

Guidelines for the antibiotic treatment of endocarditis in adults: report of the Working Party of the British Society for Antimicrobial Chemotherapy

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The BSAC Guidelines on Endocarditis were last published in 1998. The Guidelines presented here have been updated and extended to reflect changes in both the antibiotic resistance characteristics of causative organisms and the availability of new antibiotics. Randomized, controlled trials suitable for the development of evidenced-based guidelines in this area are still lacking, and therefore a consensus approach has again been adopted. The Guidelines cover diagnosis and laboratory testing, suitable antibiotic regimens and causative organisms. Special emphasis is placed on common causes of endocarditis, such as streptococci and staphylococci, however, other bacterial causes (such as enterococci, HACEK organisms, *Coxiella* and *Bartonella*) and fungi are considered. The special circumstances of prosthetic endocarditis are discussed.

Keywords: antibiotic therapy, guidelines, endocarditis, BSAC

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1. Introduction

In 1998, the Endocarditis Working Party of the British Society for Antimicrobial Chemotherapy published updated guidelines for the treatment of streptococcal, enterococcal and staphylococcal endocarditis.¹ In the light of the introduction of new antibiotic agents and the emergence of increasingly antibiotic-resistant bacteria causing endocarditis the existing guidelines have been revised. They have been widened to include recommendations for the treatment of other bacterial and fungal causes of endocarditis.

Guidelines such as these have, in the past, received criticism for not being evidence based. Whereas we appreciate that the gold standard for all clinical guidelines should ideally be based

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on good, prospective, randomized controlled trials, no such trials have ever been performed to assess the benefit of antibiotic regimens in the treatment of endocarditis. Consequently we have not attempted to classify the evidence for our recommendations, which remain consensus based. An extensive review of the literature—encompassing a number of different search methods and a range of criteria (e.g. endocarditis, staphylococci, etc.)—has been carried out, and publications used to support any changes we have made to the existing guidelines have been cited. Publications referring to *in vitro* or animal models have only been cited if appropriate clinical data are not available.

2. Diagnosis and laboratory testing

Since 1994, the Duke criteria have formed the basis for the diagnosis of infective endocarditis (IE).² Major diagnostic criteria include positive blood cultures or positive echocardiogram. A range of minor criteria are included in the Duke strategy and supplementary criteria have since been proposed to enhance diagnosis further.^{3–6}

In terms of laboratory testing, blood culture remains the cornerstone of diagnosis for the vast majority of IE cases. Patients with suspected IE, such as those with pyrexia and a heart murmur, should have blood cultures taken promptly before antimicrobial chemotherapy is given. Three sets of blood cultures should be taken in the first 24 h from separate venepunctures. It is recommended that at least 30 mL of blood is cultured in total.⁷ The timing of the initiation of therapy after this period depends upon the condition of the patient. In patients who are acutely ill, three sets of blood cultures should be taken within 2 h before starting empirical therapy.

Blood cultures should be incubated for a minimum of 7 days, which should result in a positive culture for 95% of IE cases.⁷ In exceptional circumstances, where blood cultures remain negative after 7 days in the absence of prior antibiotic therapy, and IE remains strongly suspected, extended incubation of cultures should be initiated that may facilitate the isolation of some fastidious microorganisms.^{3,8–10} In such cases, incubation of blood cultures should be continued for at least 3 weeks, with weekly subculture onto chocolate agar, which in turn should be incubated for 3 weeks in air plus 5% carbon dioxide.

Once the causative microorganism has been isolated, susceptibility testing should be performed with suitable antimicrobials. The choice and duration of treatment depend upon the type of microorganism and its susceptibility profile, allergy to antimicrobials and whether infection involves a native or prosthetic valve. A cidal antimicrobial, or combination of antimicrobials, is required to eradicate infection. A minimum inhibitory concentration (MIC) of the chosen antimicrobial should be established by a standardized laboratory method to ensure susceptibility.¹¹ Etest strips may be useful for establishing the susceptibility of fastidious or slow-growing bacteria, such as the HACEK group¹² (*Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* spp., and *Kingella* spp.).

As in previous guidelines¹ we do not recommend routine measurement of the minimum bactericidal concentration (MBC). MBC determination is affected by a range of technical factors that result in poor intra-laboratory reproducibility and there remains a lack of evidence regarding its clinical value. For the

same reasons, the measurement of serum bactericidal titres is not recommended as a routine assay.

Failure to culture a causative microorganism in IE is most commonly due to the administration of antimicrobials prior to sampling, but may also be due to IE caused by fastidious or slow-growing microorganisms. Possible microorganisms that should be considered include the HACEK group, *Bartonella* spp., *Brucella* spp., *Chlamydia* spp., *Coxiella burnetii* (Q-fever), *Legionella* spp., mycobacteria and various fungi.^{3,13–15} Diagnostic methods should include serological investigations where they are available, and such methods are central to the identification of *Bartonella* spp., *Brucella* spp., *Chlamydia* spp., *C. burnetii*, *Legionella pneumophila* and *Mycoplasma pneumoniae*. A systematic approach to the serological diagnosis of culture-negative IE is advised, based on the clinical history of the patient and their exposure to possible risk factors.^{13–16} Molecular techniques for the detection of microbial nucleic acids show promise as an adjunct to existing methods for the diagnosis of endocarditis caused by fastidious or slow-growing microorganisms.^{17–22}

3. Antibiotic regimens

3.1 Aminoglycosides

Gentamicin dosage regimens are based on 8 hourly administration of 1 mg/kg body weight, intravenously (iv)/intramuscularly (im). Once-daily regimens are now widely used for other infections, but data regarding their efficacy in endocarditis are limited. Levels should be measured regularly to ensure pre-dose (trough) levels remain <1 mg/L. Maintaining post-dose (peak) levels between 3–5 mg/L has been advocated by other authorities, although the evidence to support this is limited. Where a patient has normal renal function that is stable, twice weekly monitoring may suffice. In patients with impaired renal function, dosage should be adjusted according to measured or estimated creatinine clearance and drug monitoring results, and levels monitored on a daily basis.

Streptomycin dosage is usually 7.5 mg/kg body weight 12 hourly and should be monitored at least twice weekly, (more often in renal impairment—see above) by maintaining pre-dose levels <3 mg/kg, and adjusted according to renal function as with gentamicin.

3.2 Glycopeptides

3.2.1 Vancomycin. For patients with normal renal function we recommend 1 g iv 12 hourly. Levels should be monitored to maintain a pre-dose level between 10–15 mg/L, although in enterococcal endocarditis some authorities recommend pre-dose levels of 10–20 mg/L. Further monitoring and dose adjustment in patients with impaired renal function should be performed as for aminoglycosides.

3.2.2 Teicoplanin. Teicoplanin must be administered at a high dosage (10 mg/kg body weight 12 hourly then 10 mg/kg daily). Trough levels must be measured to ensure levels of at least 20 mg/L and repeated at least weekly.

3.3 β -Lactams

In our recommendations for sensitive organisms, amoxicillin/ampicillin 2 g iv 4–6 hourly may be used instead of benzyl

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Table 1. Recommendations for empirical therapy

Acute presentation	Flucloxacillin (8–12 g iv daily in 4–6 divided doses) plus gentamicin (1 mg/kg body weight iv 8 hourly, modified according to renal function)
Indolent presentation	Penicillin (7.2 g iv daily in 6 divided doses) or ampicillin/amoxicillin (2 g iv 6 hourly) plus gentamicin (1 mg/kg body weight 8 hourly iv, modified according to renal function)
Penicillin allergy Intra-cardiac prosthesis Suspected MRSA	Vancomycin (1 g 12 hourly iv, modified according to renal function) plus rifampicin (300–600 mg 12 hourly by mouth) plus gentamicin (1 mg/kg body weight 8 hourly iv, modified according to renal function)

penicillin. The time-dependent killing of streptococci by penicillin means that the drug should be given at least six times a day because of its short serum half-life. There are theoretical and experimental reasons for using a continuous infusion of penicillin.²³ There are, however, no prospective comparisons of continuous with intermittent penicillin for streptococcal endocarditis. Dosage modifications for β -lactams may be necessary in patients with impaired renal function and according to the patient's body weight.

3.4 Alternative antibiotics for patients with penicillin allergy

It is important to establish the nature of a reported 'allergy' to penicillin, as there is less experience with alternative antibiotics and a higher rate of side effects. For example, a history of a rash with ampicillin or amoxicillin may not indicate true allergy. Unless signs of immediate-type hypersensitivity (anaphylaxis, angio-oedema, bronchospasm, urticaria) were reported, a trial with penicillin may be warranted. The American Heart Association (AHA) advises ceftriaxone for the penicillin-allergic patient—but this should only be used for allergy other than immediate-type hypersensitivity because of the risk of cross-sensitivity with penicillin.

3.5 Empirical therapy

See Table 1 for a summary. Bacterial endocarditis (particularly prosthetic or *Staphylococcus aureus* endocarditis) may progress rapidly and in such cases antibiotic therapy must be commenced as soon as all the appropriate specimens have been collected. If the diagnosis of endocarditis is in doubt, the patient is clinically stable and has already received antibiotics, we recommend stopping any antibiotics for 2–4 days and re-culturing.

If empirical therapy is indicated, we recommend a combination of flucloxacillin (8–12 g daily in 4–6 divided doses) plus gentamicin (1 mg/kg body weight 8 hourly according to renal function) if the patient is acutely unwell, or penicillin (or ampicillin/amoxicillin) plus gentamicin if the presentation is more indolent. If the patient has intra-cardiac prosthetic material, or MRSA is suspected, we recommend vancomycin (1 g 12 hourly according to renal function) plus rifampicin (300–600 mg 12 hourly, orally) plus gentamicin (1 mg/kg 8 hourly iv). Therapy should be reviewed as soon as the aetiological agent is identified.

3.6 Duration of therapy

Apart from the treatment of certain strains of penicillin-sensitive streptococci, we recommend a minimum of 4 weeks therapy. There is evidence from patients with enterococcal endocarditis and some data from early studies of streptococcal endocarditis to suggest that patients who have had symptoms for more than 3 months benefit from 6 weeks of penicillin.^{24–25} Often these individuals have larger vegetations and mitral valve disease (also indicators of a poorer response). These factors should be taken into consideration when determining treatment length. Apparent failure to respond to treatment may indicate the need for surgical intervention. There is no evidence to support the use of oral 'follow-on' therapy after completion of a course of treatment.

3.7 Home therapy

Home therapy for endocarditis has been described. Suitability for home therapy will depend on the patient, the availability of the infrastructure to support such therapy and the sensitivity of the infecting organism to antibiotics, which lend themselves to home therapy.

Home treatment is often considered for streptococcal endocarditis, as it can be less destructive, with fewer complications, than infection caused by other organisms. Trials of home therapy have been reviewed.^{26,27} Antibiotics such as ceftriaxone or teicoplanin, which can be given once daily iv or im, have been advocated as the patient may not need a central venous catheter. Neutropenia is, however, a well described side effect of ceftriaxone, occurring in two of 55 patients in one study.²⁸ Teicoplanin also has side effects, including a high rate of drug fever (see section 5.8).

4. Staphylococcal endocarditis

See Table 2 for a summary. The choice of treatment for staphylococcal endocarditis will depend more on the antibiotic sensitivity of the isolate than whether it is coagulase positive or negative. In the previous guidelines, therapy with benzyl penicillin was recommended for penicillin-sensitive strains. In practice, such strains are uncommon.

For methicillin-sensitive strains, we recommend flucloxacillin 2 g 6 hourly^{29,30} increasing to 2 g 4 hourly in patients weighing >85 kg. There is no evidence that the addition of gentamicin is

Table 2. Summary of treatment recommendations for staphylococcal endocarditis

Methicillin sensitive	Flucloxacillin (2 g 4–6 hourly iv)
Methicillin resistant/penicillin allergy	Vancomycin (1 g iv 12 hourly), modified according to renal function plus rifampicin (300–600 mg 12 hourly by mouth)* or gentamicin (1 mg/kg body weight 8 hourly, modified according to renal function)* or sodium fusidate (500 mg 8 hourly by mouth)*
Endocarditis in presence of intracardiac prosthesis	Flucloxacillin (2 g 4–6 hourly iv) or vancomycin (1 g iv 12 hourly, modified according to renal function) plus rifampicin (300–600 mg 12 hourly by mouth)* and/or gentamicin (1 mg/kg body weight 8 hourly, modified according to renal function)* and/or sodium fusidate (500 mg 8 hourly by mouth)*

*According to sensitivity.

more likely to result in a successful outcome, but it is associated with an increased incidence of adverse effects.^{31,32} Therefore, we no longer recommend its routine use in the treatment of staphylococcal endocarditis. There is no evidence that the addition of sodium fusidate offers any advantage,³³ and the benefit of rifampicin is also controversial.³⁴ For methicillin-resistant strains, or in patients with penicillin allergy we recommend vancomycin 1 g 12 hourly. Levels should be monitored and trough levels maintained between 10–15 mg/L. Owing to the reported incidence of treatment failure, we do not recommend the routine use of teicoplanin in the treatment of staphylococcal endocarditis.^{35–37} As vancomycin is less active than flucloxacillin,^{38,39} we recommend the addition of a second antibiotic to the treatment regimen. The choice of the second antibiotic will depend on the sensitivity of the infecting organism, with rifampicin^{40,41} as the preferred choice, but may include gentamicin or sodium fusidate.⁴²

4.1 Prosthetic endocarditis

The complex nature of staphylococcal infection of prostheses leads us to recommend combination therapy including rifampicin (if sensitive) for both methicillin-sensitive and -resistant strains of staphylococci for at least the first 2 weeks of therapy. If the isolate is resistant to rifampicin, other agents may be considered (see above). The use of three antibiotics (if the isolate is sensitive) has been advocated by some authorities.⁴³

4.2 Duration of therapy

The majority of patients will require at least 4 weeks therapy, which should be extended to at least 6 weeks in patients with intra-cardiac prostheses, and after removal of infected permanent pacing. However, in patients with right-sided endocarditis (often iv drug abusers), several trials have demonstrated the efficacy of short course iv combination therapy^{32,44–48} and oral therapy.⁴⁹ Other studies have demonstrated that iv to oral switch therapy to complete a course of antibiotics is effective,⁵⁰ and may be considered in selected patients, for whom iv access is difficult.

4.3 New antibiotics

Since the publication of the last guidelines, new antibiotics such as linezolid⁵¹ and quinupristin/dalfopristin⁵² have become available. The use of these agents in the treatment of endocarditis has been described in the literature, but experience is still limited. We would only recommend the use of such agents as salvage therapy, in patients unable to tolerate conventional therapy, or from whom particularly resistant stains have been recovered. Similarly, the use of co-trimoxazole, quinolones and clindamycin has also been described in the literature, but we cannot advocate their routine use.^{53–56}

5. Streptococcal endocarditis

See Table 3 for a summary. Streptococci are common causes of native valve and late prosthetic valve endocarditis. They vary in their susceptibility to penicillin and degree of resistance to aminoglycosides. Early clinical studies showed that short courses (10–14 days) with standard doses of penicillin had a high relapse rate, even for streptococci that were extremely sensitive. The combination of penicillin with an aminoglycoside gave better results than penicillin alone, especially for streptococci that were relatively penicillin resistant or tolerant. A well considered review of clinical evidence plus animal and *in vitro* studies led to the development of the AHA guidelines for the treatment of streptococcal endocarditis.⁴³ We propose that they should be used, but there are areas where we would modify or expand the advice as follows (see also Table 1).

5.1 'Viridans-type' streptococci

For native valve endocarditis, there is evidence that 4 weeks of high-dose penicillin can be used for sensitive streptococci (MIC ≤ 0.1 mg/L), and that short-course treatment (2 weeks penicillin in combination with gentamicin) may be as effective. The short regimen should not be used if there is an intra-cardiac abscess or infected emboli. The AHA recommends 4 weeks penicillin plus gentamicin for the first 2 weeks for relatively

Table 3. Summary of treatment options for streptococcal endocarditis

Penicillin MIC (mg/L)	Penicillin and gentamicin 2 weeks ^a	Penicillin 4 weeks	Ceftriaxone 4 weeks	Vancomycin 4 weeks	Ampicillin or amoxicillin by continuous infusion	Vancomycin or penicillin 4–6 weeks and gentamicin 2 weeks	Penicillin 4–6 weeks and gentamicin 4–6 weeks	Vancomycin 4–6 weeks and gentamicin 4–6 weeks
Viridans streptococci and <i>S. bovis</i>								
≤0.1	✓	✓	✓	✓				
>0.1 – <0.5		✓ ^b		✓ ^b		✓		
0.5 – <16					✓ ^b		✓	✓
≥16								✓
Group A streptococcus								
		✓	✓	✓				
Group B, C, G streptococcus								
<0.5						✓		
≥0.5							✓	✓
<i>S. pneumoniae</i>								
<0.1		✓	✓	✓				
≥0.1			✓ ^c	✓				
Nutritionally variant streptococci								
							✓ ^d	✓ ^d
Prosthetic valve endocarditis								
≤0.1						✓ ^d		
>0.1							✓ ^d	✓ ^d

Streptomycin is an alternative to gentamicin for streptomycin-sensitive, gentamicin-resistant isolates. (See sections on susceptibility testing, drug toxicity and monitoring levels.)

^aPenicillin and gentamicin for 2 weeks should not be used if there is an intracardiac abscess or extra-cardiac focus of infection.

^bIf gentamicin or streptomycin is contraindicated (unacceptable risk of toxicity or a resistant bacterium).

^cUse only for isolates that are susceptible to ceftriaxone (MIC < 0.5 mg/L).

^dSix weeks treatment.

Dosage (NB all need to be adjusted in renal impairment): penicillin, 1.2–2.4 g, 4 hourly or by continuous infusion; gentamicin, 1 mg/kg (ideal body weight), 8–12 hourly; ampicillin or amoxicillin, 12 g, over 24 h; vancomycin, 1 g, 12 hourly; streptomycin, 7.5 mg/kg body weight, 12 hourly.

resistant strains of viridans streptococci (penicillin MIC >0.1–<0.5 mg/L), but there is little evidence for this. We would agree that aminoglycosides should ideally be given for the first 2 weeks, but where the risks of using aminoglycosides are high, 4 weeks penicillin alone at the higher dose (2.4 g 4 hourly, adjusted for renal function) could be tried. The treatment of more resistant viridans streptococci (penicillin MIC ≥ 0.5 mg/L) should follow the recommendations for treating enterococci.

5.2 *Streptococcus bovis*

Streptococcus bovis should be treated using the same regimens for the viridans-type streptococci, based on the penicillin MIC. There is a strong association between endocarditis due to *S. bovis* and benign and malignant tumours of the gut and liver disease.⁵⁷ It is easy in our experience to neglect investigation of the gut in the understandable drive to treat the endocarditis.

5.3 Nutritionally variant streptococci (NVS)

Endocarditis with NVS is characterized by an indolent course, frequent embolization and bacteriological relapse. Many NVS are relatively resistant to penicillin and show tolerance. Antibiotic susceptibility testing is difficult and may need to be carried out by a specialist laboratory. Four to six weeks of penicillin plus an aminoglycoside is recommended.⁵⁸ Until more evidence is available on alternatives, NVS should also be treated according to the recommendations for treating enterococci. In view of the high relapse rate, blood should be cultured weekly during treatment and after completion of therapy.

5.4 *Streptococcus pneumoniae*

Pneumococcal endocarditis is usually associated with pneumonia and/or meningitis.⁵⁹ The high mortality (28%–60%) seems due to the destructive nature of the disease and patient factors rather than inadequate antibiotic treatment, as no bacteriological relapses were seen in patients with sensitive pneumococci treated with penicillin alone. There is little experience with high-level penicillin-resistant pneumococci, but a similar approach to the treatment of resistant pneumococcal meningitis is proposed, using ceftriaxone or vancomycin.⁶⁰

5.5 *Streptococcus pyogenes* (Group A streptococcus)

Group A streptococci often behaves like *S. aureus*, causing acute destructive endocarditis and right-sided disease in iv drug abusers. Four weeks penicillin alone for these sensitive organisms has had a good success rate and is recommended.⁶¹

5.6 *Streptococcus agalactiae* (Group B streptococcus), Group C and G streptococci

Group B streptococci can cause acute endocarditis with a high mortality, often in patients with diabetes.⁶² Some strains are tolerant and relatively penicillin resistant; there is very little published on treatment. We therefore endorse the AHA cautionary approach of recommending 2 weeks of aminoglycosides in addition to 4 weeks penicillin for even sensitive strains. As information on endocarditis caused by group C and G streptococci is so limited, 4 weeks penicillin with 2 weeks gentamicin is also recommended.

5.7 Prosthetic valve endocarditis (PVE)

There is limited evidence on the optimum treatment of streptococcal PVE infections, and sensitive organisms may be difficult to treat. This is partly due to the involvement of the valve ring and myocardial abscesses. Early studies showed a high relapse rate with 2 weeks penicillin plus an aminoglycoside. We agree with the recommendation of a minimum of 6 weeks of penicillin, plus gentamicin for the first 2 weeks, for penicillin-sensitive streptococci (MIC ≤ 0.1 mg/L).⁶³ The same author advises 6 weeks penicillin with 4 weeks gentamicin for more penicillin-resistant strains, but there are no studies comparing 4 and 6 weeks gentamicin. In view of the difficulty in replacing a prosthetic valve and the toxicity from a second course of aminoglycosides should initial treatment fail, it seems prudent to give 6 weeks of gentamicin (see Table 1) with penicillin for strains with a penicillin MIC >0.1 mg/L.

5.8 Treatment of streptococcal endocarditis for patients allergic to penicillin

Vancomycin tolerance is said to be common, but there is evidence of synergy with aminoglycosides. The AHA advises 4 weeks of vancomycin alone for moderately penicillin-resistant streptococci (MIC >0.1 <0.5 mg/L). There is no clinical evidence to justify the omission of an aminoglycoside and the clinician has to balance the potential risks of toxicity against concern over relapse that could lead to a longer course of a potentially toxic combination. With close monitoring of vancomycin and gentamicin levels, we would advise vancomycin for 4 weeks with gentamicin for the first 2 weeks, for moderately resistant streptococci. Teicoplanin is considered less nephrotoxic by some, both alone and in combination with gentamicin. There is, however, less experience with its use and in early studies many patients on long-term teicoplanin developed drug fever.⁶⁴ A dose of 6 mg/kg is advised for streptococcal endocarditis. Loading doses should be given and a trough level of 15 mg/L established.⁶⁵ We recommend just a single measurement to establish a therapeutic level if the renal function is stable. Following a single report of *S. bovis* carrying the *vanB* gene,⁶⁶ a vancomycin MIC should be measured for streptococci, rather than relying on disc-diffusion testing.

6. Enterococcal endocarditis

Enterococci are responsible for ~10% of endocarditis episodes, an incidence that has remained stable since the introduction of penicillin. *Enterococcus faecalis* accounts for the majority of cases, but other species such as *Enterococcus faecium*, *Enterococcus durans* and *Enterococcus gallinarum* are occasionally implicated. Older men (mean age, >60 years) are most commonly affected, but younger women may also be affected in association with pregnancy. Over 40% of the patients have no underlying heart disease. Although one study has shown worse outcomes in patients with more than 3 months of symptoms prior to presentation,⁶⁷ a more recent analysis has failed to corroborate these findings.⁶⁸

Treatment of native valve infection requires a minimum of 4 weeks of iv antibiotics, whereas prosthetic valve endocarditis should be treated for a minimum of 6 weeks (see earlier comments on duration of therapy). Thereafter, the clinical response

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Table 4. Recommended regimens for treatment of enterococcal endocarditis caused by an ampicillin-susceptible (MIC ≤ 8 mg/L) isolate

Antimicrobial regimen	Dose and route	Duration (weeks)	Comment
1. Ampicillin (or penicillin) plus gentamicin ^a	2 g 4 hourly iv (2.4 g 4 hourly) 1 mg/kg 8–12 hourly iv	≥4 ≥4	
2. Vancomycin plus gentamicin ^a	1 g 12 hourly iv 1 mg/kg 8–12 hourly iv	≥4 ≥4	alternative for penicillin-allergic patient provided isolate is vancomycin susceptible (MIC ≤ 4 mg/L)
3. Teicoplanin plus gentamicin ^a	10 mg/kg 24 hourly iv 1 mg/kg 8–12 hourly iv	≥4 ≥4	alternative for penicillin-allergic patient provided isolate is teicoplanin susceptible (MIC ≤ 4 mg/L)

^aProvided isolate is high-level gentamicin-susceptible (MIC ≤ 128 mg/L).

Table 5. Regimens for treatment of enterococcal endocarditis caused by high-level gentamicin-resistant (MIC > 128 mg/L) isolate

Antimicrobial regimen	Dose and route	Duration (weeks)	Comment
1. Ampicillin (or penicillin) plus streptomycin ^a	2 g 4 hourly iv (2.4 g iv 4 hourly) 7.5 mg/kg 12 hourly im	≥4 ≥4	ampicillin-susceptible isolate (MIC ≤ 8 mg/L)
2. Vancomycin plus streptomycin ^a	1 g 12 hourly iv 7.5 mg/kg 12 hourly im	≥4 ≥4	alternative for penicillin-allergic patient or ampicillin-resistant (MIC > 8 mg/L) isolate
3. Teicoplanin plus streptomycin ^a	10 mg/kg 24 hourly iv 7.5 mg/kg 12 hourly im	≥4 ≥4	alternative for penicillin-allergic patient or ampicillin-resistant (MIC > 8 mg/L) isolate

^aStreptomycin can be added if the isolate is not high-level resistant. If streptomycin is considered inappropriate or the isolate is streptomycin resistant, the cell-wall acting agent should be continued for a minimum of 8 weeks.

Table 6. Regimens for treatment of enterococcal endocarditis caused by an ampicillin-resistant isolate (MIC > 8 mg/L)

Antimicrobial regimen	Dose	Duration (weeks)
1. Vancomycin plus gentamicin ^a	1 g 12 hourly iv 1 mg/kg 8–12 hourly iv	≥4 ≥4
2. Teicoplanin plus gentamicin ^a	10 mg/kg 24 hourly iv 1 mg/kg 8–12 hourly iv	≥4 ≥4

^aIf high-level gentamicin-susceptible (MIC ≤ 128 mg/L) isolate.

to therapy, inflammatory markers, repeat cultures and echocardiographic findings should guide the need for further antibiotics. Recommended regimens for the more frequently encountered resistance patterns are given in Tables 4–6. Endocarditis caused by penicillin-resistant, glycopeptide-resistant, high-level aminoglycoside-resistant enterococci is reported infrequently. In the event of such a case, antimicrobial options include linezolid, or quinupristin/dalfopristin or combinations of antibiotics according to *in vitro* susceptibility and new agents in development. Endocarditis caused by isolates displaying a

VanB phenotype (vancomycin resistant, teicoplanin susceptible) have been treated with teicoplanin, but resistance may develop during monotherapy with this agent and treatment failures have occurred.⁶⁹

7. HACEK endocarditis

The HACEK group of microorganisms includes *Haemophilus parainfluenzae*, *Haemophilus influenzae*, *Haemophilus aphrophilus*, *Haemophilus paraphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella spp.* These fastidious extracellular Gram-negative bacteria cause an estimated 3% of all cases of IE.^{16,58,70–74}

Previously, treatment was based on ampicillin and gentamicin. As a result of the emergence of β-lactamase-producing strains, a β-lactamase-stable cephalosporin should be selected for empirical treatment.^{12,43} Native valve IE should receive 4 weeks of treatment and those with prosthetic valve IE, 6 weeks.

Treatment

If amoxicillin sensitive, 2 g amoxicillin/ampicillin should be administered iv 4–6 hourly, plus gentamicin 1 mg/kg body

weight according to renal function (for the first 2 weeks only). Monitoring should be regular. If amoxicillin resistant: ceftriaxone 2 g should be administered (to a maximum of 4 g) iv (once daily) plus gentamicin as above.

8. Q fever

C. burnetii is an obligate intracellular pathogen. Endocarditis is the prime manifestation of chronic Q-fever^{16,75,76} and *C. burnetii* causes up to 3% of all cases of IE in England and Wales.⁷⁷ The estimated incidence of IE in those who contract Q-fever ranges from 7%⁷⁸ to 67%.⁷⁹ Patients likely to develop Q-fever IE are those with predisposing valvular damage or prosthetic heart valves.⁸⁰ Antibody titres should be determined every 6 months while on treatment and then every 3 months once treatment has been discontinued, for a minimum of 2 years. Long-term treatment (3 years) with tetracycline and a quinolone has been recommended.^{81,82}

Treatment

Doxycycline 100 mg should be administered once daily orally, plus ciprofloxacin 500 mg 8 hourly orally for at least 3 years.

9. Bartonella endocarditis

Bartonella spp. are facultative intracellular Gram-negative aerobic bacteria that cause up to 3% of all cases of IE.^{14,16,83–89}

Treatment

Amoxicillin/ampicillin 2 g iv should be administered 4–6 hourly, plus gentamicin 1 mg/kg 8 hourly. If penicillin allergic, use a tetracycline or a macrolide. Treatment should be continued for a minimum of 4 weeks.

10. Other Gram-negative bacteria

A wide range of other Gram-negative species with different susceptibility patterns has been described and it is therefore difficult to recommend general treatment guidelines.^{3,16,58,90–108} Clinical experience has been well reviewed,^{16,91} and the contribution of animal studies to combination therapy has been described.⁹⁶ The general themes are that a combination of antibiotics may offer synergy and prevent the emergence of resistance in long-term treatment. The prognosis is generally poor, but best outcomes result from using high-dose antibiotics (chosen after careful sensitivity testing) and early surgery.

11. Fungal endocarditis

Fungal endocarditis is an unusual form of endocarditis comprising 2%–4% of all cases. It is most common in iv drug abuse and prosthetic valve endocarditis, but has also been described in patients with neutropenia or haematological malignancy, following cardiac surgery, solid organ transplantation and chronic granulomatous disease. The most common fungi causing endocarditis are *Candida* spp. and *Aspergillus* spp., with rarer examples including *Trichosporon* spp. and Mucorales.

The treatment of fungal endocarditis is currently unsatisfactory and usually requires surgical intervention. Analogous to

bacterial endocarditis, antifungal regimens that are fungicidal may be preferable, although considerable work in terms of validation remains. Specific regimens must be given for a minimum of 6 weeks, but usually for much longer and in some circumstances (e.g. prosthetic valves) therapy may be life long.

Amphotericin B does not penetrate well into vegetations, but has been used successfully in *Candida* endocarditis. It is, however, toxic, particularly if given for prolonged periods, and there are few data concerning the efficacy of lipid-associated formulations in the treatment of endocarditis. Fluconazole is fungistatic and is only active against some *Candida* spp., *Trichosporon* spp. and some other yeasts. Flucytosine is also fungistatic, although the combination of amphotericin plus flucytosine is more likely to be fungicidal. Flucytosine, however, is associated with bone marrow toxicity and trough levels should not exceed 50 mg/L. Caspofungin is usually fungicidal for *Candida* spp. (although some isolates of *Candida parapsilosis* and *Candida guilliermondii* are less susceptible). However, there is as yet no experience of the use of caspofungin in endocarditis, and the penetration of caspofungin and other echinocandins into vegetations is unknown.

Susceptibility testing must be undertaken for any fungus causing endocarditis, including the determination of minimal fungicidal concentrations. For drugs with variable bioavailability, therapeutic drug monitoring is important.

Treatment^{109,110}

Candida. Amphotericin B 1 mg/kg/day and flucytosine 100 mg/kg should be administered in four divided doses, according to renal function (first choice).

Or

Fluconazole 400 mg 12 hourly orally (second choice)

Or

Caspofungin 70 mg as a loading dose followed by 50 mg once daily, or 70 mg per day if weight >80 kg (first choice if intolerance or resistance precludes other options).

Aspergillus. Voriconazole 6 mg/kg 12 hourly for two doses (loading) should be administered, then 4 mg/kg 12 hourly intravenously or 400 mg 12 hourly for 24 h, followed by 200 mg 12 hourly orally

Or

Amphotericin B 1 mg/kg daily according to renal function.

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