

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

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The BSAC guidelines on treatment of infectious endocarditis (IE) were last published in 2004. The guidelines presented here have been updated and extended to reflect developments in diagnostics, new trial data and the availability of new antibiotics. The aim of these guidelines, which cover both native valve and prosthetic valve endocarditis, is to standardize the initial investigation and treatment of IE. An extensive review of the literature using a number of different search criteria has been carried out and cited publications used to support any changes we have made to the existing guidelines. Publications referring to *in vitro* or animal models have only been cited if appropriate clinical data are not available. 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 for most recommendations; however, we have attempted to grade the evidence, where possible. The guidelines have also been extended by the inclusion of sections on clinical diagnosis, echocardiography and surgery.

Keywords: antimicrobial therapy, staphylococci, enterococci, *Streptococcus* spp., fungal infections

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1. Introduction

In 2004 the Endocarditis Working Party of the British Society for Antimicrobial Chemotherapy (BSAC) published updated guidelines for the treatment of streptococcal, enterococcal and staphylococcal endocarditis, as well as HACEK (*Haemophilus*

spp., *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* spp. and *Kingella* spp.), Q fever and *Bartonella*.¹ In the light of the introduction of new antibiotic agents, developments in diagnostics and new trial data, the existing guidelines have been revised. In addition to considering the microbiological and therapeutic aspects of infective endocarditis (IE), we have now included sections on clinical diagnosis, echocardiography and surgery. The guidelines include native valve endocarditis (NVE) and prosthetic valve endocarditis (PVE). For the purposes of these guidelines, PVE includes prosthetic valves of all types, annuloplasty rings, intracardiac patches and shunts. We have excluded IE where it is related to pacemakers, defibrillators or ventricular-assist devices, which are the subject of a separate BSAC Working Party review. The aim of these guidelines is to standardize the initial investigation and treatment of IE; however, it is well recognized that patients can develop adverse drug reactions to the recommended regimens and/or fail to respond to initial antimicrobial therapy and may require a change in therapy. Several treatment options are therefore provided for most scenarios.

Guidelines such as these have, in the past, received criticism for not being evidence based. We appreciate that clinical guidelines should ideally be based on high-quality, prospective, randomized controlled trials; however, few such trials have been performed to assess the benefit of antibiotic regimens in the treatment of endocarditis. Since the last guidelines were published, there has been at least one randomized controlled trial that included patients with endocarditis. Therefore, for the first time we have graded the evidence for our recommendations, although the majority remain based on consensus.

For clarity, recommendations are presented in bold text, and throughout this document we have inserted identifying letters after recommendations to identify their provenance. These letters are: A, high-quality randomized controlled trials and meta-analysis of randomized controlled trials; B, observational data and non-randomized trials; and C, expert opinion or Working Party consensus.

An extensive review of the literature using a number of different search methods incorporating a range of criteria (e.g. endocarditis, staphylococci) has been carried out and cited publications used to support any changes we have made to the existing guidelines. Publications referring to *in vitro* or animal models have only been cited if appropriate clinical data are not available. The text has been largely confined to justification for changes to previous recommendations and differences from European Society for Cardiology (ESC) recommendations.

2. Clinical assessment and diagnosis

2.1 Clinical features

Recommendation 2.1: IE should be considered and actively investigated in patients with any of the criteria shown in Figure 1. [B/C]

The diverse nature and evolving epidemiological profile of IE ensure it remains a diagnostic challenge and delayed or missed diagnoses continue to be a problem.² For this reason we have attempted to highlight key clinical scenarios where IE should be considered. Initial investigation in this context may

involve appropriate blood culture or echocardiography or both, depending on the index of suspicion or the situation.

The clinical presentation is highly variable, according to the causative microorganism, the presence or absence of pre-existing cardiac disease, and the presence of co-morbidities and risk factors for the development of IE. It may present as an acute, rapidly progressive infection, but also as a subacute or chronic disease, with low-grade fever and non-specific symptoms that may thwart or confuse initial assessment. Patients present to a variety of specialists who may consider a range of alternative diagnoses, including chronic infection, rheumatological and autoimmune disease or malignancy. The early and ongoing involvement of a cardiologist and an infection specialist to guide investigation and management is highly recommended.

The majority (~90%) of patients present with fever, often associated with systemic symptoms of chills, poor appetite and weight loss. Heart murmurs are found in up to 85% and new murmurs have been recently reported in 48%.³ A pre-existing heart murmur is frequently indicative of a pre-existing 'at risk' valvular pathology and should heighten awareness of the possibility of IE, while new valvular regurgitation is more specific for a diagnosis of IE in an appropriate clinical setting. Classic textbook signs may still be seen in the developing world, but peripheral stigmata of IE are increasingly uncommon elsewhere, because patients generally present at an early stage of the disease. Immunological phenomena, such as splinter haemorrhages, Roth spots and glomerulonephritis, are now less common,³ but emboli to brain, lung or spleen occur in 30% of patients and are often the presenting feature. A high index of suspicion and low threshold for investigation to exclude IE are therefore essential in at-risk groups (see Figure 2). Laboratory signs of infection, such as elevated C-reactive protein or erythrocyte sedimentation rate, leucocytosis, anaemia and microscopic haematuria, may be present in patients with IE but are non-specific findings. Atypical presentation (e.g. absence of fever) is more common in the elderly, after antibiotic pre-treatment, in the immunocompromised patient⁴ and in IE involving less virulent or atypical organisms. The diagnosis of IE should also be considered in patients who present with a stroke or transient ischaemic attack and a fever.

2.2 Echocardiography

Recommendation 2.2: Echocardiography must be performed as soon as possible (ideally within 24 h) in all patients with suspected IE. [C]

Recommendation 2.3: Transthoracic echocardiography (TTE) is the initial investigation of choice (Figure 3). [C]

Recommendation 2.4: In cases with an initially negative TTE/transoesophageal echocardiography (TOE) examination, repeat TTE/TOE should be performed 7–10 days later if the clinical suspicion of IE remains high. [C]

Recommendation 2.5: All patients with *Staphylococcus aureus* bacteraemia or candidaemia require echocardiography (ideally within the first week of treatment or within 24 h if there is other evidence to suggest IE). [B]

Recommendation 2.6: TTE is recommended at completion of antibiotic therapy for evaluation of cardiac and valve morphology and function. [C]

Recommendation 2.7: Follow-up echocardiography should be performed if there is evidence of cardiac complications or

1. A febrile illness and a murmur of new valvular regurgitation;
2. A febrile illness, a pre-existing at-risk cardiac lesion (see Figure 2) and no clinically obvious site of infection;
3. A febrile illness associated with any of:
 - Predisposition and recent intervention with associated bacteraemia,
 - Evidence of congestive heart failure,
 - New conduction disturbance,
 - Vascular or immunological phenomena: embolic event, Roth spots, splinter haemorrhages, Janeway lesions, Osler's nodes,
 - A new stroke,
 - Peripheral abscesses (renal, splenic, cerebral, vertebral) of unknown cause;
4. A protracted history of sweats, weight loss, anorexia or malaise and an at-risk cardiac lesion (Figure 2);
5. Any new unexplained embolic event (e.g. cerebral or limb ischaemia);
6. Unexplained, persistently positive blood cultures;
7. Intravascular catheter-related bloodstream infection with persistently positive blood cultures 72 h after catheter removal.

Figure 1. Criteria for consideration and investigation of possible infective endocarditis.

a suboptimal response to treatment—the timing and mode of assessment (TTE or TOE) is a clinical decision. [B]⁶

Recommendation 2.8: Routine repeat echocardiography while in therapy is not required. [C]

TTE/TOE are now ubiquitous, and their fundamental importance in the diagnosis, management and follow-up of IE is clearly recognized (Figure 3).⁷ The recommendations are summarized in Figure 4 and an algorithm for scanning is shown in Figure 2, which highlights the prominent role that TOE plays in the contemporary management of patients in whom there is a high suspicion of IE. The utility of both modes of investigation is diminished when applied indiscriminately, however, and appropriate application in the context of simple clinical criteria improves diagnostic yield.⁸ Two exceptions are patients with *S. aureus* bacteraemia or candidaemia, where routine echocardiography is justified in view of the frequency of IE in this setting, the virulence of these organisms, the devastating effects once intracardiac infection is established and/or the need for surgery.⁹ Sometimes multiple scans are needed to demonstrate vegetations.

Echocardiographic findings are major criteria in the diagnosis of IE, and may include the presence of a vegetation, abscess, new dehiscence of a prosthetic valve and newly noted valvular regurgitation. The sensitivity of TTE ranges from 70% to 80% and that of TOE from 90% to 100%.

2.3 Diagnostic criteria and their limitations

Recommendation 2.9: Duke criteria can be used to assist in the diagnosis of IE but are not a substitute for clinical judgement. [C]

The Duke criteria (Table 1),⁶ based upon clinical, echocardiographic and microbiological findings, were developed as a research tool, and therefore provide high specificity and moderate sensitivity for the diagnosis of IE. These criteria can help by providing an objective tool for evaluating the strength of evidence to support a diagnosis of IE, particularly in difficult cases. Clinical judgement remains essential, especially in settings where the sensitivity of the modified Duke criteria is diminished, e.g. when blood cultures are negative, when too few blood

- Valvular heart disease with stenosis or regurgitation
- Valve replacement
- Structural congenital heart disease, including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect or fully repaired patent ductus arteriosus, and closure devices that are judged to be endothelialized
- Previous infective endocarditis
- Hypertrophic cardiomyopathy

Figure 2. Cardiac conditions considered to increase a patient's risk of developing infective endocarditis, i.e. 'at risk' heart valve lesions.⁵

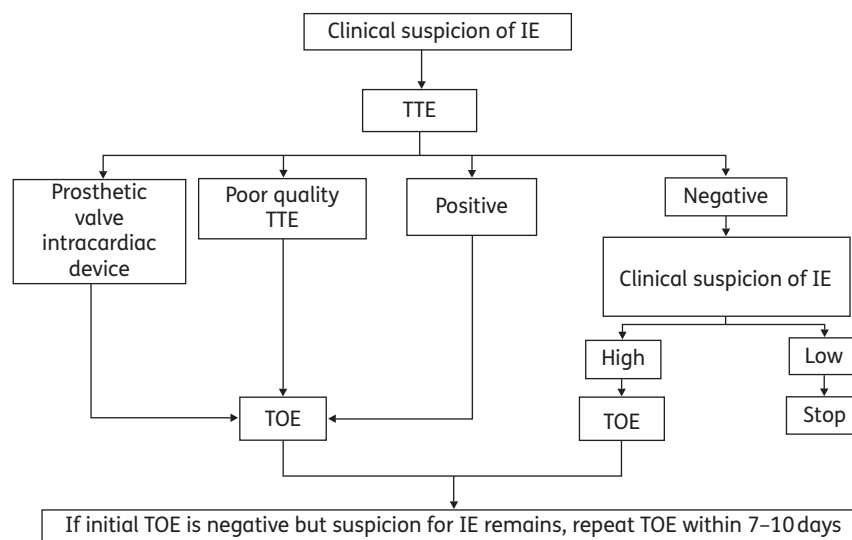


Figure 3. Indications for echocardiography in suspected infective endocarditis. IE, infective endocarditis; TTE, transthoracic echocardiography; TOE, transoesophageal echocardiography. TOE is not mandatory in isolated right-sided native valve IE with good quality TTE examination and unequivocal echocardiographic findings.

culture sets have been taken, or when infection affects a prosthetic valve or the right side of the heart.¹⁰ Recent amendments recognize the role of Q fever, increasing prevalence of staphylococcal infection and widespread use of TOE. The resultant so-called modified Duke criteria are now recommended.^{11,12}

2.4 The multidisciplinary team

Recommendation 2.10: A cardiologist and infection specialist should be closely involved in the diagnosis, treatment and follow-up of patients with IE. [C]

Recommendation 2.11: Specialist teams managing patients with IE should have rapid access to cardiac surgical services. [C]

There is no evidence to support these recommendations other than a widely held view that this represents good clinical care.

3. Microbiological diagnosis

3.1 Blood cultures

Recommendation 3.1: Blood cultures remain a cornerstone of the diagnosis of IE cases and should be taken prior to starting treatment in all cases. [B]

Recommendation 3.2: Meticulous aseptic technique is required when taking blood cultures, to reduce the risk of contamination with skin commensals, which can lead to misdiagnosis. Guidelines for best practice should be consulted.¹³ [B]

Recommendation 3.3: In patients with a chronic or subacute presentation, three sets of optimally filled blood cultures should be taken from peripheral sites with ≥ 6 h between them prior to commencing antimicrobial therapy. [C]

| Diagnosis |
|---|
| <ul style="list-style-type: none"> TTE is the first-line imaging modality. Use TOE in patients with high clinical suspicion of IE and a non-diagnostic TTE. Consider TOE in all adults with a positive TTE. TOE is not indicated in patients with a good-quality negative TTE and low clinical suspicion of IE. Repeat TTE/TOE 7–10 days after a negative scan when clinical suspicion of IE remains high. |
| Follow-up during medical therapy |
| <ul style="list-style-type: none"> Repeat TTE or TOE are recommended as soon as a new complication is suspected. |
| Intra-operative echocardiography |
| <ul style="list-style-type: none"> All cases of IE requiring surgery. |
| Following completion of therapy |
| <ul style="list-style-type: none"> TTE is recommended for baseline evaluation. |

Figure 4. Summary of echocardiography recommendations in infective endocarditis (IE). TTE, transthoracic echocardiography; TOE, transoesophageal echocardiography.

Table 1. Modified Duke criteria for diagnosis of infective endocarditis^a (reproduced with permission from Table 4, Li et al.¹²)

| Criterion | Diagnostic | Type | Tick if met ^a |
|---|---|---|--------------------------|
| Major criteria | | | |
| Positive blood culture for infective endocarditis | typical microorganism consistent with IE from two separate blood cultures, as noted below microorganisms consistent with IE from persistently positive blood cultures, defined as: | viridans streptococci, <i>Streptococcus bovis</i> or HACEK group, OR community-acquired <i>S. aureus</i> or enterococci, in the absence of a primary focus two positive cultures of blood samples drawn >12 h apart OR all of three or a majority of four separate cultures of blood (with first and last sample drawn 1 h apart) a single positive blood culture for <i>C. burnetii</i> ; or antiphase I IgG antibody titre >1:800 | |
| Evidence of endocardial involvement | positive echocardiogram for IE, OR new valvular regurgitation (worsening or changing of pre-existing murmur not sufficient) | oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, OR abscess, OR new partial dehiscence of prosthetic valve | |
| Minor criteria | | | |
| Predisposition | | predisposing heart condition or intravenous drug use | |
| Fever | | temperature >38.0°C (100.4°F) | |
| Vascular phenomena | | major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhages and Janeway lesions | |
| Immunological phenomena | | glomerulonephritis, Osler's nodes, Roth spots and rheumatoid factor | |
| Microbiological phenomena | | positive blood culture but does not meet a major criterion as noted above ^a or serological evidence of active infection with organism consistent with IE | |
| PCR | | broad-range PCR of 16S | |
| Echocardiographic findings | | consistent with IE but do not meet a major criterion as noted above | |

IE, infective endocarditis.

^aClinical criteria for definite infective endocarditis requires: two major criteria; or one major and three minor criteria; or five minor criteria.

There is no evidence to support the commonly perpetuated view that blood cultures should be taken from different sites. All skin surfaces are colonized by bacteria and adequate skin disinfection is key to reducing contamination. Taking blood cultures at different times is critical to identifying a constant bacteraemia, a hallmark of endocarditis.

Recommendation 3.4: In patients with suspected IE and severe sepsis or septic shock at the time of presentation, two sets of optimally filled blood cultures should be taken at different times within 1 h prior to commencement of empirical therapy, to avoid undue delay in commencing empirical antimicrobial therapy. [C]

This recommendation reflects recent evidence of improved outcomes in severe infection with rapid instigation of appropriate therapy.¹⁴ It is not always appropriate to withhold antimicrobial therapy while three sets of blood cultures are taken over a 12 h period. This recommendation is intended to be pragmatic, allowing time to take at least two sets of blood cultures (the minimum for a secure microbiological diagnosis) prior to commencing antimicrobial therapy. Taking three sets of blood cultures within 1 h does not add anything to the diagnostic pathway (which ideally attempts to confirm sustained/persistent bacteraemia). Although modified Duke criteria specify 1 h between blood cultures, the Working Party did not feel that the evidence to support this criterion was sufficient to justify the inevitable delay in administering antibiotics.

Recommendation 3.5: Bacteraemia is continuous in IE rather than intermittent, so positive results from only one set out of several blood cultures should be regarded with caution. [B]

Recommendation 3.6: Sampling of intravascular lines should be avoided, unless part of paired through-line and peripheral sampling to diagnose concurrent intravascular catheter-related bloodstream infection.¹⁵ [B]

Recommendation 3.7: In groin-injecting intravenous drug users, a groin sinus should not be used to sample blood for culture. [C]

Recommendation 3.8: If a stable patient has suspected IE but is already on antibiotic treatment, consideration should be given to stopping treatment and performing three sets of blood cultures off antibiotics. Antibiotic therapy may need to be stopped for 7–10 days before blood cultures become positive. [C]

Previous ESC guidelines¹⁶ and the experience of Working Party members indicate that blood cultures may only become positive in partially treated IE after 7–10 days off antibiotic therapy.

Recommendation 3.9: Routine incubation of blood cultures for >7 days is not necessary. [B]

In the previous BSAC guideline,¹ the traditional recommendation for extended incubation and terminal subculture was maintained to increase the yield of fastidious and slow-growing bacteria, although the evidence for this was tenuous in the era of automated continuous-monitoring blood culture systems. In the light of further data and the proven utility of complementary non-culture-based technologies, we feel that the case for extended incubation and blind subculture is not justified and therefore it is not recommended.^{17–19}

Recommendation 3.10: Once a microbiological diagnosis has been made, routine repeat blood cultures are not recommended. [C]

Recommendation 3.11: Blood cultures should be repeated if a patient is still febrile after 7 days of treatment. [C]

3.2 Susceptibility testing

Recommendation 3.12: When the causative microorganism has been isolated, the MIC of the chosen antimicrobial should be established by a standardized laboratory method to ensure susceptibility.²⁰ [C]

Recommendation 3.13: Gradient tests (such as Etest) may be useful for establishing the susceptibility of fastidious or slow-growing bacteria, such as the HACEK group.²¹ [B]

Recommendation 3.14: Routine measurement of the MBC or serum bactericidal titres is not required. [C]

As documented in previous guidelines, these measurements are affected by a range of technical factors that result in poor intralaboratory reproducibility and there remains a lack of evidence regarding their clinical value.

3.3 Serology

Failure to culture a causative microorganism in IE is often due to the administration of antimicrobials prior to blood culture, but may also be due to infection caused by fastidious or slow-growing microorganisms.²² Diagnostic methods should include serological investigations where they are available and a systematic approach is advised, based on the clinical history of the patient and their exposure to possible risk factors.^{22–26}

Recommendation 3.15: In patients with blood culture-negative IE, serological testing for *Coxiella* and *Bartonella* should be performed. [B]

Microorganisms that should be considered first include *Coxiella burnetii* (Q fever) and *Bartonella* spp. In a large study of 348 cases of blood culture-negative IE in France, the documented aetiological agent was *C. burnetii* and *Bartonella* spp. in 48% and 28% of cases, respectively.²⁶

Recommendation 3.16: In patients with blood culture-negative IE, routine serological testing for *Chlamydia*, *Legionella* and *Mycoplasma* should not be performed, but considered if serology in Recommendation 3.15 is negative. [C]

The combined total of infections attributed to *Mycoplasma* species, *Legionella* species and *Tropheryma whippelii* in a recent study amounted to <1% of all culture-negative cases, and there were no cases in which *Chlamydia* species were implicated during an 18 year study period.²⁶ IE due to *Chlamydia* is rarer than previously thought, owing to false-positive *Chlamydia* serology caused by antibodies to *Bartonella*.²⁷ Endocarditis caused by these microorganisms is extremely rare and serology has not been shown to be of value. Given their rarity, there is also a significant risk of false-positive serology leading to erroneous therapy.

Recommendation 3.17: Consider *Brucella* in patients with negative blood cultures and a risk of exposure (dietary, occupational or travel). [C]

The serology of Q fever is considered positive when antiphase I IgG antibody titres are $\geq 1:800$ and for *Bartonella* when anti-*Bartonella quintana* or anti-*Bartonella henselae* IgG antibody titres are $\geq 1:800$.²⁶ Serology may be useful for the diagnosis of IE caused by *Brucella* species in areas where the clinical history suggests exposure to this agent.^{24,28}

Recommendation 3.18: *Candida* antibody and antigen tests should not be used to diagnose *Candida* IE.

There is currently no evidence to support the use of either *Candida* antibody or antigen testing in the diagnosis of IE. Basing treatment on these tests may therefore lead to inappropriate therapeutic decisions.

3.4 Investigation of excised heart valves

Recommendation 3.19: Tissues from excised heart valves or vegetations following surgical intervention in patients with suspected IE should be investigated for the presence of infection, including culture and histological examination. [B]

At least 25% of patients with IE will have valve tissue removed.²⁹ Culture of the homogenized tissue is recommended, but results should be regarded with caution due to the relatively poor predictive value. This is due to the high percentage of false-negative results attributable to antimicrobial treatment and the possibility that tissue may have been contaminated during manipulation, leading to frequent false positives.³⁰

Recommendation 3.20: Samples of excised heart valve (or tissue from embolectomy) from cases of culture-negative IE should be referred for broad-range bacterial PCR and sequencing. [B]

Recommendation 3.21: A positive broad-range bacterial PCR result can be reliably used to identify the cause of endocarditis, but cannot be used to infer ongoing presence of infection and should not therefore be used alone to judge the duration of post-operative antimicrobial therapy. [B]

An increasing number of studies have demonstrated the diagnostic utility of broad-range PCR plus sequencing for detecting microbial pathogens in heart valve tissue.^{22,29,31–37} DNA is extracted from homogenized tissue and subjected to PCR using broad-range primers targeting the bacterial DNA that codes for the 16S ribosomal subunit (16S rDNA). Universal primers may also be used to target the 28S ribosomal subunit of fungi. Any amplicons generated are then sequenced to identify the species present. These PCR assays are particularly useful in assisting the diagnosis of IE in patients who have had prior antimicrobial therapy, as detectable microbial DNA has been shown to persist for many months or even years *in vivo* after successful therapy.^{38,39} Such procedures can also identify the presence of rare causes of IE that may not be detected using routine procedures, such as *Mycoplasma* species⁴⁰ or fungi.⁴¹ Broad-range PCR can be attempted from histopathological specimens, but sensitivity may be reduced.

PCR assays are not without their drawbacks, and these include the presence of PCR inhibitors in clinical samples or the risk of contamination in clinical samples and PCR reagents. The risk of false-positive results can be reduced by the use of real-time PCR, the use of specially designed PCR laboratories, carry-over prevention techniques and limiting the sensitivity of the PCR assay by reducing the number of PCR cycles.^{35,42} The clinical history of the patient must also be considered given that DNA may persist in valve tissue from past infections and may therefore not be indicative of current active infection. In conclusion, there is accumulating evidence that such techniques, if rigorously controlled, can provide a useful adjunct to blood culture and serology for the diagnosis of IE. DNA sequencing is not available in most laboratories, but many reference laboratories will provide

a service for the investigation of tissue samples. Laboratories with ready access to such techniques are likely to use them more widely to support an existing diagnosis, even when blood cultures are positive.

Real-time PCR has been applied to whole blood and serum for the detection of fastidious bacteria and fungi causing IE, but there are insufficient data, at present, to recommend the routine use of such techniques for the diagnosis of culture-negative IE.^{43–45}

The above recommendations have concentrated on the investigations available to the microbiology laboratory, but a comprehensive diagnosis will involve integration of clinical, microbiological, biochemical, haematological, histopathological and echocardiographic data.^{46–50}

4. The role of surgery

Recommendation 4.1: A surgical opinion should be sought at the earliest opportunity for every patient with endocarditis affecting intracardiac prosthetic material. [C]

Recommendation 4.2: A surgical opinion should be sought for every patient with endocarditis and any of the indications for surgery listed in Figure 5. [C]

Recommendation 4.3: The timing of surgery should be judged on a case-by-case basis, but the relative urgency of different indications is given in Figure 5. [C]

Recommendation 4.4: Samples of valve or other infected tissue should be sent for microbiological and histopathological investigation. [B]

5. Antibiotic dosing, delivery and monitoring

5.1 Aminoglycosides

Recommendation 5.1: Gentamicin should be dosed according to actual body weight unless patients are obese, in which case dosing should be discussed with a pharmacist. [C]

Recommendation 5.2: When used for treatment of Gram-positive endocarditis, serum gentamicin levels should be measured regularly to ensure pre-dose (trough) levels remain ≤ 1 mg/L and post-dose levels 3–5 mg/L. [C]

Recommendation 5.3: In patients with impaired renal function, dose should be adjusted according to measured or estimated creatinine clearance and serum levels should be monitored daily. [C]

Recommendation 5.4: If 'once-daily' gentamicin dosing regimens (e.g. Hartford regimen) are used as part of treatment regimens for IE caused by Enterobacteriaceae or *Pseudomonas aeruginosa*, use local protocols to monitor and adjust dosing regimens. [C]

The use of aminoglycosides is regularly questioned and is discussed in more detail in the individual sections. Gentamicin dose regimens in IE are usually based on the administration of 1 mg/kg body weight, intravenously (iv)/intramuscularly every 12 h. Gentamicin is poorly lipid soluble and there is a risk of accidental overdose in obese patients dosed according to actual body weight. Evidence to support the recommended therapeutic levels is limited. Once-daily regimens are now widely used for other infections, but data regarding their efficacy in endocarditis

| Heart failure |
|--|
| <p>Aortic or mitral IE with:</p> <ol style="list-style-type: none"> 1. Severe acute regurgitation or valve obstruction causing refractory pulmonary oedema/shock (emergency). 2. Fistula into a cardiac chamber or pericardium causing refractory pulmonary oedema/shock (emergency). 3. Severe acute regurgitation or valve obstruction and persisting heart failure or echocardiographic signs of poor haemodynamic tolerance (urgent). 4. Severe regurgitation and no heart failure (elective). |
| Uncontrolled infection |
| <ol style="list-style-type: none"> 1. Locally uncontrolled infection including abscess, false aneurysm, enlarging vegetation (urgent). 2. Persisting fever and positive blood culture for ≥ 10 days after commencing appropriate antimicrobial therapy (urgent). 3. Infection caused by fungi or multiresistant micro organisms (urgent/elective). |
| Prevention of embolism |
| <ol style="list-style-type: none"> 1. Aortic or mitral IE with large vegetations (>10 mm) resulting in one or more embolic episodes despite appropriate antibiotic therapy (urgent). 2. Aortic or mitral IE with large vegetations (>10 mm) and other predictors of complicated course like heart failure, persistent infection or abscess (urgent). 3. Isolated very large vegetations >15 mm (urgent). |

Figure 5. Indications for cardiac surgery in the management of infective endocarditis (IE) adapted from the European Society for Cardiology guidelines⁴⁹ and the American Heart Association.⁵⁰

still remain limited. However, for IE caused by Enterobacteriaceae (see later), once-daily gentamicin may be appropriate.

Streptomycin is usually administered at a dose of 7.5 mg/kg body weight every 12 h and blood levels should be monitored at least twice weekly (more often in renal impairment—see above), in order to maintain pre-dose levels ≤ 3 mg/kg. Dosing should be adjusted according to renal function, as with gentamicin.

5.2 Glycopeptides

5.2.1 Vancomycin

Recommendation 5.5: Vancomycin should be dosed and levels monitored according to local protocols. [C]

Recommendation 5.6: Vancomycin levels should be monitored and dose adjusted to maintain a serum pre-dose level between 15 and 20 mg/L. [C]

Since the previous version of these guidelines, vancomycin breakpoints have been revised and higher pre-dose vancomycin levels have been recommended.⁵¹ Vancomycin dosing is in a state of flux as hospitals attempt to consistently achieve the higher pre-dose levels recommended for serious infections.

Until new protocols have been evaluated, the optimum dosing regimen is not known and more detailed guidelines cannot be provided.

Recommendation 5.7: There is insufficient evidence to support the use of continuous infusions of vancomycin in IE patients.

5.2.2 Teicoplanin

Recommendation 5.8: Teicoplanin should be administered initially at a high dose (10 mg/kg body weight every 12 h then 10 mg/kg daily) with dosing interval adjusted according to renal function. [B]

Recommendation 5.9: Teicoplanin serum trough levels must be measured to ensure levels of ≥ 20 mg/L (and <60 mg/L) and repeated at least weekly. [C]

There is no new evidence to justify a change to these previous recommendations.

Recommendation 5.10: Teicoplanin is less nephrotoxic than vancomycin and should be considered for susceptible isolates (excluding staphylococci) when combination therapy with gentamicin is required.⁵²

5.3 β -Lactams

Amoxicillin and ampicillin are considered microbiologically equivalent and either can be used. Amoxicillin may be used instead of benzylpenicillin for susceptible isolates, but is broader spectrum and has a greater risk of *Clostridium difficile* infection. The time-dependent killing of streptococci by penicillin means that it should be given six times a day, because of its short serum half-life. There are no prospective comparisons of continuous with intermittent penicillin administration for streptococcal endocarditis. Dose modifications for β -lactams may be necessary in patients with impaired renal function and according to the patient's body weight.

5.4 Alternative antibiotics for patients with penicillin allergy

Where β -lactams are recommended as first-line agents, alternative regimens are listed in the Tables for patients with a β -lactam allergy. It is important to establish the nature of a reported 'allergy' to penicillin, as there is less experience with alternative antibiotics, a higher rate of side effects and concerns about the efficacy of alternatives. 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 and urticaria) were reported, a trial with penicillin may be warranted, but access to resuscitation facilities should be available immediately. Penicillin antibody testing and skin prick testing can be useful.

If a rash occurs after 72 h it is likely to be a delayed-type hypersensitivity reaction rather than an immediate IgE-mediated reaction (type I hypersensitivity). In a recent study, 72% of patients with a delayed-type hypersensitivity reaction to aminopenicillins had no cross-reactivity with penicillin. There may be a role for skin testing in the 'penicillin allergic' patient who does not have a history of anaphylaxis or angio-oedema, rather than avoidance of all β -lactam agents for the treatment of endocarditis.⁵³ 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.

5.5 Other antibiotics

Since the previous guidelines were published, other antibiotics such as linezolid and daptomycin have been introduced. Their use, where relevant, is described in the text of the individual sections.

5.6 Home therapy

Recommendation 5.10: Home/community/outpatient intravenous therapy is an appropriate method for managing selected patients with IE. [B]

Recommendation 5.11: IE patients need to satisfy general suitability criteria for home/community/outpatient therapy in addition to the condition-specific requirements in Recommendation 5.12.

Recommendation 5.12: IE patients who might be considered for home/community/outpatient therapy would include those: who are stable and responding well to therapy;

without signs of heart failure; without any of the indications for surgery listed in Figure 5; or without uncontrolled extracardiac foci of infection. [C]

Recommendation 5.13: IE caused by any microorganism may be appropriate for home/community/outpatient therapy provided the conditions in Recommendation 5.12 are satisfied. However, *S. aureus* is the microorganism associated with highest mortality and complications, and caution is therefore advised where this is the cause. [C]

Recommendation 5.14: Patients who have valve replacement surgery for IE and are in hospital solely to complete a planned treatment course and satisfy the conditions in Recommendation 5.12 may be suitable for home/community/outpatient therapy. [C]

Recommendation 5.15: When patients are managed using home/community/outpatient intravenous therapy, systems should be in place to monitor the patient's clinical condition on a daily basis. [C]

Recommendation 5.16: Ceftriaxone, teicoplanin, daptomycin and vancomycin are suitable agents for home/community/outpatient therapy for endocarditis, depending whether once- or twice-daily administration is available locally. [B]

Recommendation 5.17: The dosing regimens for treating patients on home/community/outpatient therapy are the same as those recommended for specific pathogens. [C]

Home/community/outpatient 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 susceptibility of the infecting microorganism to antibiotics, which lend themselves to home therapy. Home/community/outpatient therapy for endocarditis treatment is often considered for streptococcal endocarditis, as these microorganisms can be less destructive with fewer complications than IE caused by other microorganisms. Trials of home therapy have been reviewed.^{54,55} Antibiotics such as ceftriaxone, daptomycin or teicoplanin that can be given once daily iv are suitable agents, but others can be used depending on who is administering the antimicrobials. Patients may not need a central venous catheter (such as a peripherally inserted central catheter), if antimicrobial therapy can be administered via peripheral cannulae. This approach may be preferable, as these devices have the lowest infection and complication rates of all vascular access devices. Agents such as teicoplanin or daptomycin, which can be given as a bolus, can be administered via a butterfly needle; thus, avoiding the need for any indwelling vascular access and minimizing the risk of infection.

Any of the recommended antimicrobial agents have potential side effects. For example, neutropenia is a well-described side effect of ceftriaxone, occurring in 2 of 55 patients in one study⁵⁶ and can predispose to *C. difficile* infection; teicoplanin also has side effects, including drug fever (25% of cases in one IE series);⁵⁷ and daptomycin may cause a myositis and resistance may develop on therapy. Patients being managed in this way need to be carefully monitored for side effects as well as their response to therapy.

5.7 Oral therapy

Oral therapy for endocarditis has been described but is rarely advocated in guidelines, owing to the paucity of data and concerns about efficacy. In general, intravenous therapy is

Table 2. Empirical treatment regimens for endocarditis (pending blood culture results)

| Antimicrobial | Dose/route | Comment |
|--|---|--|
| 1. NVE—indolent presentation | | |
| Amoxicillin ^a AND (optional) | 2 g q4h iv | If patient is stable, ideally await blood cultures. Better activity against enterococci and many HACEK microorganisms compared with benzylpenicillin. Use Regimen 2 if genuine penicillin allergy. |
| gentamicin ^a | 1 mg/kg ABW | The role of gentamicin is controversial before culture results are available. |
| 2. NVE, severe sepsis (no risk factors for Enterobacteriaceae, Pseudomonas) | | |
| Vancomycin ^a AND | dosed according to local guidelines | In severe sepsis, staphylococci (including methicillin-resistant staphylococci) need to be covered. If allergic to vancomycin, replace with daptomycin 6 mg/kg q24h iv. |
| gentamicin ^a | 1 mg/kg IBW q12h iv | If there are concerns about nephrotoxicity/acute kidney injury, use ciprofloxacin in place of gentamicin ^a . |
| 3. NVE, severe sepsis AND risk factors for multiresistant Enterobacteriaceae, Pseudomonas | | |
| Vancomycin ^a AND | dosed according to local guidelines, iv | Will provide cover against staphylococci (including methicillin-resistant staphylococci), streptococci, enterococci, HACEK, Enterobacteriaceae and <i>P. aeruginosa</i> . |
| meropenem ^a | 2 g q8h iv | |
| 4. PVE pending blood cultures or with negative blood cultures | | |
| Vancomycin ^a AND | 1 g q12h iv | |
| gentamicin ^a AND | 1 mg/kg q12h iv | Use lower dose of rifampicin in severe renal impairment. |
| rifampicin ^a | 300–600 mg q12h po/iv | |

NVE, native valve endocarditis; PVE, prosthetic valve endocarditis; ABW, actual body weight; IBW, ideal body weight; iv, intravenous; po, orally; q4h, every 4 h; q8h, every 8 h; q12h, every 12 h.

^aDoses require adjustment according to renal function.

recommended to ensure adequate dosing and administration for an infection with high mortality. Routine 'oral switch' is not recommended. Occasionally, particularly in intravenous drug users, problems obtaining or maintaining safe intravenous access mean that oral therapy may be the safest treatment option. The appropriateness of oral therapy depends on the oral bioavailability of the antimicrobials concerned as well as patient factors. Agents with oral bioavailability that is close to that achieved with intravenous administration can be given during therapy for endocarditis, provided the patient can tolerate oral medicine and is likely to be absorbing from the gastrointestinal tract. Ciprofloxacin, linezolid and rifampicin have excellent oral bioavailability.

6. Empirical treatment regimens

The recommended regimens are summarized in Table 2.

Recommendation 6.1: Empirical antimicrobial regimens for patients with suspected endocarditis should be based on severity of infection, type of valve affected and risk factors for unusual or resistant pathogens. [C]

Recommendation 6.2: Empirical therapy should be directed towards the most common causes of endocarditis. [C]

Recommendation 6.3: If a patient with suspected IE is clinically stable, we recommend waiting for the results of blood cultures before starting any antimicrobials. [C]

Recommendation 6.4: If the diagnosis of IE is in doubt, the patient is clinically stable and has already received antibiotics, we recommend stopping any antibiotics and reculturing. [C]

The most common causes of NVE in non-intravenous drug users are currently *S. aureus* (28%), coagulase-negative staphylococci (CoNS; 9%), streptococci (35%) and enterococci (11%); 9% are culture-negative.³ Methicillin resistance is common among staphylococci. *S. aureus* infection and severity of illness at presentation (APACHE II score) are independent predictors of mortality in IE patients.⁵⁸ IE occasionally presents acutely with severe sepsis when caused by less-virulent microorganisms, such as enterococci, oral streptococci and CoNS. It is likely, though unproven, that early administration of effective antimicrobial therapy in the most severely ill patients will improve outcomes, as is the case for other critically ill patients with infection.¹⁴ Empirical regimens for the critically ill patient therefore need to provide broad-spectrum coverage. Patient risk factors for multiresistant pathogens need to be taken into consideration, e.g. colonization with methicillin-resistant *S. aureus* or extended-spectrum β -lactamase (ESBL)-producing Enterobacteriaceae, or intravenous drug use. If the patient is critically ill and has risk factors for ESBL-producing Enterobacteriaceae or *P. aeruginosa*, we recommend vancomycin plus meropenem [C].

Conversely, to avoid the risks and toxicity of broad-spectrum regimens, it is entirely reasonable to wait for the results of blood cultures in patients who are stable. If empirical therapy is indicated, for NVE with indolent presentation we recommend 2 g of amoxicillin every 4 h. The addition of empirical gentamicin in this situation is controversial. When intracardiac prosthetic material is present, the previous recommendation for vancomycin, gentamicin and rifampicin is unchanged. This applies to both

Table 3. Summary of treatment recommendations for staphylococcal endocarditis

| Agent | Dose/route | Duration (weeks) | Comment |
|--|--------------------|------------------|--|
| NVE, methicillin-susceptible <i>Staphylococcus</i> spp. | | | |
| Flucloxacillin | 2 g every 4–6 h iv | 4 | Use q4h regimen if weight >85 kg. |
| NVE, methicillin-resistant, vancomycin-susceptible (MIC ≤2 mg/L) rifampicin-susceptible <i>Staphylococcus</i> or penicillin allergy | | | |
| Vancomycin AND | 1 g iv q12h | 4 | or dose according to local guidelines. Modify dose according to renal function and maintain pre-dose level 15–20 mg/L. |
| Rifampicin | 300–600 mg q12h po | 4 | Use lower dose of rifampicin if creatinine clearance <30 mL/min. |
| NVE, methicillin-resistant, vancomycin-resistant (MIC >2 mg/L), daptomycin-susceptible (MIC ≤1 mg/L) <i>Staphylococcus</i> spp. or patient unable to tolerate vancomycin | | | |
| Daptomycin AND | 6 mg/kg q24h iv | 4 | Monitor creatine phosphokinase weekly. Adjust dose according to renal function. |
| Rifampicin OR | 300–600 mg q12h po | 4 | Use lower dose of rifampicin if creatinine clearance <30 mL/min. |
| Gentamicin | 1 mg/kg iv, q12h | 4 | |
| PVE, methicillin, rifampicin-susceptible <i>Staphylococcus</i> spp. | | | |
| Flucloxacillin AND | 2 g every 4–6 h iv | 6 | Use q4h regimen if weight >85 kg. |
| Rifampicin AND | 300–600 mg q12h po | 6 | Use lower dose of rifampicin if creatinine clearance <30 mL/min. |
| Gentamicin | 1 mg/kg iv, q12h | 6 | |
| PVE, methicillin-resistant, vancomycin-susceptible (MIC ≤2 mg/L), <i>Staphylococcus</i> spp. or penicillin allergy | | | |
| Vancomycin AND | 1 g iv q12h | 6 | or dose according to local guidelines. Modify dose according to renal function and maintain pre-dose level 15–20 mg/L. |
| Rifampicin AND | 300–600 mg q12h po | 6 | Use lower dose of rifampicin if creatinine clearance <30 mL/min. |
| Gentamicin | 1 mg/kg q12h iv | ≥2 | Continue gentamicin for the full course if there are no signs or symptoms of toxicity. |
| PVE, methicillin-resistant, vancomycin-resistant (MIC >2 mg/L), daptomycin-susceptible (MIC ≤1 mg/L) <i>Staphylococcus</i> spp. or patient unable to tolerate vancomycin | | | |
| Daptomycin AND | 6 mg/kg q24h iv | 6 | Increase daptomycin dosing interval to 48 hourly if creatinine clearance <30 mL/min. |
| Rifampicin AND | 300–600 mg q12h po | 6 | Use lower dose of rifampicin if creatinine clearance <30 mL/min. |
| Gentamicin | 1 mg/kg q12h iv | ≥2 | Continue gentamicin for the full course if there are no signs or symptoms of toxicity. |

NVE, native valve endocarditis; PVE, prosthetic valve endocarditis; iv, intravenously; po, orally; q12h, every 12 h; q24h, every 24 h.

early (within 1 year of surgery) and late (>1 year after surgery) PVE, because staphylococci remain key pathogens in PVE, regardless of time *in situ*.

7. Staphylococcal endocarditis

See Table 3 for recommended regimens.

7.1 NVE

Recommendation 7.1: First-line therapy for methicillin-susceptible staphylococci is 2 g of flucloxacillin every 6 h, increasing to 2 g every 4 h in patients weighing >85 kg. [A]

This recommendation is unchanged from previous guidelines.

Recommendation 7.2: Gentamicin should not be added to flucloxacillin for the initial treatment of native valve staphylococcal IE. [A]

There is no evidence that the addition of gentamicin results in improved survival, reduced surgery or reduced complications. This recommendation is unchanged from previous guidelines, but since their publication, analysis of data from a randomized controlled trial has confirmed previous findings of increased nephrotoxicity in patients.⁵⁹ There is no evidence that the addition of sodium fusidate or rifampicin to flucloxacillin offers any advantage in this setting.⁶⁰

Recommendation 7.3: First-line therapy for methicillin-resistant staphylococci or in patients with penicillin allergy is vancomycin iv plus rifampicin [C].

As vancomycin is less active than flucloxacillin, we recommend the addition of a second antibiotic to the treatment regimen; the recommendation to add rifampicin to vancomycin has not changed since previous recommendations.^{61,62} The addition of gentamicin was recommended previously in these guidelines; however, vancomycin and gentamicin are synergistically nephrotoxic, and the potential benefit of gentamicin may be outweighed by the risk of toxicity, particularly if higher trough levels of vancomycin are being used.

Recommendation 7.4: For patients intolerant of vancomycin or with vancomycin-resistant staphylococci we recommend 6 mg/kg daptomycin every 24 h with another active agent. [A]

One randomized controlled study has demonstrated non-inferiority of daptomycin when compared with standard therapy (flucloxacillin or vancomycin plus gentamicin) in the treatment of *S. aureus* bloodstream infections, including IE.⁶³ Although this study included patients with IE, the number of patients was small. Of all the daptomycin-treated patients (120), 19 (15.8%) had persisting or relapsing bacteraemia and seven isolates had reduced susceptibility to daptomycin.⁶³ Of the 28 IE patients treated with daptomycin, 3 developed daptomycin-resistant isolates on therapy (1 right-sided and 2 left-sided IE; none of these received concurrent gentamicin).⁶⁴ Daptomycin treatment

Table 4. Summary of treatment recommendations for streptococcal endocarditis

| Regimen | Antimicrobial | Dose and route | Duration (weeks) | Comment |
|--|--|---|------------------|---|
| Treatment options for streptococci (penicillin MIC \leq0.125 mg/L) | | | | |
| 1. | benzylpenicillin ^a monotherapy | 1.2 g q4h iv | 4–6 | preferred narrow-spectrum regimen, particularly for patients at risk of <i>C. difficile</i> or high risk of nephrotoxicity |
| 2. | ceftriaxone monotherapy | 2 g once a day iv/im | 4–6 | not advised for patients at risk of <i>C. difficile</i> infection; suitable for OPAT |
| 3. | benzylpenicillin ^a AND gentamicin | 1.2 g q4h iv 1 mg/kg q12h iv | 2 2 | not advised for patients with PVE, extra-cardiac foci of infection, any indications for surgery (Figure 5), high risk of nephrotoxicity or at risk of <i>C. difficile</i> |
| 4. | ceftriaxone AND gentamicin | 2 g once a day iv/im 1 mg/kg q12h iv | 2 2 | not advised for patients with PVE, extra-cardiac foci of infection, any indications for surgery (Figure 5), high risk of nephrotoxicity or at risk of <i>C. difficile</i> |
| Treatment of streptococci (penicillin MIC $>$0.125 to \leq0.5 mg/L) | | | | |
| 5. | benzylpenicillin ^a AND gentamicin | 2.4 g q4h iv 1 mg/kg q12h iv | 4–6 2 | preferred regimen, particularly for patients at risk of <i>C. difficile</i> |
| Treatment of <i>Abiotrophia</i> and <i>Granulicatella</i> spp. (nutritionally variant streptococci) | | | | |
| 6. | benzylpenicillin ^a AND gentamicin | 2.4 g q4h iv 1 mg/kg q12h iv | 4–6 4–6 | preferred regimen, particularly for patients at risk of <i>C. difficile</i> |
| Treatment of streptococci penicillin MIC $>$0.5 mg/L^b | | | | |
| Treatment of streptococci in patients with significant penicillin allergy | | | | |
| 7. | vancomycin AND gentamicin | 1 g q12h 1 mg/kg q12h iv | 4–6 \geq 2 | or dosed according to local guidelines |
| 8. | teicoplanin AND gentamicin | see Section 5.2.2 1 mg/kg iv q12h | 4–6 \geq 2 | preferred option when high risk of nephrotoxicity |

OPAT, outpatient antimicrobial therapy; PVE, prosthetic valve endocarditis; im, intramuscularly; iv, intravenously; q4h, every 4 h; q12h, every 12 h. All drug dosages to be adjusted in renal impairment; gentamicin, vancomycin and teicoplanin levels to be monitored.

^aAmoxicillin 2 g every 4–6 h may be used in place of benzylpenicillin 1.2–2.4 g every 4 h.

^bSee guidelines for the treatment of enterococci.

failure for IE, associated with the development of resistance to daptomycin, is well described.^{65–73} All but one of the separately reported cases of daptomycin resistance have occurred in patients treated with daptomycin monotherapy.^{63–73} Nevertheless, daptomycin is more rapidly bactericidal than vancomycin, which makes it an attractive agent for the treatment of endocarditis. Current UK prescribing guidelines recommend 6 mg/kg once daily, but higher doses have been advocated by other authorities. Because rates of development of resistance are high and because of the serious implications of treatment failure, we recommend the addition of another active agent (e.g. rifampicin, gentamicin or linezolid, depending on susceptibility) to daptomycin, pending further information.

No new data have been reviewed to change previous recommendations regarding teicoplanin for staphylococcal IE. Linezolid has been used successfully to treat staphylococcal endocarditis in individual cases for whom conventional therapy has either been contraindicated or unsuccessful. Linezolid is a bacteriostatic agent and so we cannot recommend it as monotherapy.

7.2 PVE

Recommendation 7.5: First-line therapy for susceptible isolates is vancomycin, rifampicin and gentamicin. [C]

Recommendation 7.6: Daptomycin can be used in place of vancomycin for patients unresponsive to or intolerant of vancomycin or with vancomycin-resistant isolates. [C]

Recommendations for first-line therapy and penicillin allergy have not changed from previous guidelines. Daptomycin has been used successfully, in combination with other agents, to treat PVE caused by staphylococci, but published data are limited.⁷³

7.3 Duration of therapy

Recommendation 7.7: Intravenous therapy for 4 weeks is recommended for staphylococcal NVE, which should be extended to \geq 6 weeks in patients with intracardiac prostheses, secondary lung abscesses and osteomyelitis. [B]

This is unchanged from previous recommendations.

Recommendation 7.8: Routine switch to oral antimicrobials is not recommended.

8. Streptococcal endocarditis

Regimens for streptococcal IE are summarized in Table 4.

Recommendation 8.1: Options for treatment should be determined based on the level of penicillin susceptibility and patient risk factors (See Table 4). [B]

Recommendation 8.2: Treatment for endocarditis caused by streptococci with a penicillin MIC $>$ 0.5 mg/L should follow the guidelines for enterococci. [B]

Recommendation 8.3: Where a range of time for treatment length is given, we advise that the longer course is used for

PVE, or patients with secondary brain abscesses or vertebral osteomyelitis. [C]

Since the publication of the 2004 guidelines, the areas of further debate around the treatment of streptococcal endocarditis have included the role of gentamicin, the appropriate breakpoints for moderate and high-level penicillin resistance, and the treatment of patients with penicillin allergy.

The role of gentamicin has been questioned because of concerns of toxicity. A meta-analysis of the use of gentamicin only identified one randomized controlled trial for the treatment of streptococcal endocarditis and therefore concluded that there was insufficient evidence.⁷⁴ A recent endocarditis study showed that a combination of gentamicin and a β -lactam led to a reduction in the estimated creatinine clearance compared with β -lactam monotherapy, but there was no association between the change in renal function during treatment and the post-discharge mortality for streptococcal or enterococcal endocarditis. The authors concluded that gentamicin did have a role in the treatment of endocarditis.⁷⁵ The potential risk of aminoglycosides has to be balanced against the benefit of shorter treatment length for the very susceptible streptococci (see Table 4) and more effective treatment of moderately penicillin-resistant streptococci. (See also the discussion on reducing gentamicin toxicity under enterococcal endocarditis.)

There have been concerns that the prevalence of penicillin-resistant streptococci may be increasing. A recent BSAC study reviewed 2344 streptococci causing bacteraemia, from 2001 to 2006. No β -haemolytic streptococci (groups A, B, C and G) were resistant to penicillin (breakpoint of 0.125 mg/L), whereas rates of penicillin resistance for non-haemolytic and α -haemolytic streptococci varied between 13% and 17% each year, with no significant change over 6 years. Most resistant isolates had an MIC between 0.25 and 1 mg/L; none had an MIC >8 mg/L. All isolates were susceptible to vancomycin and teicoplanin (MIC \leq 4 mg/L).⁷⁶

A combination of 4–6 weeks of high-dose benzylpenicillin with 2 weeks of an aminoglycoside has been recommended for streptococci with moderate penicillin resistance. Moderate penicillin resistance was defined in the 2005 AHA guidelines as an MIC >0.125 and \leq 0.5 mg/L. A treatment regimen for enterococci (e.g. 4–6 weeks of a penicillin plus an aminoglycoside) was advised for streptococci with an MIC >0.5 mg/L.⁵⁰ In the more recent ESC guidelines, relative resistance to penicillin was defined as an MIC between 0.125 and 2 mg/L.⁴⁹ In justification, the authors describe treatment of 60 patients with streptococcal endocarditis. If cases with inadequate information, those given additional antibiotics or those where the patient had valve replacement are excluded, there were 11 individuals infected with streptococci with MICs between 0.5 and 8 mg/L who were successfully treated with just 2 weeks of high-dose benzylpenicillin and aminoglycoside.^{77,78} While this appears encouraging, it is possible that the patients treated for the shorter period had good prognostic indicators or a very prompt response to treatment. In the absence of a randomized controlled trial, therefore, we continue to advise 4–6 weeks of high-dose benzylpenicillin with 2 weeks of an aminoglycoside for streptococci with a penicillin MIC >0.125 and \leq 0.5 mg/L, and treatment for streptococci with an MIC >0.5 and \leq 2 mg/L to follow the guidelines for enterococci.

Streptococci more commonly cause late- rather than early-onset PVE. There are limited clinical data on the treatment

of this condition. Where a range of time for treatment length is given, we advise that the longer course is used for PVE.

Endocarditis caused by *Abiotrophia* and *Granulicatella* species (collectively referred to as nutritionally variant streptococci) has a high rate of complications and treatment failure. It is also difficult to reliably measure antibiotic susceptibility *in vitro* and tolerance is common.^{79,80} A retrospective case review published in 2007 described eight cases of endocarditis that were successfully treated with a combination of surgery, benzylpenicillin or vancomycin for 6 weeks combined with \geq 2 weeks of gentamicin.⁸¹ We therefore advise that 4–6 weeks of the combination of benzylpenicillin/amoxicillin plus gentamicin is used to treat these microorganisms.

It is difficult to determine the appropriate breakpoint for 'high-level' penicillin resistance such that an alternative agent, such as vancomycin, should be used. Penicillin breakpoints quoted for infections other than IE are not helpful, as IE is treated with far higher penicillin doses than are used for most other infections and peak serum levels can be >100-fold greater than the MIC. In addition, combination with gentamicin is synergistic. The AHA guidelines advise treating streptococci with an MIC >0.5 mg/L according to the regimen for enterococci (e.g. 6 weeks penicillin plus gentamicin) and, by inference, the breakpoint for 'high-level' penicillin resistance for streptococci would be the same as the CLSI penicillin breakpoint for enterococci (\geq 16 mg/L). Accepting that there are still insufficient clinical data, the ESC suggest that vancomycin is used for streptococci with an MIC >4 mg/L. We have followed the ESC lead and adopted this advice.

There has been recent debate about the appropriate penicillin breakpoints for *Streptococcus pneumoniae*.⁸² We advise the use of the same endocarditis breakpoints as for other streptococci. As 28% of patients with pneumococcal endocarditis also have meningitis,⁸³ we advise that the meningitis breakpoints should be used when meningitis is also present (i.e. a penicillin breakpoint of 0.06 mg/L and ceftriaxone 0.5 mg/L).

Vancomycin or teicoplanin are still the preferred treatment for patients with immediate-type (IgE-mediated) penicillin allergy. In the ESC guidelines, vancomycin plus gentamicin is recommended for allergic patients who are infected with relatively penicillin-resistant streptococci (MIC 0.125–2 mg/L), while vancomycin monotherapy is recommended for penicillin-susceptible isolates. We would question the logic of determining whether gentamicin should be added on the basis of penicillin resistance. Animal models have shown that the combination of vancomycin with gentamicin is better than vancomycin monotherapy,⁸⁴ but a recent small clinical study and case report described successful vancomycin monotherapy for seven patients with streptococcal endocarditis, although two underwent surgery.^{85,86} As vancomycin-tolerant streptococci have been described with a vancomycin MBC well in excess of peak levels, it would seem prudent to treat penicillin-allergic patients with 4–6 weeks of vancomycin plus \geq 2 weeks of gentamicin.

9. Enterococcal endocarditis

See Table 5 for recommended regimens.

Recommendation 9.1: First-line therapy for susceptible enterococci is amoxicillin or high-dose penicillin with gentamicin. [B]

Table 5. Summary of treatment recommendations for enterococcal endocarditis

| Regimen | Antimicrobial | Dose and route | Duration (weeks) | Comment |
|---------|---|---|---|---|
| 1. | amoxicillin OR penicillin AND gentamicin ^a | 2 g q4h iv 2.4 g q4h iv 1 mg/kg q12h iv | 4–6 4–6 4–6 (see Recommendation 9.3) | for amoxicillin-susceptible (MIC \leq 4 mg/L), penicillin MIC \leq 4 mg/L AND gentamicin-susceptible (MIC \leq 128 mg/L) isolates duration 6 weeks for PVE |
| 2. | vancomycin ^a AND gentamicin ^a | 1 g q12h iv or dosed according to local guidelines 1 mg/kg IBW q12h iv | 4–6 4–6 | for penicillin-allergic patient or amoxicillin- or penicillin-resistant isolate; ensure vancomycin MIC \leq 4 mg/L duration 6 weeks for PVE |
| 3. | teicoplanin ^a AND gentamicin ^a | 10 mg/kg q24h iv 1 mg/kg q12h iv | 4–6 4–6 | alternative to Regimen 2, see comments for Regimen 2; ensure teicoplanin MIC \leq 2 mg/L |
| 4. | amoxicillin ^{a,b} | 2 g q4h iv | \geq 6 | for amoxicillin-susceptible (MIC \leq 4 mg/L) AND high-level gentamicin resistant (MIC >128 mg/L) isolates |

PVE, prosthetic valve endocarditis; IBW, ideal body weight; iv, intravenously; q4h, every 4 h; q12h, every 12 h; q24h, every 24 h.

^aAmend dose according to renal function.

^bStreptomycin 7.5 mg/kg every 12 h intramuscularly can be added if isolate is susceptible.

Recommendation 9.2: Glycopeptides in combination with gentamicin are second-line therapy for susceptible enterococci. [B]

Recommendation 9.3: There should be a low threshold for stopping gentamicin in patients with deteriorating renal function or other signs of toxicity. [B]

Enterococci remain the third most common cause of IE after staphylococci and oral streptococci, accounting for 10% of episodes.³ There have been no randomized clinical trials or significant changes in epidemiology since the publication of the previous guidelines to justify major changes to the treatment recommendations. Our recommendations are consistent with ESC guidelines⁴⁹ except for minor differences in the gentamicin dosing regimen and suggestions for resistant strains (see below).

The addition of gentamicin to a cell wall-acting agent is still recommended for enterococcal endocarditis, but this is based more on established practice rather than evidence of superiority of combination therapy over monotherapy. We remain concerned about the toxicity of gentamicin, particularly as the majority of enterococcal endocarditis occurs in older patients.⁸⁷ The anecdotal experience of the Working Party members suggests that starting 1 mg/kg gentamicin twice a day achieves appropriate levels in most cases, but longer dosing intervals may be required in patients with pre-existing renal impairment and according to serum levels. Since shorter courses of aminoglycosides can still effect a clinical cure,⁸⁸ we now recommend a low threshold for stopping aminoglycosides if renal function deteriorates or if signs of ototoxicity develop. Since there is no evidence that a short delay in the addition of an aminoglycoside to the primary treatment agent is detrimental to outcome, it would seem prudent to wait for the results of susceptibility testing before starting gentamicin to avoid the possibility of administering a potentially toxic antimicrobial until it has been proven that it has activity against the infecting microorganism.

There has been anecdotal success treating high-level aminoglycoside-resistant (HLAR) enterococcal endocarditis with

penicillin and ceftriaxone combinations.^{89–92} However, in a non-randomized open-label multicentre evaluation of this combination, an in-hospital mortality rate of 23% was reported,⁹⁰ which is much higher than the 11% seen in international studies.⁸⁷ Given the lack of evidence that such penicillin with cephalosporin combination therapy is superior to monotherapy with penicillin, the current UK epidemic of *C. difficile* infection and increasing concerns about ESBL-producing microorganisms, the Working Party does not recommend the routine addition of ceftriaxone to a penicillin for HLAR enterococci.

Sporadic cases of IE caused by penicillin- and vancomycin-resistant enterococci (VRE) continue to present treatment problems. Several case reports and series describe both successes and failures treating VRE IE with regimens containing both linezolid and daptomycin.^{93–101} Daptomycin resistance has developed during therapy for enterococcal IE.¹⁰² Animal model data suggest that both daptomycin and linezolid are superior to glycopeptides for the treatment of glycopeptide-resistant enterococci.^{103,104} There are insufficient data to make recommendations for VRE IE, which should be discussed on a case-by-case basis.

10. HACEK endocarditis

Recommendation 10.1: Treatment should be with a β -lactamase-stable cephalosporin²¹ or amoxicillin if the isolate is susceptible. [B]

Recommendation 10.2: Gentamicin should only be added for the first 2 weeks of therapy. [C]

Recommendation 10.3: Ciprofloxacin can be considered an alternative agent. [C]

Recommendation 10.4: NVE should receive 4 weeks and PVE 6 weeks of treatment. [C]

The HACEK group of fastidious extracellular Gram-negative bacteria are uncommon and cause an estimated 3% of all

Table 6. Summary of treatment recommendations for Q fever

| Regimen | Antimicrobial | Dose | Duration |
|---------|--|---------------------------------|---|
| 1. | doxycycline ^a and hydroxychloroquine ^b | 100 mg q12h po 200 mg q8h po | both antibiotics for ≥ 18 months and < 4 years |
| 2. | doxycycline ^a and ciprofloxacin | 100 mg po 200 mg q12h po | ≥ 3 years |

q8h, every 8 h; q12h, every 12 h; po, orally.

^aIn slow responders, defined as $< 50\%$ reduction in mean phase 1 titres, doxycycline dosing should be adjusted to achieve serum levels of ≤ 5 mg/L.¹¹⁹

^bPlasma levels to be maintained at 0.8–1.2 mg/L. Monthly serum levels must be obtained and dose adjusted accordingly. Photosensitivity is common. Retinal accumulation necessitates regular examination.

cases of IE.^{105,106} Ciprofloxacin has been successfully used to treat HACEK IE and can be administered orally; it has therefore been included as an alternative agent for therapy.

11. Q fever

See Table 6 for recommended regimens.

Recommendation 11.1: A combination of doxycycline and hydroxychloroquine for ≥ 18 months provides bactericidal activity and adequate protection from relapse.¹⁰⁷ [B]

Recommendation 11.2: Antibody titres should be determined every 6 months whilst on treatment and then every 3 months for a minimum of 2 years once treatment has been discontinued. [B]

Recommendation 11.3: Patients should be considered cured when IgG antibodies to *C. burnetii* phase I are $< 1:800$ and phase I IgM and IgA antibodies are $< 1:50$.¹⁰⁷

C. burnetii is an obligate intracellular pathogen and is the causative microorganism of Q fever. *C. burnetii* causes up to 3% of all cases of IE in England and Wales.¹⁰⁸ The estimated incidence of IE in those who contract Q fever ranges from 7%¹⁰⁹ to 67%¹¹⁰ and is the primary manifestation of chronic infection.¹¹¹ Patients likely to develop Q-fever IE are those with predisposing valvular damage or prosthetic heart valves.^{112,113} *C. burnetii* is the commonest cause of culture-negative IE.¹¹⁴ Relative resistance to doxycycline has been reported recently and higher doses have been recommended in patients whose phase I antibody titres are slow to decrease.^{115,116}

12. Bartonella endocarditis

See Table 7 for recommended regimens.

Recommendation 12.1: Treatment should be with gentamicin in combination with a β -lactam or doxycycline for a minimum of 4 weeks.^{117,118}

Bartonella spp. are facultative intracellular Gram-negative aerobic bacteria that cause up to 3% of all cases of IE.²³ *B. quintana* can cause trench fever and IE, and is transmitted by the body louse. Predisposing factors to infection include homelessness and alcoholism.^{119,120} *B. henselae* is the causative microorganism of cat-scratch fever and rarely IE. IE is a feature of

Table 7. Summary of treatment recommendations for *Bartonella* IE

| Agent | Dose/route | Duration (weeks) | Comment |
|----------------------------|----------------------------------|------------------|--|
| Amoxicillin AND gentamicin | 2 g q4h iv 1 mg/kg q8h iv | 6 4 | if penicillin allergic use tetracycline regular serum levels are needed to guide maintenance dose |
| Doxycycline AND gentamicin | 200 mg q24h po 1 mg/kg q8h iv | | |

po, orally; iv, intravenously; q4h, every 4 h; q8h, every 8 h; q24h, every 24 h.

chronic *Bartonella* infection.¹²¹ Only aminoglycosides have bactericidal activity against *Bartonella* spp.,¹²² although susceptibility to macrolides, rifampicin and tetracycline has been demonstrated.¹²³

13. Other Gram-negative bacteria

A wide range of other Gram-negative bacteria continue to cause a small proportion ($< 5\%$) of IE.¹²⁴ Risk factors include intravenous drug use, end-stage liver disease, central venous catheters and old age. Members of the Enterobacteriaceae, *Acinetobacter* spp. and *P. aeruginosa* have all been implicated. Ever-changing resistance patterns, such as the spread of ESBL-producing isolates, and multidrug- or pan-drug-resistant strains complicate therapy and preclude clear evidence-based recommendations for therapy. The Working Party continues to support the principle that combination therapy [where possible comprising a β -lactam (which could be amoxicillin, a cephalosporin or a carbapenem) and aminoglycoside] may offer synergy and prevent the emergence of resistance, but acknowledges that there are a lack of supporting clinical data in this context. It seems reasonable to consider therapeutic 'once-daily' gentamicin dosing regimens (e.g. 7 mg/kg 'Hartford' dosing regimen) for the treatment of these infections, rather than the lower 'synergistic' dose recommended for IE caused by Gram-positive bacteria, because the post-dose levels recommended for the latter (3–5 mg/kg) are likely to be unreliable for Gram-negative sepsis. As in the previous edition of these guidelines, high-dose therapy, based on careful *in vitro* susceptibility testing, and early consideration of surgery are recommended. It may not always be appropriate to add an aminoglycoside because of concerns about nephrotoxicity. Likewise, prolonged high-dose gentamicin carries a significant risk of nephrotoxicity and careful monitoring for toxicity, including audiometry, is advised for courses longer than 2 weeks.

14. Fungal endocarditis

See Table 8 for recommended regimens.

Fungi cause endocarditis in $\sim 2\%$ – 4% of all endocarditis cases.¹²⁵ Of these, *Candida albicans* causes $\sim 25\%$ of cases, other *Candida* species cause $\sim 25\%$, *Aspergillus* species (notably *Aspergillus fumigatus*, *Aspergillus flavus* and *Aspergillus terreus*) cause 25% and a wide variety of other fungi are implicated in

Table 8. Summary of treatment recommendations for fungal endocarditis

| Antifungal agent | Dose/route | Serum levels required? | Role in treating <i>Candida</i> endocarditis | Role in treating <i>Aspergillus</i> endocarditis |
|------------------|---|---------------------------------------|--|--|
| Fluconazole | 400 mg daily, only reduced in severe renal failure/dialysis | no | long-term suppressive therapy | none |
| Voriconazole | intravenous therapy preferred initially, licensed doses | yes, with dose modification important | long-term suppressive therapy for fluconazole-resistant, voriconazole-susceptible isolates | first-line therapy with long-term suppression |
| Amphotericin B | 3 mg/kg/24 h (AmBisome) 5 mg/kg/day (Abelcet) 1 mg/kg/day (Fungizone) | no | second-line therapy | second-line therapy, or first line if azole resistance; should not be used for <i>A. terreus</i> or <i>A. nidulans</i> infection |
| Micafungin | 200 mg daily | no | first-line therapy | third- or fourth-line therapy |
| Caspofungin | 70 mg loading, 50–100 mg daily | no | first-line therapy | no role |
| Anidulafungin | licensed doses | no | first-line therapy | no role |
| Posaconazole | 400 mg twice daily | yes | no role | third- or fourth-line therapy, long-term suppressive therapy |
| Flucytosine | 100 mg/kg/day in three doses, reduced with renal dysfunction | yes, with dose modification important | as combination therapy with amphotericin B | as combination therapy with amphotericin B |
| Itraconazole | NA | NA | no role | no role |

NA, not applicable.

the remaining 25% of cases.¹²⁶ Fungal endocarditis is most common in patients with prosthetic valves, but also occurs in intravenous drug abusers, neonates and immunocompromised patients. *Candida* endocarditis is usually a healthcare-associated infection (87%),¹²⁵ and ~75% of *Aspergillus* endocarditis cases follow some form of cardiac surgery and may occur in clusters related to contaminated operating room air¹²⁷ or high spore counts in the ward environment.¹²⁸ Almost all cases of *Aspergillus* endocarditis have occurred in adults, but premature neonates with candidaemia may also develop *Candida* endocarditis.

14.1 *Candida* endocarditis

Recommendation 14.1: Initial treatment should be with an echinocandin or amphotericin B (preferably a lipid preparation), and modified, once the species and susceptibility profile is known, if required. [C]

Recommendation 14.2: Surgical valve replacement is highly desirable, if technically feasible. [C]

The outcome following antifungal treatment for *Candida* endocarditis may have improved slightly over the past 5 years. Some reports indicate better outcomes following medical and surgical intervention; others indicate equivalent outcomes. In neonates, medical therapy alone is as successful as combined therapy,¹²⁹ although each case should be considered on its merits. In adults, the outcome following medical therapy alone was as good as that following combined medical and surgical therapy.¹³⁰ However, individual circumstances vary substantially and clinical judgement is required to assess the relative risks in each patient. The surgical excision of infected material may be critically important in patients with relatively resistant

organisms, systemic emboli, valvular dysfunction or other complicating factors preventing adequate medical therapy, such as drug intolerance or significant renal dysfunction. For those infected with susceptible *Candida* isolates, antifungal treatment with lipid-associated amphotericin B or an echinocandin (most experience is with caspofungin) is first line. Many authorities recommend the addition of flucytosine to amphotericin B. Amphotericin B therapy is preferred to echinocandin therapy in those infected with *Candida parapsilosis*, *Candida guilliermondii* and *Candida famata*, as these organisms are intrinsically less susceptible to, and rarely killed by, the echinocandins. Echinocandin therapy is preferred in those with *Candida krusei* infection, as this organism is less susceptible to amphotericin B. Intravenous therapy should not be for <4 weeks and may need to be for much longer. Long-term oral fluconazole therapy, for those with susceptible organisms, is appropriate after prolonged intravenous therapy.¹³¹ In those with infected prosthetic material, fluconazole may need to be lifelong.

14.2 *Aspergillus* endocarditis

Recommendation 14.3: Initial treatment should be with voriconazole, with confirmation of susceptibility of the isolate to voriconazole and therapeutic drug monitoring. [C]

Recommendation 14.4: Surgical valve replacement is mandatory for survival. [B]

Surgical excision and valve replacement is important for a successful outcome in *Aspergillus* valvular endocarditis; exceptionally few patients have ever survived without surgical intervention. Optimal antifungal therapy is not clear, but voriconazole as first-line therapy is recommended for several reasons. In

an animal model of *Aspergillus* endocarditis, voriconazole at adequate doses was curative.¹³² Several case reports have indicated success with voriconazole. Voriconazole is the recommended primary therapy for other sites of invasive *Aspergillus*.^{133–135} However, the pre-clinical data indicate that it is critical in *Aspergillus* endocarditis to achieve adequate plasma concentrations of voriconazole, that some patients cannot tolerate voriconazole and that some azole resistance has been described in *A. fumigatus*. In these circumstances lipid-associated amphotericin B would be appropriate, possibly with flucytosine. Both *A. terreus* and *Aspergillus nidulans* are amphotericin B resistant, in which case oral posaconazole therapy might be a better substitute for voriconazole than amphotericin B, if required. Echinocandins are not recommended as they are never fungicidal for *Aspergillus* species.

14.3 Endocarditis due to other fungi

A large number of other fungi have caused fungal endocarditis, including *Histoplasma capsulatum*,¹³⁶ *Penicillium* spp.,¹³⁷ various Mucorales species,¹²⁶ *Trichosporon* spp., *Paecilomyces* spp. and numerous other rare fungi. Overall, these rare fungi may account for as many as 25% of all mycological cases, but publication bias is probably partly responsible for this disproportionately high frequency compared with other forms of invasive fungal disease. Management requires optimizing antifungal therapy, recognizing a much higher proportion of intrinsic antifungal resistance amongst these fungi than among *Aspergillus* and *Candida* spp.

14.4 General recommendations

A positive culture result is highly desirable, so excised valves and tissue should be cultured for fungi as well as bacteria, and isolates should not be discarded. Susceptibility testing must be undertaken for any fungus causing endocarditis, including the determination of minimal fungicidal concentrations. Azole resistance in *A. fumigatus* and both echinocandin and azole resistance in *Candida* spp. are of particular concern. If fungi continue to be isolated from blood cultures obtained after 1 week of treatment, they should also be susceptibility tested, as resistance may emerge on therapy. Fungal blood cultures should continue to be taken for at least the first 2 weeks on therapy and if any deterioration occurs, after this. In cases where no cultures have been positive, but tissue is available, molecular methods of speciation should be used as histopathology interpretation is inadequate to guide therapy optimally. For drugs with variable bioavailability (especially the azoles and flucytosine), therapeutic drug monitoring is important. Key biomarkers (antigen, PCR, glucan, imaging to include vegetation size measurements and antibody) should be obtained before therapy to assist with monitoring antifungal therapy, including recognizing breakthrough infection.

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