring. The procedure appeared to be cost-effective. The study however did not classify patients according to type of infection (e.g., sepsis, endocarditis), so the results are not generalizable to the population of patients with endocarditis.

In another study by Welty and Copa,⁵⁶ patients were randomized to receive or not vancomycin TDM. The study was supported by a TDM pharmacist. TDM of vancomycin was associated with fewer episodes of renal failure (7/61, 11.4% in the TDM arm vs. 24/55, 43.6% in the non-TDM arm), decreased length of therapy (11.1 ± 5.8 days vs. 13.4 ± 13.6 days), and possibly reduced length of stay (36.8 ± 30.4 days vs. 44.5 ± 51.4 days). Only two patients (both in the non-TDM group) had endocarditis, so results are not immediately generalizable to this subgroup of patients.

4.6. Diagnostic/laboratory monitoring area – query 2

In the treatment of infective endocarditis caused by multi-resistant Gram-positive microorganisms, is the use of serum bactericidal and synergy testing (along with traditional methods such as MIC determination) effective in reducing adverse events and costs, and in increasing treatment efficacy?

4.6.1. Comparative studies

No comparative studies were retrieved.

4.6.2. Single case reports

Matsumura and Simor³¹ reported a case of VRE aortic valve endocarditis in which time-kill synergy studies and serum bactericidal testing were used to test an association of quinupristin/dalfopristin + doxycycline + rifampin. Serum bactericidal testing showed the absence of activity of single drugs, while synergy testing showed that the association was synergistic. The patient received this treatment for 8 weeks and the outcome was successful.

Schwartz et al.⁴¹ reported another case of endocarditis caused by a vancomycin-resistant *E. faecium*, in which serum bactericidal testing and synergy testing were used to guide treatment. After

failure of various regimens, an association of daptomycin 8 mg/kg + gentamicin + doxycycline was tried. Synergy tests showed the absence of synergy for any antibiotic combination, while serum bactericidal tests at a dilution of 1:2 showed the absence of bactericidal or bacteriostatic activity while on daptomycin 8 mg/kg.

4.7. From the evidence to the recommendations

After thorough revision of the retrieved studies, four queries were eliminated because of paucity of data: three from the therapeutic area (regarding the administration of aminoglycosides in single or fractioned doses, the optimal duration of treatment in IE, and the use of new antibiotics in the treatment of infections of vascular prostheses) and one from the diagnostic/laboratory monitoring area (on the use of serum bactericidal and synergy testing). Therefore, the following discussion is limited to the five queries for which comparative studies and other evidence allowed the drawing up of recommendations.

4.8. Therapeutic area

4.8.1. Query 1

In the treatment of infective endocarditis caused by Gram-positive microorganisms, is combination therapy with an aminoglycoside plus another antibiotic more effective than monotherapy?

The use of gentamicin (or other aminoglycosides) in association with cell-wall active antibiotics has long been a mainstay of therapy for severe infections, and it is still recommended in the treatment of endocarditis due to *E. faecalis*, where the combination of ampicillin and gentamicin is synergistic. The use of combination therapy in infective endocarditis caused by *S. aureus* and other Gram-positive microorganisms is, however, less well founded, and based more on theoretical considerations and animal experiments than clinical evidence. Moreover, aminoglycosides are potentially nephro- and ototoxic, and their use requires monitoring of plasma levels of antibiotics.

Few comparative studies have tried to assess whether combination therapy with aminoglycosides in the treatment of Gram-positive IE is better than single therapy. Abrams et al.¹⁶ (GRADE score 1) compared single vs. combination (i.e., with aminoglycoside) drug therapy of *S. aureus* endocarditis in intravenous drug users in a randomized, open trial. The considered outcomes were time to defervescence, bacteriological failure, congestive heart failure, surgery, and mortality. There were no differences in the two groups, and mortality was uniformly low. Ribera et al.¹⁵ (GRADE score 2) compared the efficacy of cloxacillin alone with that of cloxacillin plus gentamicin for the 2-week treatment of right-sided *S. aureus* endocarditis in intravenous drug users in a randomized, open trial. Again, there were no differences in the two groups. In another randomized, open trial, Sexton et al.¹⁹ (GRADE score 2) compared two antibiotic regimens (ceftriaxone alone for 4 weeks or ceftriaxone + gentamicin for 2 weeks) for the treatment of adults with penicillin-susceptible *Streptococcus* endocarditis. No differences in the microbiological success were found, while more patients in the combination therapy arm were cured with surgery. These three studies, all showing no advantage of combination therapy, are limited by their open design and by the paucity of data on randomization; moreover, they were mainly conducted on populations of patients with a low mortality risk, so generalization to other groups of patients is uncertain.

More recently, Cosgrove et al.²⁰ (GRADE score 3) studied the clinical impact of initial low-dose gentamicin on renal function in a group of patients treated for *S. aureus* infective endocarditis or bacteremia. The patients were enrolled in a randomized, open trial

comparing daptomycin and standard anti-staphylococcal therapy in the treatment of bloodstream infections caused by *S. aureus*. Patients in the standard treatment arm were treated with an association of an anti-staphylococcal antibiotic (either vancomycin or an anti-staphylococcal penicillin) and gentamicin, while patients in the daptomycin arm received gentamicin if they had left-sided endocarditis. The trial was not designed to assess the effect of gentamicin on renal dysfunction, and the effect of gentamicin on clinical outcome was not assessed. Nevertheless, the results of this study show that small initial doses of gentamicin are also significantly associated with a decrease in renal function.

In summary, the limited available evidence shows that aminoglycosides are not useful in the treatment of Gram-positive infective endocarditis in low-risk populations (i.e., drug addicts with tricuspid valve *S. aureus* endocarditis and patients with endocarditis caused by susceptible strains of *Streptococcus*). There is also evidence that even short courses of aminoglycosides in the treatment of *S. aureus* bloodstream infections are associated with renal toxicity.

Recommendations

In the treatment of native valve MSSA infective endocarditis, there is no convincing evidence of the usefulness of a combination of gentamicin with either vancomycin or an anti-staphylococcal penicillin, while there is evidence that this combination is associated with an increase in toxicity, especially in patients aged over 65 years. Gentamicin in this condition must therefore be used with caution (B). In the treatment of native valve IE caused by MRSA there is limited evidence on the utility of combination therapy (D). The use of combination therapy is still indicated in the treatment of prosthetic valve *S. aureus* endocarditis (D).

4.8.2. Query 3

In the treatment of infective endocarditis caused by Gram-positive microorganisms, is therapy with teicoplanin as effective, and associated with fewer adverse events, than therapy with vancomycin?

Few studies compared vancomycin and teicoplanin in the treatment of infective endocarditis. Gilbert et al.¹⁷ (GRADE score 3) published the results of a randomized, double-blind study comparing a higher teicoplanin dose, i.e., a 12-mg/kg loading dose followed by 6 mg/kg/day, with a standard dose of vancomycin of 30 mg/kg/day in the treatment of patients with documented bacteremia due to Gram-positive cocci. The patients in the teicoplanin arm received it at a dose of 6 mg/kg every 12 h for three doses and then 6 mg/kg alternating with placebo every 12 h. A small subset of patients had infective endocarditis. The enrolment was interrupted because of a high failure rate in the teicoplanin arm. The interim analysis showed that the failure rate of teicoplanin in patients with left-sided endocarditis almost achieved statistical significance ($p = 0.07$), and the authors concluded that teicoplanin at this dosage is not effective in the treatment of left-sided endocarditis caused by Gram-positive microorganisms.

Huang and Hsu¹⁸ (GRADE score 2) studied 51 patients with MRSA endocarditis (only definite cases according to Duke's criteria) in a retrospective, comparative study directly comparing teicoplanin and vancomycin in the treatment of IE. No differences emerged between the two treatment groups.

In the study by Fortún et al.¹⁴ (GRADE score 2), patients with right-sided *S. aureus* endocarditis were randomly assigned in an open way to three arms: cloxacillin plus gentamicin; vancomycin plus gentamicin; and teicoplanin (12 mg/kg, given every 24 h, with

a loading dose of 24 mg/kg given on the first day) plus gentamicin. The results in the group treated with teicoplanin and vancomycin were comparable, but results in both arms were inferior to the results in the cloxacillin arm. There is some additional evidence demonstrating the inferiority of glycopeptides in the treatment of endocarditis caused by susceptible strains of *S. aureus*. The same author¹³ (GRADE score 2) compared teicoplanin at decreasing doses (10 mg/kg/12 h for the first 3 days, followed by 6 mg/kg/12 h for 4 days, and 7 mg/kg/24 h for 21 days) vs. cloxacillin plus gentamicin in intravenous drug users with right-sided *S. aureus* IE. The cure rate was only 33% in the teicoplanin group as opposed to 87.5% in the cloxacillin/gentamicin group.

In conclusion, in the treatment of Gram-positive infectious endocarditis there is limited evidence that teicoplanin is inferior to vancomycin in the treatment of left-sided IE caused by Gram-positive microorganisms, while in right-sided endocarditis caused by MRSA, teicoplanin and vancomycin achieve similar results. It must be remembered, however, that both drugs are inferior with respect to anti-staphylococcal penicillins in the treatment of MSSA endocarditis.

Recommendations

Teicoplanin can be considered equivalent to vancomycin in the treatment of right-sided endocarditis (D). In the treatment of left-sided endocarditis, teicoplanin was inferior to vancomycin when used at a loading dose of 6 mg/kg every 12 h for three doses and then 6 mg/kg/day. In the treatment of left-sided endocarditis the use of teicoplanin at higher dosages, though common, is not supported by clinical evidence (D). Both drugs are inferior to anti-staphylococcal penicillin when the strain of *S. aureus* is susceptible to methicillin (C).

4.8.3. Query 5

In the treatment of infective endocarditis caused by multi-resistant Gram-positive microorganisms, is therapy with quinupristin/dalfopristin, linezolid, daptomycin, and tigecycline effective?

Only two randomized studies, both on daptomycin, were found, one by Fowler et al.²¹ (GRADE score 2) and the other by Rehm et al.²² (GRADE score 2). Both refer to a randomized controlled trial comparing daptomycin to standard therapy in the treatment of bacteremia and endocarditis caused by *S. aureus*. Daptomycin was used at a dose of 6 mg/kg. The overall success rate was reported to be around 43% in the treatment of right-sided infectious endocarditis, a rate comparable to standard treatment. Failures in the daptomycin group were more commonly secondary to microbiological failure, while those in the control group were more commonly secondary to toxicity (mainly renal toxicity). The success rate in the treatment of left-sided endocarditis was very low for both treatment arms. In the subgroup of patients with MRSA, the success rate was 50% for right-sided endocarditis and 0% for left-sided endocarditis. Surgical treatment is reported in 2/9 patients with left-sided endocarditis in the daptomycin group and 1/9 patients with left-sided endocarditis in the standard treatment group, but no additional data on the outcome are given. This study adopted a very strict definition of success, with failure of obtaining a blood culture at 42 days of follow-up considered as a clinical failure.

No randomized studies were found addressing the role of quinupristin/dalfopristin, linezolid, and tigecycline in the treatment of infectious endocarditis.

A series of cases (single case reports and case series) describing the use of these antibiotics in the treatment of infective endocarditis caused by multi-resistant Gram-positive microorganisms were found.

Daptomycin

Falagas et al.²⁵ (GRADE score 1) reported a series of 19 patients with endocarditis treated with daptomycin. In five of them (26%) the cause was MSSA, while the remaining 14 cases were caused by multi-resistant or difficult-to-treat Gram-positive microorganisms (MRSA 8/19, 42%; VRE 4/19, 21%; CoNS, *E. faecalis*, *C. striatum* one case each). No growth was reported in one case. The left side of the heart was involved in 13 cases and the right side in four; also reported were infection of the aortic arch and of a pacemaker wire, while for one case no description of the involved valve was given. Data on surgery were not reported. The reported success rate was 57.8% and the overall mortality 38.9%. Eight out of 13 (61.5%) patients with left-sided IE were considered cured, as compared to 2/4 (50%) of those with right-sided IE. The relatively high success rate in left-sided endocarditis is in contrast with the results of the randomized controlled trial²¹ in which the success rate in left-sided IE was close to zero, but the high risk of bias inherent to case reports must be considered, such as reporting bias (exclusion of failures from reporting) and incompleteness of reporting. For example, in the series published by Falagas, in the majority of cases an adequate follow-up was not reported, data crucial for the determination of the real outcome in patients with IE. In the randomized trial, on the other hand, the definition of cure was stringent, with failure to obtain a blood culture during follow-up considered as a clinical failure; this can partially account for the marked differences in the outcome of left-sided IE treated with daptomycin in the different types of studies. All patients but three were treated with the standard dose (6 mg/kg), and in six cases side effects were reported: elevation of creatine kinase in four cases, renal failure in one case, and eosinophilic pneumonia in one case.

Of the single case reports, some reported a clinical success with daptomycin, alone or in combination with other antibiotics, in the treatment of infectious endocarditis, while other reported failure. Of nine reported single cases of treatment of IE with daptomycin, three^{28,29,35} (GRADE score 1 for each) reported a clinical success. In two cases, daptomycin was used at a higher dosage (9 mg/kg and 12 mg/kg, respectively), and in combination with other antibiotics (ampicillin + gentamicin in one case, linezolid in the other). Of note, in one case, failure with daptomycin alone at the standard dose of 6 mg/kg was reported before the successful use of combination therapy with a higher dose of daptomycin. The mitral valve was involved in both cases; the offending organism was VRE in one case and MRSA in the other. In the third case³⁵ (GRADE score 1), successful treatment of left-sided endocarditis caused by community-acquired MRSA with the association daptomycin/rifampin and mitral repair was reported; data on follow-up were, however, lacking.

Six reports described clinical failure of daptomycin in the treatment of IE^{37,38,40–43} (GRADE score 1 for each). All but one were left-sided IE. In one case of mitral valve endocarditis caused by VRE⁴⁰ daptomycin at a higher dose (8 mg/kg) in association with gentamicin and doxycycline was used. Four authors^{38,40,42,43} (GRADE score 1 each) reported a progressive increase in the MIC of daptomycin during treatment, associated with clinical failure. Patients were infected with *S. aureus* and had previously been treated with vancomycin, or the isolate was resistant to vancomycin.

Finally, a quantity of unpublished data regarding the treatment of IE with daptomycin, mainly based on retrospective multicenter observational studies, has recently been presented at an international conference. The panel experts believe that the recommendations will probably be revised following the publication of these data.

In conclusion, in the treatment of right-sided *S. aureus* IE, daptomycin is not inferior to the standard treatment, and it is currently approved for this indication. The use of daptomycin to treat left-sided endocarditis, at least at the standard dose (6 mg/kg)

and as a single antibiotic, awaits further evidence. In patients with *S. aureus* infection pretreated with vancomycin or harboring strains of *S. aureus* with hetero-resistance to vancomycin, loss of activity of daptomycin during treatment must be considered.

Recommendations

Daptomycin has been shown to be non-inferior to the standard treatment in the treatment of right-sided Gram-positive IE caused by MRSA (C) and can also be considered in the treatment of right-sided IE caused by other Gram-positive resistant strains (D)

In the treatment of left-sided IE, daptomycin alone at the dosage of 6 mg/kg may be used, but the evidence supporting its use is still scarce. The use of higher doses (up to 12 mg/kg) is a possible option. Association with other antibiotics must be considered on an individual basis (D)

Linezolid

No randomized trials addressing the use of linezolid in the treatment of IE were retrieved. A number of cases describe the use of linezolid in this condition. Two case series (Falagas et al.²³ and Muñoz et al.²⁴) report 33 and nine cases, respectively. In the case series described by Falagas et al.²³ (GRADE score 1), IE was left-sided in 22 cases and right-sided in 10, while one case involved both sides. Seven patients had an infection of a prosthetic valve. The involved microorganisms were MRSA (8/33, 24.2%), VISA or *S. aureus* with reduced susceptibility to vancomycin (10/33, 30.3%), CoNS (5/33, 15.2%), vancomycin-resistant *E. faecalis* (2/33, 6.1%) and *E. faecium* (4/33, 12.1%), and vancomycin-susceptible *E. faecalis* (2/33, 6.1%). The reported success rate was 63.6% and the overall mortality 33%. As in many reports, data on prolonged follow-up are lacking in the series by Falagas, so these figures must be viewed with caution. Moreover, some of the patients reported to have been cured, died because of co-morbidities during follow-up. If the patients who died during follow-up and those classified as improved are considered as clinical failures, the overall success rate is 57.5%. Surprisingly, better results were obtained in patients with left-sided endocarditis (success rate 60.8%) than in those with right-sided endocarditis (success rate 50%), and also surprising is the high success rate (71.4%) reported in patients with prosthetic valve endocarditis. The impact of surgery on outcome could not be assessed from these data, however only a minority of patients (8/33, 24%) were treated with surgery.

Muñoz et al.²⁴ (GRADE score 1) reported nine cases of IE treated with linezolid for refractory disease or intolerance to other antibiotics, and in three cases as an oral consolidation treatment for outpatients. All nine patients were cured, with a reasonable length of follow-up. Seven patients had left-sided IE, and in four of them a prosthetic valve was involved. The involved agent was MSSA in four cases and MRSA in two; *E. faecalis* was isolated (in association with MRSA) in one case, while the remaining three cases were caused by *S. mutans*, *C. striatum*, and CoNS. Surgery was performed in four cases.

In single case reports, linezolid has been used with variable success. In three cases^{41–43} (GRADE score 1 for each) treatment with linezolid was associated with clinical failure. All were left-sided IE. In one case of mitral valve IE caused by MRSA⁴² (GRADE score 1), linezolid was reported to be associated with negativity of blood cultures, though the patient died because of a *Candida* sepsis. Clinical success was reported in a further three cases^{30,37,38} (GRADE score 1 for each); two were right-sided IE and one was left-sided IE; linezolid was used in combination with high dose daptomycin in one case³⁰ (GRADE score 1).

In conclusion, the use of linezolid in the treatment of IE is not supported by comparative studies; however in the 50 cases reported in the medical literature, linezolid appears to be associated with a reasonable success rate, around 50%. A selection bias must nonetheless be considered, as successful treatments are probably more likely to be published than treatment failures. In some cases^{37,45} (GRADE score 1 for each) successful treatment with linezolid after failure of other regimens was attributed to the presence of metastatic embolization in the lung and brain, respectively, while in another case complicated with cerebral embolization⁴⁶ (GRADE score 1), failure of treatment with linezolid was reported. Treatment with linezolid was associated with thrombocytopenia in about 30% of cases.

Recommendations

Linezolid can be considered in selected cases for the treatment of IE caused by Gram-positive resistant microorganisms, either alone or in combination with other antibiotics (D). Linezolid can also be used as an oral agent after an initial phase of intravenous antibiotic therapy, but this indication needs further studies (D). Owing to its peculiar pharmacokinetic profile, linezolid can also be proposed in IE caused by Gram-positive resistant microorganisms associated with metastatic septic foci (e.g., meningitis, brain abscesses, and splenic and pulmonary emboli) (D).

Quinupristin/dalfopristin

No clinical trials addressing the use of quinupristin/dalfopristin in infectious endocarditis have been reported in the literature, and also evidence from case reports is scarce. There have been reports of successful treatment with quinupristin/dalfopristin in cases of infectious endocarditis caused by MRSA, vancomycin-resistant *E. faecium*, and *S. epidermidis*, either right- or left-sided. In these successful cases, quinupristin/dalfopristin has been used either alone or in combination with other antibiotics (vancomycin; vancomycin + levofloxacin; doxycycline + rifampin). Some of these cases also underwent heart surgery. There have also been reports of failure of quinupristin/dalfopristin. The cumulative number of case reports is however very small and does not allow conclusions to be drawn.

Tigecycline

There is insufficient literature regarding the use of tigecycline in the treatment of infectious endocarditis.

Recommendations

Quinupristin/dalfopristin can be considered in selected cases in the treatment of resistant Gram-positive infectious endocarditis, especially when caused by vancomycin-resistant *E. faecium*, and preferably in combination with other antibiotics (D).

There is insufficient available evidence on the use of tigecycline in the treatment of IE.

4.8.4. Query 6

In the treatment of sepsis caused by multi-resistant Gram-positive microorganisms, is therapy with quinupristin/dalfopristin, linezolid, daptomycin, and tigecycline effective?

The literature on sepsis is somehow confusing, owing to the incorrect use of the terms bloodstream infection, sepsis, and bacteremia as synonyms. For the purpose of this study, we chose to limit the search to the MeSH term 'sepsis', but to use the term

'bloodstream infection' in the statements of the recommendations. The majority of comparative studies on the use of the new antibiotics in the treatment of sepsis^{47–51} (GRADE scores 2, 2, 1, 1, and 3, respectively) have compared linezolid with the glycopeptides vancomycin and teicoplanin. Few differences between linezolid and comparators were noted in these studies, so that it can be stated that linezolid is at least comparable to glycopeptides in the treatment of sepsis caused by resistant Gram-positive microorganisms. Only one study⁴⁹ (GRADE score 1) showed linezolid to be superior to teicoplanin, whose dosage was, however, at the discretion of the investigator. The quality of the studies is generally poor except for one study with a double-blind, double-dummy design. One out of the six studies on linezolid⁵² (GRADE score 2) was a comparative study of two different modalities of administration (continuous vs. intermittent) of the drug. There were no differences in the two arms. The limited evidence does not support continuous administration of linezolid in this condition.

In conclusion, the studies seem to show that linezolid activity is comparable to that of glycopeptides in the treatment of sepsis by Gram-positive microorganisms.

The only comparative study on quinupristin/dalfopristin⁵³ (GRADE score 2) did not show a difference with the comparator (standard treatment) in a population of patients with sepsis and severe underlying conditions. The quinupristin/dalfopristin arm had better microbiological responses, but the overall mortality was high in both groups.

No data on daptomycin and tigecycline were found.

Recommendations

In the treatment of bloodstream infections caused by multi-resistant Gram-positive microorganisms, linezolid may be used in selected cases (C). The use of continuous infusion of linezolid is currently being investigated, but it is not yet supported by the current evidence (C).

Quinupristin/dalfopristin can be considered in the treatment of selected cases of bloodstream infections caused by vancomycin-resistant *E. faecium* (C). There is insufficient evidence to support the use of tigecycline in the treatment of bloodstream infections.

4.9. Diagnostic/laboratory monitoring area

4.9.1. Query 1

In the treatment of infective endocarditis caused by multi-resistant Gram-positive microorganisms, is monitoring of plasma levels of vancomycin, gentamicin, and teicoplanin effective in reducing adverse events and costs, and increasing treatment efficacy?

The evidence to answer this query is very scarce. Monitoring of plasma levels of drugs is useful when these are critical to obtain a therapeutic effect, or when the therapeutic levels of the drugs are close to the toxic concentrations. In the treatment of infectious endocarditis, the need to maintain adequate plasma levels of drugs also has a theoretical basis, given the difficulty of attaining adequate antibiotic concentrations in the vegetations. Many studies on pharmacokinetics and/or pharmacodynamics of antibiotics have been conducted in this field, but the analysis of this type of evidence is beyond the scope of this work. In clinical practice, monitoring of plasma levels of the antibiotics used for the treatment of infective endocarditis is limited to the monitoring of vancomycin, gentamicin and, less frequently, teicoplanin. Monitoring of plasma levels of drugs is costly, so the analysis was

restricted to cost-effectiveness studies. Only two studies were retrieved, showing that monitoring of plasma levels of vancomycin can be cost-effective, and can be associated with fewer episodes of renal failure, decreased length of therapy, and possibly reduced length of stay. None of the studies, however, was conducted on populations with infective endocarditis.

In the study by Fernández de Gatta et al.⁵⁵ (GRADE score 2) the study population was composed of immunocompromised febrile patients with hematological malignancies, assigned to vancomycin either because of fever resistant to antibiotic treatment (ceftazidime + amikacin) or because of strong suspicion of infection due to Gram-positive organism. The proportion of patients with infective endocarditis is unknown. In the study by Welty and Copa⁵⁶ (GRADE score 1), only two patients (among the 116 studied) had infective endocarditis.

In conclusion, there is only indirect evidence of the clinical usefulness of therapeutic drug monitoring of antibiotics in the management of infective endocarditis, and the evidence is limited to the monitoring of vancomycin.

Recommendations

Therapeutic drug monitoring of plasma levels of vancomycin in the management of infective endocarditis is useful and probably cost-effective (C). Trough levels of at least 15–20 µg/ml should be obtained. There is a lack of published evidence regarding the use of TDM for teicoplanin. When using teicoplanin, a trough concentration of ≥ 20 µg/ml should be obtained (D). Monitoring of plasma levels of other antibiotics is supported only by animal or PK/PD studies and cannot therefore be generalized to all clinical situations (D).

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Conflict of interest

All members of the faculty of GISIG – E. Boumis, G. Carosi, G. Gesu, G. Ippolito, F.N. Lauria, F. Menichetti, M. Moroni, E. Nicastrì, M. Ranieri, M. Rinaldi and F. Suter – report no other potential conflict of interest except as reported in the specific section.

The members of the working group have no specific conflict of interest to report.

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For the present research, except for G. Gesu, all members of the faculty of GISIG received a fee from the organizing secretariat of the GISIG Project.

The members of the working group have no funding to report.

Additional Conflict of interest

G. Ippolito and F.N. Lauria have received expert opinion fees from Pfizer. E. Nicastrì has received paid expert opinion fees from MSD and Pfizer. F. Suter has served as a consultant on advisory boards for Bristol-Myers-Squibb, and Roche, he has also served as speaker for GlaxoSmithKline and Boehringer Ingelheim, and has received research and educational grants from Bristol, Gilead, Boehringer, GSK, Janssen-Cilag, and Roche.

Appendix A. Inclusion criteria and search strings for each query

Therapeutic area	Inclusion criteria	Search string
1. In the treatment of infective endocarditis caused by Gram-positive microorganisms, is combination therapy with an aminoglycoside plus another antibiotic more effective than monotherapy?	Population: adults with infective endocarditis caused by a Gram-positive microorganism Intervention: treatment with an antibiotic Comparator: treatment with another drug or schedule Outcome: clinical success; mortality; hospital stay; costs Description of studies: randomized controlled trials; other comparative studies (also retrospective); systematic revisions; meta-analyses	('endocarditis'[MeSH Terms] OR 'endocarditis'[All Fields]) AND ('humans'[MeSH Terms] AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Comparative Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Multicenter Study[ptyp])) AND 'adult'[MeSH Terms] ^a
2. In the treatment of infective endocarditis caused by Gram-positive microorganisms, is therapy with an aminoglycoside in a single daily dose more effective than therapy in three divided doses?	Population: adults with infective endocarditis caused by a Gram-positive microorganism Intervention: treatment with an antibiotic Comparator: treatment with another drug or schedule Outcome: clinical success; mortality; hospital stay; costs Description of studies: randomized controlled trials; other comparative studies (also retrospective); systematic revisions; meta-analyses	('endocarditis'[MeSH Terms] OR 'endocarditis'[All Fields]) AND ('humans'[MeSH Terms] AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Comparative Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Multicenter Study[ptyp])) AND 'adult'[MeSH Terms] ^a
3. In the treatment of infective endocarditis caused by Gram-positive microorganisms, is therapy with teicoplanin as effective, and associated with fewer adverse events, than therapy with vancomycin?	Population: adults with infective endocarditis caused by a Gram-positive microorganism Intervention: treatment with an antibiotic Comparator: treatment with another drug or schedule Outcome: clinical success; mortality; hospital stay; costs Description of studies: randomized controlled trials; other comparative studies (also retrospective); systematic revisions; meta-analyses	('endocarditis'[MeSH Terms] OR 'endocarditis'[All Fields]) AND ('humans'[MeSH Terms] AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Comparative Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Multicenter Study[ptyp])) AND 'adult'[MeSH Terms] ^a
4. In the treatment of infective endocarditis caused by Gram-positive microorganisms, what is the optimal duration of treatment?	Population: adults with infective endocarditis caused by a Gram-positive microorganism Intervention: treatment with an antibiotic Comparator: treatment with another drug or schedule Outcome: clinical success; mortality; hospital stay; costs Description of studies: randomized controlled trials; other comparative studies (also retrospective); systematic revisions; meta-analyses	('endocarditis'[MeSH Terms] OR 'endocarditis'[All Fields]) AND ('humans'[MeSH Terms] AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Comparative Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Multicenter Study[ptyp])) AND 'adult'[MeSH Terms] ^a
5. In the treatment of infective endocarditis caused by multi-resistant Gram-positive microorganisms, is therapy with quinupristin/dalfopristin, linezolid, daptomycin and tigecycline effective?	Population: adults with infective endocarditis caused by a Gram-positive microorganism Intervention: treatment with quinupristin/dalfopristin, daptomycin, linezolid or tigecycline Comparator: treatment with other drugs Outcome: clinical success; mortality; hospital stay; costs Description of studies: randomized controlled trials; other comparative studies (also retrospective); systematic revisions; meta-analyses	('linezolid '[Substance Name] OR 'tigecycline '[Substance Name] OR 'Daptomycin'[MeSH] OR 'quinupristin-dalfopristin '[Substance Name]) AND 'endocarditis/drug therapy'[MeSH] AND ('humans'[MeSH Terms] AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Comparative Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Multicenter Study[ptyp]))
6. In the treatment of sepsis caused by multi-resistant Gram-positive microorganisms, is therapy with quinupristin/dalfopristin, linezolid, daptomycin and tigecycline effective?	Population: adults with sepsis caused by a Gram-positive microorganism Intervention: treatment with quinupristin/dalfopristin, daptomycin, linezolid or tigecycline Comparator: treatment with other drugs Outcome: clinical success; mortality; hospital stay; costs Description of studies: randomized controlled trials; other comparative studies (also retrospective); systematic revisions; meta-analyses	('linezolid '[Substance Name] OR 'tigecycline '[Substance Name] OR 'Daptomycin'[MeSH] OR 'quinupristin-dalfopristin '[Substance Name]) AND 'Sepsis'[MeSH] AND ('humans'[MeSH Terms] AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Comparative Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Multicenter Study[ptyp]))
7. In the treatment of infections of vascular prostheses caused by multi-resistant Gram-positive microorganisms, is therapy with quinupristin/dalfopristin, linezolid, daptomycin and tigecycline effective?	Population: adults with infection of vascular prostheses caused by a Gram-positive microorganism Intervention: treatment with quinupristin/dalfopristin, daptomycin, linezolid or tigecycline Comparator: treatment with other drugs Outcome: clinical success; mortality; hospital stay; costs Description of studies: randomized controlled trials; other comparative studies (also retrospective); systematic revisions; meta-analyses	('Prosthesis-Related Infections'[MeSH] AND 'drug therapy '[Subheading]) AND 'Blood Vessel Prosthesis'[MeSH] ^a

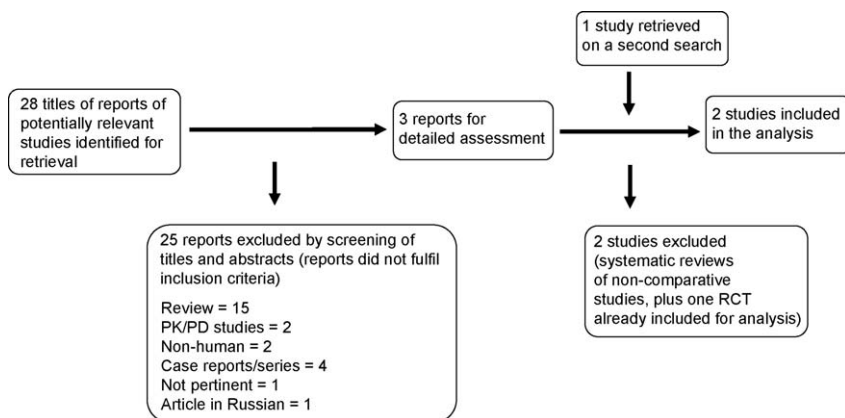
^a With a more specific search strategy no study was retrieved.

Diagnostic/laboratory monitoring area

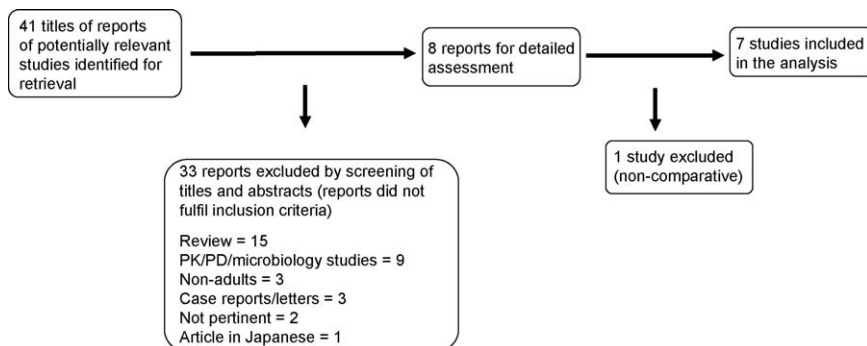
Query	Inclusion criteria	Search string
1. In the treatment of infective endocarditis caused by multi-resistant Gram-positive microorganisms, is monitoring of plasma levels of vancomycin, gentamicin and teicoplanin effective in reducing adverse events and costs, and in increasing treatment efficacy?	Population: adults with infective endocarditis caused by a Gram-positive microorganism Intervention: treatment with monitoring of plasma levels of antibiotics Comparator: treatment without monitoring Outcome: clinical success; mortality; hospital stay; costs Description of studies: randomized controlled trials; other comparative studies (also retrospective); systematic revisions; meta-analyses	(('Teicoplanin'[MeSH] OR 'Vancomycin'[MeSH]) OR 'Gentamicin'[MeSH]) AND 'Drug Monitoring'[MeSH] AND ('humans'[MeSH Terms] AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Comparative Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Multicenter Study[ptyp])) AND 'adult'[MeSH Terms])
2. In the treatment of infective endocarditis caused by multi-resistant Gram-positive microorganisms, is the use of serum bactericidal and synergy testing (along with traditional methods such as MIC determination) effective in reducing adverse events and costs, and in increasing treatment efficacy?	Population: adults with infective endocarditis caused by a Gram-positive microorganism Intervention: treatment with use of serum bactericidal and synergy testing Comparator: treatment without this testing Outcome: clinical success; mortality; hospital stay; costs Description of studies: randomized controlled trials; other comparative studies (also retrospective); systematic revisions; meta-analyses	((synergy[All Fields] AND ('research design'[MeSH Terms] OR ('research'[All Fields] AND 'design'[All Fields]) OR 'research design'[All Fields] OR 'testing'[All Fields])) OR (bactericidal[All Fields] AND ('serum'[MeSH Terms] OR 'serum'[All Fields]))) AND ('endocarditis'[MeSH Terms] OR 'endocarditis'[All Fields]) AND ('humans'[MeSH Terms] AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Comparative Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Multicenter Study[ptyp])) AND 'adult'[MeSH Terms])

Appendix B. Flow charts with details of the results of the research for each query

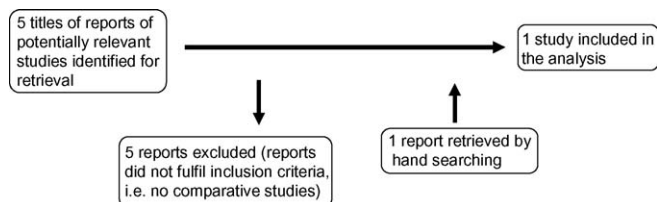
Results of MEDLINE search – Query 5 – therapeutic area



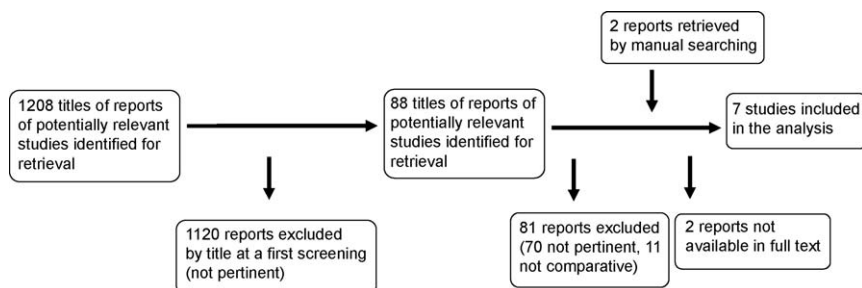
Results of MEDLINE search – Query 6 – therapeutic area



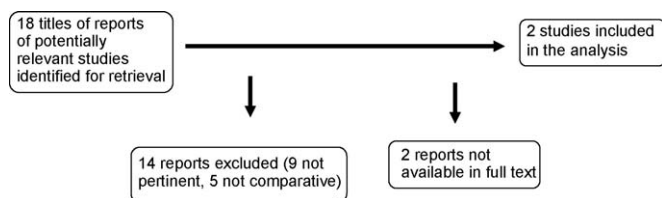
Results of MEDLINE search – Query 7 – therapeutic area



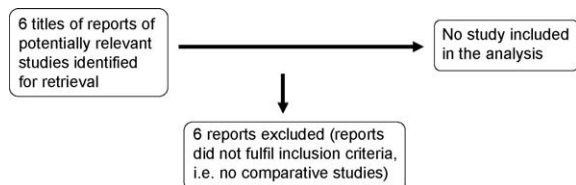
Results of MEDLINE search – Queries 1–4 – therapeutic area



Results of MEDLINE search – Query 1 – diagnostic/laboratory monitoring area



Results of MEDLINE search – Query 2 – diagnostic/laboratory monitoring area



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