



Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009)

The Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC)

Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and by the International Society of Chemotherapy (ISC) for Infection and Cancer

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Table of Contents

A. Preamble	2371	J. Other complications of infective endocarditis	
B. Justification/scope of the problem	2372	Part 1. Neurological complications, antithrombotic therapy	2395
C. Epidemiology	2372	Part 2. Other complications (infectious aneurysms, acute renal failure, rheumatic complications, splenic abscess, myocarditis, pericarditis)	2396
A changing epidemiology	2372	K. Outcome after discharge and long-term prognosis	2397
Incidence of infective endocarditis	2373	Recurrences: relapses and reinfections	2397
Types of infective endocarditis	2373	Heart failure and need for valvular surgery	2398
Microbiology	2373	Long-term mortality	2398
D. Pathophysiology	2374	Follow-up	2398
The valve endothelium	2374	L. Specific situations	
Transient bacteraemia	2374	Part 1. Prosthetic valve endocarditis	2398
Microbial pathogens and host defences	2374	Part 2. Infective endocarditis on pacemakers and implantable defibrillators	2400
E. Preventive measures	2375	Part 3. Right-sided infective endocarditis	2401
Evidence justifying the use of antibiotic prophylaxis for infective endocarditis in previous ESC recommendations	2375	Part 4. Infective endocarditis in congenital heart disease	2403
Reasons justifying revision of previous ESC Guidelines	2375	Part 5. Infective endocarditis in the elderly	2404
Principles of the new ESC Guidelines	2376	Part 6. Infective endocarditis during pregnancy	2404
Limitations and consequences of the new ESC Guidelines	2378	M. References	2404
F. Diagnosis	2378		
Clinical features	2378		
Echocardiography	2379		
Microbiological diagnosis	2380		
Diagnostic criteria and their limitations	2382		
G. Prognostic assessment at admission	2383		
H. Antimicrobial therapy: principles and methods	2383		
General principles	2383		
Penicillin-susceptible oral streptococci and group D streptococci	2384		
Penicillin-resistant oral streptococci and group D streptococci	2384		
<i>Streptococcus pneumoniae</i> , β-haemolytic streptococci (groups A, B, C, and G)	2384		
Nutritionally variant streptococci	2384		
<i>Staphylococcus aureus</i> and coagulase-negative staphylococci	2386		
Methicillin-resistant and vancomycin-resistant staphylococci	2387		
<i>Enterococcus</i> spp.	2387		
Gram-negative bacteria	2387		
Blood culture-negative infective endocarditis	2387		
Fungi	2388		
Empirical therapy	2388		
Outpatient parenteral antibiotic therapy for infective endocarditis	2389		
I. Complications and indications for surgery in left-sided native valve infective endocarditis	2391		
Part 1. Indications and optimal timing of surgery	2391		
Heart failure	2391		
Uncontrolled infection	2392		
Prevention of systemic embolism	2393		
Part 2. Principles, methods, and immediate results of surgery	2394		
Pre- and peri-operative management	2394		
Surgical approach and techniques	2394		
Operative mortality, morbidity, and post-operative complications	2394		

A. Preamble

Guidelines and Expert Consensus Documents summarize and evaluate all currently available evidence on a particular issue with the aim of assisting physicians in selecting the best management strategy for an individual patient suffering from a given condition, taking into account the impact on outcome, as well as the risk/benefit ratio of particular diagnostic or therapeutic means. Guidelines are no substitutes for textbooks. The legal implications of medical guidelines have been discussed previously.

A great number of Guidelines and Expert Consensus Documents have been issued in recent years by the European Society of Cardiology (ESC) as well as by other societies and organizations. Because of the impact on clinical practice, quality criteria for development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines and Expert Consensus Documents can be found on the ESC website (<http://www.escardio.org/knowledge/guidelines/rules>).

In brief, experts in the field are selected and undertake a comprehensive review of the published evidence for management and/or prevention of a given condition. A critical evaluation of diagnostic and therapeutic procedures is performed including assessment of the risk/benefit ratio. Estimates of expected health outcomes for larger societies are included, where data exist. The level of evidence and the strength of recommendation of particular treatment options are weighed and graded according to predefined scales, as outlined in Tables 1 and 2.

The experts of the writing panels have provided disclosure statements of all relationships they may have which might be perceived as real or potential sources of conflicts of interest. These disclosure forms are kept on file at the European Heart House, headquarters of the ESC. Any changes in conflict of interest that

arise during the writing period must be notified to the ESC. The Task Force report received its entire financial support from the ESC and was developed without any involvement of the pharmaceutical, device, or surgical industry.

The ESC Committee for Practice Guidelines (CPG) supervises and coordinates the preparation of new Guidelines and Expert Consensus Documents produced by Task Forces, expert groups, or consensus panels. The Committee is also responsible for the endorsement process of these Guidelines and Expert Consensus Documents or statements. Once the document has been finalized and approved by all the experts involved in the Task Force, it is submitted to outside specialists for review. The document is revised, and finally approved by the CPG and subsequently published.

After publication, dissemination of the message is of paramount importance. Pocket-sized versions and personal digital assistant (PDA)-downloadable versions are useful at the point of care. Some surveys have shown that the intended users are sometimes unaware of the existence of guidelines, or simply do not translate them into practice. Thus, implementation programmes for new guidelines form an important component of knowledge dissemination. Meetings are organized by the ESC, and directed towards its member National Societies and key opinion leaders in Europe. Implementation meetings can also be undertaken at national levels, once the guidelines have been endorsed by the ESC member societies, and translated into the national language. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Thus, the task of writing Guidelines or Expert Consensus documents covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. The loop between clinical research, writing of guidelines, and implementing them into clinical

Table I Classes of recommendations

Classes of Recommendations	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

Table 2 Levels of evidence

Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of Evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

practice can then only be completed if surveys and registries are performed to verify that real-life daily practice is in keeping with what is recommended in the guidelines. Such surveys and registries also make it possible to evaluate the impact of implementation of the guidelines on patient outcomes. Guidelines and recommendations should help the physicians to make decisions in their daily practice. However, the ultimate judgement regarding the care of an individual patient must be made by the physician in charge of his/her care.

B. Justification/scope of the problem

Infective endocarditis (IE) is a peculiar disease for at least three reasons:

First, neither the incidence nor the mortality of the disease have decreased in the past 30 years.¹ Despite major advances in both diagnostic and therapeutic procedures, this disease still carries a poor prognosis and a high mortality.

Secondly, IE is not a uniform disease, but presents in a variety of different forms, varying according to the initial clinical manifestation, the underlying cardiac disease (if any), the microorganism involved, the presence or absence of complications, and underlying patient characteristics. For this reason, IE requires a collaborative approach, involving primary care physicians, cardiologists, surgeons, microbiologists, infectious disease specialists, and frequently others, including neurologists, neurosurgeons, radiologists, and pathologists.²

Thirdly, guidelines are often based on expert opinion because of the low incidence of the disease, the absence of randomized trials, and the limited number of meta-analyses.^{3,4}

Several reasons justify the decision of the ESC to update the previous guidelines published in 2004.³ IE is clearly an evolving disease, with changes in its microbiological profile, a higher incidence of health care-associated cases, elderly patients, and patients with intracardiac devices or prostheses. Conversely, cases related to rheumatic disease have become less frequent in industrialized nations. In addition, several new national and international guidelines or state-of-the-art papers have been published in recent years.^{3–13} Unfortunately, their conclusions are not uniform, particularly in the field of prophylaxis, where conflicting recommendations have been formulated.^{3,4,6,8–13} Clearly, an objective for the next few years will be an attempt to harmonize these recommendations.

The main objective of the current Task Force was to provide clear and simple recommendations, assisting health care providers

in clinical decision making. These recommendations were obtained by expert consensus after thorough review of the available literature. An evidence-based scoring system was used, based on a classification of the strength of recommendation and the levels of evidence.

C. Epidemiology

A changing epidemiology

The epidemiological profile of IE has changed substantially over the last few years, especially in industrialized nations.¹ Once a disease affecting young adults with previously well-identified (mostly rheumatic) valve disease, IE is now affecting older patients who more often develop IE as the result of health care-associated procedures, either in patients with no previously known valve disease¹⁴ or in patients with prosthetic valves.¹⁵

A recent systematic review of 15 population-based investigations accounting for 2371 IE cases from seven developed countries (Denmark, France, Italy, The Netherlands, Sweden, the UK, and the USA) showed an increasing incidence of IE associated with a prosthetic valve, an increase in cases with underlying mitral valve prolapse, and a decrease in those with underlying rheumatic heart disease.¹⁶

Newer predisposing factors have emerged—valve prostheses, degenerative valve sclerosis, intravenous drug abuse—associated with increased use of invasive procedures at risk for bacteraemia, resulting in health care-associated IE.¹⁷ In a pooled analysis of 3784 episodes of IE, it was shown that oral streptococci had fallen into second place to staphylococci as the leading cause of IE.¹ However, this apparent temporal shift from predominantly streptococcal to predominantly staphylococcal IE may be partly due to recruitment/referral bias in specialized centres, since this trend is not evident in population-based epidemiological surveys of IE.¹⁸ In developing countries, classical patterns persist. In Tunisia, for instance, most cases of IE develop in patients with rheumatic valve disease, streptococci predominate, and up to 50% may be associated with negative blood cultures.¹⁹ In other African countries, the persistence of a high burden of rheumatic fever, rheumatic valvular heart diseases, and IE has also been highlighted.²⁰

In addition, significant geographical variations have been shown. The highest increase in the rate of staphylococcal IE has been reported in the USA,²¹ where chronic haemodialysis, diabetes mellitus, and intravascular devices are the three main factors

associated with the development of *Staphylococcus aureus* endocarditis.^{21,22} In other countries, the main predisposing factor for *S. aureus* IE may be intravenous drug abuse.²³

Incidence of infective endocarditis

The incidence of IE ranges from one country to another within 3–10 episodes/100 000 person-years.^{14,24–26} This may reflect methodological differences between surveys rather than true variation. Of note, in these surveys, the incidence of IE was very low in young patients but increased dramatically with age—the peak incidence was 14.5 episodes/100 000 person-years in patients between 70 and 80 years of age. In all epidemiological studies of IE, the male:female ratio is $\geq 2:1$, although this higher proportion of men is poorly understood. Furthermore, female patients may have a worse prognosis and undergo valve surgery less frequently than their male counterparts.²⁷

Types of infective endocarditis

IE should be regarded as a set of clinical situations which are sometimes very different from each other. In an attempt to avoid overlap, the following four categories of IE must be separated, according to the site of infection and the presence or absence of intracardiac foreign material: left-sided native valve IE, left-sided

prosthetic valve IE, right-sided IE, and device-related IE (the latter including IE developing on pacemaker or defibrillator wires with or without associated valve involvement) (Table 3). With regard to acquisition, the following situations can be identified: community-acquired IE, health care-associated IE (nosocomial and non-nosocomial), and IE in intravenous drug abusers (IVDAs).

Microbiology

According to microbiological findings, the following categories are proposed:

1. Infective endocarditis with positive blood cultures

This is the most important category, representing $\sim 85\%$ of all IE. Causative microorganisms are most often staphylococci, streptococci, and enterococci.²⁸

a. Infective endocarditis due to streptococci and enterococci

Oral (formerly viridans) streptococci form a mixed group of microorganisms, which includes species such as *S. sanguis*, *S. mitis*, *S. salivarius*, *S. mutans*, and *Gemella morbillorum*. Microorganisms of this group are almost always susceptible to penicillin G. Members of the '*S. milleri*' or '*S. anginosus*' group (*S. anginosus*, *S. intermedius*, and *S. constellatus*) must be distinguished since they

Table 3 Classification and definitions of infective endocarditis

IE according to localization of infection and presence or absence of intracardiac material	
• Left-sided native valve IE	
• Left-sided prosthetic valve IE (PVE)	
- Early PVE: < 1 year after valve surgery	
- Late PVE: > 1 year after valve surgery	
• Right-sided IE	
• Device-related IE (permanent pacemaker or cardioverter-defibrillator)	
IE according to the mode of acquisition²²	
• Health care-associated IE	
- Nosocomial:	IE developing in a patient hospitalized > 48 hours prior to the onset of signs / symptoms consistent with IE
- Non nosocomial:	Signs and / or symptoms of IE starting < 48 hours after admission in a patient with health care contact defined as: 1) home-based nursing or intravenous therapy, haemodialysis, or intravenous chemotherapy < 30 days before the onset of IE; or 2) hospitalized in an acute care facility < 90 days before the onset of IE; or 3) resident in a nursing home or long-term care facility
• Community-acquired IE	Signs and / or symptoms of IE starting < 48 hours after admission in a patient not fulfilling the criteria for health care-associated infection
• Intravenous drug abuse-associated IE	IE in an active injection drug user without alternative source of infection
Active IE	
• IE with persistent fever and positive blood cultures or	
• Active inflammatory morphology found at surgery or	
• Patient still under antibiotic therapy or	
• Histopathological evidence of active IE	
Recurrence	
• Relapse:	Repeat episodes of IE caused by the same microorganism < 6 months after the initial episode
• Reinfection:	Infection with a different microorganism Repeat episode of IE caused by the same microorganism > 6 months after the initial episode

tend to form abscesses and cause haematogenously disseminated infection, often requiring a longer duration of antibiotic treatment. Likewise, nutritionally variant ‘defective’ streptococci, recently reclassified into other species (*Abiotrophia* and *Granulicatella*), should also be distinguished since they are often tolerant to penicillin [minimal bactericidal concentration (MBC) much higher than the minimal inhibitory concentration (MIC)]. Group D streptococci form the ‘*Streptococcus bovis/Streptococcus equinus*’ complex, including commensal species of the human intestinal tract, and were until recently gathered under the name of *Streptococcus bovis*. They are usually sensitive to penicillin G, like oral streptococci. Among enterococci, *E. faecalis*, *E. faecium*, and to a lesser extent *E. durans*, are the three species that cause IE.

b. Staphylococcal infective endocarditis

Traditionally, native valve staphylococcal IE is due to *S. aureus*, which is most often susceptible to oxacillin, at least in community-acquired IE. In contrast, staphylococcal prosthetic valve IE is more frequently due to coagulase-negative staphylococci (CNS) with oxacillin resistance. However, in a recent study of 1779 cases of IE collected prospectively in 16 countries, *S. aureus* was the most frequent cause not only of IE but also of prosthetic valve IE.²² Conversely, CNS can also cause native valve IE,^{29–31} especially *S. lugdunensis*, which frequently has an aggressive clinical course.

2. Infective endocarditis with negative blood cultures because of prior antibiotic treatment

This situation arises in patients who received antibiotics for unexplained fever before any blood cultures were performed and in whom the diagnosis of IE was not considered; usually the diagnosis is eventually considered in the face of relapsing febrile episodes following antibiotic discontinuation. Blood cultures may remain negative for many days after antibiotic discontinuation, and causative organisms are most often oral streptococci or CNS.

3. Infective endocarditis frequently associated with negative blood cultures

They are usually due to fastidious organisms such as nutritionally variant streptococci, fastidious Gram-negative bacilli of the HACEK group (*Haemophilus parainfluenzae*, *H. aphrophilus*, *H. paraphrophilus*, *H. influenzae*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*, and *K. denitrificans*), *Brucella*, and fungi.

4. Infective endocarditis associated with constantly negative blood cultures

They are caused by intracellular bacteria such as *Coxiella burnetii*, *Bartonella*, *Chlamydia*, and, as recently demonstrated, *Tropheryma whipplei*, the agent of Whipple’s disease.³² Overall, these account for up to 5% of all IE. Diagnosis in such cases relies on serological testing, cell culture or gene amplification.

D. Pathophysiology

The valve endothelium

The normal valve endothelium is resistant to colonization and infection by circulating bacteria. However, mechanical disruption of the endothelium results in exposure of underlying extracellular matrix proteins, the production of tissue factor, and the deposition of fibrin and platelets as a normal healing process. Such non-bacterial thrombotic endocarditis (NBTE) facilitates bacterial adherence and infection. Endothelial damage may result from mechanical lesions provoked by turbulent blood flow, electrodes or catheters, inflammation, as in rheumatic carditis, or degenerative changes in elderly individuals, which are associated with inflammation, microulcers, and microthrombi. Degenerative valve lesions are detected by echocardiography in up to 50% of asymptomatic patients over 60 years,³³ and in a similar proportion of elderly patients with IE. This might account for the increased risk of IE in the elderly.

Endothelial inflammation without valve lesions may also promote IE. Local inflammation triggers endothelial cells to express integrins of the β1 family (very late antigen). Integrins are transmembrane proteins that can connect extracellular determinants to the cellular cytoskeleton. Integrins of the β1 family bind circulating fibronectin to the endothelial surface while *S. aureus* and some other IE pathogens carry fibronectin-binding proteins on their surface. Hence, when activated endothelial cells bind fibronectin they provide an adhesive surface to circulating staphylococci. Once adherent, *S. aureus* trigger their active internalization into valve endothelial cells, where they can either persist and escape host defences and antibiotics, or multiply and spread to distant organs.³⁴ Thus, there are at least two scenarios for primary valve infection: one involving a physically damaged endothelium, favouring infection by most types of organism, and one occurring on physically undamaged endothelium, promoting IE due to *S. aureus* and other potential intracellular pathogens.

Transient bacteraemia

The role of bacteraemia has been studied in animals with catheter-induced NBTE. Both the magnitude of bacteraemia and the ability of the pathogen to attach to damaged valves are important.³⁵ Of note, bacteraemia does not occur only after invasive procedures, but also as a consequence of chewing and tooth brushing. Such spontaneous bacteraemia is of low grade and short duration [1–100 colony-forming units (cfu)/ml of blood for <10 min], but its high incidence may explain why most cases of IE are unrelated to invasive procedures.^{26,36}

Microbial pathogens and host defences

Classical IE pathogens (*S. aureus*, *Streptococcus* spp., and *Enterococcus* spp.) share the ability to adhere to damaged valves, trigger local procoagulant activity, and nurture infected vegetations in which they can survive.³⁷ They are equipped with numerous surface determinants that mediate adherence to host matrix molecules present on damaged valves (e.g. fibrinogen, fibronectin, platelet proteins) and trigger platelet activation. Following colonization, adherent bacteria must escape host defences. Gram-

positive bacteria are resistant to complement. However, they may be the target of platelet microbicidal proteins (PMPs), which are produced by activated platelets and kill microbes by disturbing their plasma membrane. Bacteria recovered from patients with IE are consistently resistant to PMP-induced killing, whereas similar bacteria recovered from patients with other types of infection are susceptible.³⁸ Thus, escaping PMP-induced killing is a typical characteristic of IE-causing pathogens.

E. Preventive measures

Evidence justifying the use of antibiotic prophylaxis for infective endocarditis in previous ESC recommendations

The principle of prophylaxis for IE was developed on the basis of observational studies in the early 20th century.³⁹ The basic hypothesis is based on the assumption that bacteraemia subsequent to medical procedures can cause IE, particularly in patients with predisposing factors, and that prophylactic antibiotics can prevent IE in these patients by minimizing or preventing bacteraemia, or by altering bacterial properties leading to reduced bacterial adherence on the endothelial surface. The recommendations for prophylaxis are based in part on the results of animal studies showing that antibiotics could prevent the development of experimental IE after inoculation of bacteria.⁴⁰

Reasons justifying revision of previous ESC Guidelines

Within these guidelines, the Task Force aimed to avoid extensive, non-evidence-based use of antibiotics for all at-risk patients undergoing interventional procedures, but to limit prophylaxis to the highest risk patients. The main reasons justifying the revision of previous recommendations are the following:

1. Incidence of bacteraemia after dental procedures and during daily routine activities

The reported incidence of transient bacteraemia after dental procedures is highly variable and ranges from 10 to 100%.⁴¹ This may be a result of different analytical methods and sampling procedures, and these results should be interpreted with caution. The incidence after other types of medical procedures is even less well established. In contrast, transient bacteraemia is reported to occur frequently in the context of daily routine activities such as tooth brushing, flossing, or chewing.^{42,43} It therefore appears plausible that a large proportion of IE-causing bacteraemia may derive from these daily routine activities. In addition, in patients with poor dental health, bacteraemia can be observed independently of dental procedures, and rates of post-procedural bacteraemia are higher in this group. These findings emphasize the importance of good oral hygiene and regular dental review to prevent IE.⁴⁴

2. Risks and benefits of prophylaxis

The following considerations are critical with respect to the assumption that antibiotic prophylaxis can efficiently prevent IE in patients who are at increased lifetime risk of the disease:

- (a) Increased lifetime risk of IE is not an ideal measure of the extent to which a patient may benefit from antibiotic prophylaxis for distinct procedures. A better parameter, the procedure-related risk, ranges from 1:14 000 000 for dental procedures in the average population to 1:95 000 in patients with previous IE.^{45,46} These estimations demonstrate the huge number of patients that will require treatment to prevent one single case of IE.
- (b) In the majority of patients, no potential index procedure preceding the first clinical appearance of IE can be identified.²⁶ Even if effectiveness and compliance are assumed to approximate 100%, this observation leads to two conclusions: (i) IE prophylaxis can at best only protect a small proportion of patients;⁴⁷ and (ii) the bacteraemia that causes IE in the majority of patients appears to derive from another source.
- (c) Antibiotic administration carries a small risk of anaphylaxis. However, no case of fatal anaphylaxis has been reported in the literature after oral amoxicillin administration for prophylaxis of IE.⁴⁸
- (d) Widespread and often inappropriate use of antibiotics may result in the emergence of resistant microorganisms. However, the extent to which antibiotic use for IE prophylaxis could be implicated in the general problem of resistance is unknown.⁴⁴

3. Lack of scientific evidence for the efficacy of infective endocarditis prophylaxis

Studies reporting on the efficacy of antibiotic prophylaxis to prevent or alter bacteraemia in humans after dental procedures are contradictory,^{49,50} and so far there are no data demonstrating that reduced duration or frequency of bacteraemia after any medical procedure leads to a reduced procedure-related risk of IE.

Similarly, no sufficient evidence exists from case-control studies^{36,51,52} to support the necessity of IE prophylaxis. Even strict adherence to generally accepted recommendations for prophylaxis might have little impact on the total number of patients with IE in the community.⁵²

Finally, the concept of antibiotic prophylaxis efficacy itself has never been investigated in a prospective randomized controlled trial,⁵³ and assumptions on efficacy are based on non-uniform expert opinion, data from animal experiments, case reports, studies on isolated aspects of the hypothesis, and contradictory observational studies.

Recent guideline committees of national cardiovascular societies have re-evaluated the existing scientific evidence in this field.^{6,9–11} Although the individual recommendations of these committees differ in some aspects, they did uniformly and independently draw four conclusions:

- (1) The existing evidence does not support the extensive use of antibiotic prophylaxis recommended in previous guidelines.
- (2) Prophylaxis should be limited to the highest risk patients (patients with the highest incidence of IE and/or highest risk of adverse outcome from IE).
- (3) The indications for antibiotic prophylaxis for IE should be reduced in comparison with previous recommendations.

- (4) Good oral hygiene and regular dental review are of particular importance for the prevention of IE.

Principles of the new ESC Guidelines

Although recent guidelines proposed limitation of prophylaxis to patients at increased risk of adverse outcome of IE⁶ or even complete cessation of antibiotic prophylaxis in any patient groups,¹² the Task Force decided:

- to maintain the principle of antibiotic prophylaxis when performing procedures at risk of IE in patients with predisposing cardiac conditions, *but*

- to limit its indication to patients with the highest risk of IE (Table 4) undergoing the highest risk procedures (Table 5).

1. Patients with the highest risk of infective endocarditis (Table 4)

They include three categories of patients:

- (a) Patients with a prosthetic valve or a prosthetic material used for cardiac valve repair: these patients have a higher risk of IE, a higher mortality from IE and more often develop complications of the disease than patients with native valves and an identical pathogen.^{54,55}

Table 4 Cardiac conditions at highest risk of infective endocarditis for which prophylaxis is recommended when a high risk procedure is performed

Recommendations: prophylaxis	Class ^a	Level ^b
Antibiotic prophylaxis should only be considered for patients at highest risk of IE 1. Patients with a prosthetic valve or a prosthetic material used for cardiac valve repair 2. Patients with previous IE 3. Patients with congenital heart disease a. cyanotic congenital heart disease, without surgical repair; or with residual defects, palliative shunts or conduits b. congenital heart disease with complete repair with prosthetic material whether placed by surgery or by percutaneous technique, up to 6 months after the procedure c. when a residual defect persists at the site of implantation of a prosthetic material or device by cardiac surgery or percutaneous technique	IIa	C
Antibiotic prophylaxis is no longer recommended in other forms of valvular or congenital heart disease	III	C

^aClass of recommendation.

^bLevel of evidence.

Table 5 Recommendations for prophylaxis of infective endocarditis in highest risk patients according to the type of procedure at risk

Recommendations: prophylaxis	Class ^a	Level ^b
A - Dental procedures: Antibiotic prophylaxis should only be considered for dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa	IIa	C
Antibiotic prophylaxis is not recommended for local anaesthetic injections in non-infected tissue, removal of sutures, dental X-rays, placement or adjustment of removable prosthodontic or orthodontic appliances or braces. Prophylaxis is also not recommended following the shedding of deciduous teeth or trauma to the lips and oral mucosa	III	C
B - Respiratory tract procedures*: Antibiotic prophylaxis is not recommended for respiratory tract procedures, including bronchoscopy or laryngoscopy, transnasal or endotracheal intubation	III	C
C - Gastrointestinal or urogenital procedures*: Antibiotic prophylaxis is not recommended for gastroscopy, colonoscopy, cystoscopy or transoesophageal echocardiography	III	C
D - Skin and soft tissue*: Antibiotic prophylaxis is not recommended for any procedure	III	C

^aClass of recommendation.

^bLevel of evidence.

*For management when infections are present, please refer to text.

- (b) Patients with previous IE: they also have a greater risk of new IE, higher mortality and incidence of complications than patients with a first episode of IE.^{56,57}
- (c) Patients with congenital heart disease (CHD), in particular those with complex cyanotic heart disease and those who have post-operative palliative shunts, conduits, or other prostheses.^{58,59} After surgical repair with no residual defects, the Task Force recommends prophylaxis for the first 6 months after the procedure until endothelialization of the prosthetic material occurs.

Although AHA guidelines recommend prophylaxis in cardiac transplant recipients who develop cardiac valvulopathy,⁶ this is not supported by strong evidence. In addition, although the risk of adverse outcome is high when IE occurs in transplant patients, the probability of IE from dental origin is extremely low in these patients.⁶⁰ The ESC Task Force does not recommend prophylaxis in such situations.

Prophylaxis is not recommended for any other form of native valve disease (including the most commonly identified conditions, bicuspid aortic valve, mitral valve prolapse, and calcific aortic stenosis).

2. Highest risk procedures (*Table 5*)

a. Dental procedures

Procedures at risk involve the manipulation of the gingival or periapical region of teeth or perforation of the oral mucosa (including scaling and root canal procedures). Prophylaxis should only be considered for patients described in *Table 4* undergoing any of these procedures, and is not recommended in other situations. The main targets for antibiotic prophylaxis in these patients are oral streptococci. *Table 6* summarizes the main regimens of antibiotic prophylaxis recommended before dental procedures. The impact of increasing resistance of these pathogens for the efficacy of antibiotic prophylaxis is unclear.

Fluoroquinolones and glycopeptides are not recommended due to their unclear efficacy and the potential induction of resistance.

b. Other at-risk procedures

There is no compelling evidence that bacteraemia resulting from either respiratory tract procedures, gastrointestinal or genitourinary procedures, dermatological or musculoskeletal procedures

cause IE. Thus, prophylaxis is not recommended in patients undergoing these procedures.

i. Respiratory tract procedures. Patients listed in *Table 4* who undergo an invasive respiratory tract procedure to treat an established infection, e.g. drainage of an abscess, should receive an antibiotic regimen which contains an anti-staphylococcal penicillin or cephalosporin. Vancomycin should be given to patients unable to tolerate a β-lactam. Vancomycin or another suitable agent should be administered if the infection is known or suspected to be caused by a methicillin-resistant strain of *S. aureus* (MRSA).

ii. Gastrointestinal or genitourinary procedures. In the case of an established infection or if antibiotic therapy is indicated to prevent wound infection or sepsis associated with a gastrointestinal or genitourinary tract procedure in patients described in *Table 4*, it is reasonable that the antibiotic regimen includes an agent active against enterococci, e.g. ampicillin, amoxicillin, or vancomycin. Vancomycin should only be administered to patients unable to tolerate β-lactams. If infection is caused by a known or suspected strain of resistant enterococcus, consultation with an infectious diseases specialist is recommended.

iii. Dermatological or musculoskeletal procedures. For patients described in *Table 4* undergoing surgical procedures involving infected skin (including oral abscesses), skin structure, or musculoskeletal tissue, it is reasonable that the therapeutic regimen contains an agent active against staphylococci and β-haemolytic streptococci, e.g. an anti-staphylococcal penicillin or cephalosporin. Vancomycin or clindamycin may be used in patients unable to tolerate a β-lactam. If the infection is known or suspected to be caused by MRSA, vancomycin or another suitable agent should be administered.

iv. Body piercing and tattooing. These growing social trends are a cause for concern, particularly for those individuals with CHD who are at increased susceptibility for the acquisition of IE. Case reports of IE after piercing and tattooing are increasing,⁶¹ particularly when piercing involves the tongue,^{62,63} although publication bias may overestimate the problem since millions of people are tattooed and pierced around the world and CHD concerns only 1% of the general population. Currently no data are available on (a) the incidence of IE after such procedures and (b) the efficacy of antibiotics for prevention. Education of patients at risk of IE is paramount, and piercing and tattooing procedures should be discouraged. If undertaken, procedures should be performed under strictly sterile conditions though antibiotic prophylaxis is not recommended.

Table 6 Recommended prophylaxis for dental procedures at risk

Situation	Antibiotic	Single dose 30–60 minutes before procedure	
		Adults	Children
No allergy to penicillin or ampicillin	Amoxicillin or ampicillin*	2 g p.o. or i.v.	50 mg/kg p.o. or i.v.
Allergy to penicillin or ampicillin	Clindamycin	600 mg p.o. or i.v.	20 mg/kg p.o. or i.v.

Cephalosporins should not be used in patients with anaphylaxis, angio-oedema, or urticaria after intake of penicillin and ampicillin.

* Alternatively cephalexin 2 g i.v. or 50 mg/kg i.v. for children, cefazolin or ceftiraxone 1 g i.v. for adults or 50 mg/kg i.v. for children.

v. *Cardiac or vascular surgery.* In patients undergoing implantation of a prosthetic valve or intravascular prosthetic or other foreign material, peri-operative antibiotic prophylaxis should be considered due to the increased risk and adverse outcome of an infection. The most frequent microorganisms underlying early (<1 year after surgery) prosthetic valve infections are CNS and *S. aureus*. Prophylaxis should be started immediately before the procedure, repeated if the procedure is prolonged, and terminated 48 h afterwards. It is strongly recommended that potential sources of dental sepsis are eliminated at least 2 weeks before implantation of a prosthetic valve or other intracardiac or intravascular foreign material, unless the latter procedure is urgent.

vi. *Procedures causing health care-associated IE.* They represent up to 30% of all cases of IE and are characterized by an increasing incidence and a severe prognosis, thus representing an important health problem.⁶⁴ Although routine antimicrobial prophylaxis administered before most invasive procedures is not recommended, aseptic measures during the insertion and manipulation of venous catheters and during any invasive procedures are mandatory to reduce the rate of this infection.

Limitations and consequences of the new ESC Guidelines

The Task Force understands that these updated recommendations dramatically change long-established practice for physicians, cardiologists, dentists, and their patients. Ethically, these practitioners need to discuss the potential benefit and harm of antibiotic prophylaxis with their patients before a final decision is made. Following informed review and discussion, many may wish to continue with routine prophylaxis, and these views should be respected. Practitioners may also have a reasonable fear of litigation should prophylaxis be withdrawn,⁶⁵ though unnecessarily so since adherence to recognized guidelines affords robust legal protection.⁶⁶

Finally, the current recommendations are not based on appropriate evidence, but reflect an expert consensus of opinion. As

neither the previous guidelines nor the current proposed modifications are based on strong evidence, the Task Force strongly recommends prospective evaluation in the wake of these new guidelines to evaluate whether reduced use of prophylaxis is associated with a change in the incidence of IE.

In summary, the Task Force proposes limitation of antibiotic prophylaxis to patients with the highest risk of IE undergoing the highest risk dental procedures. Good oral hygiene and regular dental review have a very important role in reducing the risk of IE. Aseptic measures are mandatory during venous catheters manipulation and during any invasive procedures in order to reduce the rate of health care-associated IE

F. Diagnosis

Clinical features

The diverse nature and evolving epidemiological profile of IE ensure it remains a diagnostic challenge.⁶⁷ The clinical history of IE is highly variable according to the causative microorganism, the presence or absence of pre-existing cardiac disease, and the mode of presentation. Thus, IE should be suspected in a variety of very different clinical situations (Table 7). 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 which may thwart or confuse initial assessment. Patients may therefore 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 involvement of a cardiologist and an infectious disease specialist to guide management is highly recommended.

Up to 90% of patients present with fever, often associated with systemic symptoms of chills, poor appetite, and weight loss. Heart

Table 7 Clinical presentation of infective endocarditis

IE must be suspected in the following situations

1. New regurgitant heart murmur
 2. Embolic events of unknown origin
 3. Sepsis of unknown origin (especially if associated with IE causative organism)
 4. Fever: the most frequent sign of IE.*
- IE should be suspected if fever is associated with:
- a. Intracardiac prosthetic material (e.g. prosthetic valve, pacemaker, implantable defibrillator, surgical baffle/conduit)
 - b. Previous history of IE
 - c. Previous valvular or congenital heart disease
 - d. Other predisposition for IE (e.g. immunocompromised state, IVDA)
 - e. Predisposition and recent intervention with associated bacteraemia
 - f. Evidence of congestive heart failure
 - g. New conduction disturbance
 - h. Positive blood cultures with typical IE causative organism or positive serology for chronic Q fever (microbiological findings may precede cardiac manifestations)
 - i. Vascular or immunologic phenomena: embolic event, Roth spots, splinter haemorrhages, Janeway lesions, Osler's nodes
 - j. Focal or non-specific neurological symptoms and signs
 - k. Evidence of pulmonary embolism/infiltration (right-sided IE)
 - l. Peripheral abscesses (renal, splenic, cerebral, vertebral) of unknown cause

*NB: Fever may be absent in the elderly, after antibiotic pre-treatment, in the immunocompromised patient and in IE involving less virulent or atypical organisms.

Table 8 Role of echocardiography in infective endocarditis

Recommendations: echocardiography	Class ^a	Level ^b
A - Diagnosis:		
1. TTE is recommended as the first-line imaging modality in suspected IE	I	B
2. TEE is recommended in patients with high clinical suspicion of IE and a normal TTE	I	B
3. Repeat TTE / TEE within 7–10 days are recommended in the case of an initially negative examination when clinical suspicion of IE remains high	I	B
4. TEE should be considered in the majority of adult patients with suspected IE, even in cases with positive TTE, owing to its better sensitivity and specificity, particularly for the diagnosis of abscesses and measurement of vegetation size.	IIa	C
5. TEE is not indicated in patients with a good-quality negative TTE and low clinical suspicion of IE	III	C
B - Follow-up under medical therapy		
1. Repeat TTE and TEE are recommended as soon as a new complication of IE is suspected (new murmur, embolism, persisting fever, heart failure, abscess, atrioventricular block)	I	B
2. Repeat TTE and TEE should be considered during follow-up of uncomplicated IE, in order to detect new silent complication and monitor vegetation size. The timing and mode (TTE or TEE) of repeat examination depend on the initial findings, type of microorganism, and initial response to therapy	IIa	B
C - Intra-operative echocardiography		
Intra-operative echocardiography is recommended in all cases of IE requiring surgery	I	C
D - Following completion of therapy		
TTE is recommended at completion of antibiotic therapy for evaluation of cardiac and valve morphology and function	I	C

^aClass of recommendation.^bLevel of evidence.

TEE = transoesophageal echocardiography; TTE = transthoracic echocardiography.

murmurs are found in up to 85% of patients. Classic textbook signs may still be seen in the developing world, although peripheral stigmata of IE are increasingly uncommon elsewhere, as patients generally present at an early stage of the disease. However, vascular and immunological phenomena such as splinter haemorrhages, Roth spots, and glomerulonephritis remain common, and emboli to the brain, lung or spleen occur in 30% of patients and are often the presenting feature.⁶⁸ In a febrile patient, the diagnostic suspicion may be strengthened by laboratory signs of infection, such as elevated C-reactive protein or sedimentation rate, leukocytosis, anaemia, and microscopic haematuria.³ However, these lack specificity and have not been integrated into current diagnostic criteria.⁷

Atypical presentation is common in elderly or immunocompromised patients,⁶⁹ in whom fever is less frequent than in younger individuals. A high index of suspicion and low threshold for investigation to exclude IE are therefore essential in these and other high-risk groups.

Echocardiography

Transthoracic and transoesophageal echocardiography (TTE/TEE) are now ubiquitous and their fundamental importance in diagnosis, management, and follow-up (Table 8) of IE is clearly recognized.⁷⁰

Echocardiography must be performed rapidly, as soon as IE is suspected. 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 yield⁷¹ (Figure 1). An exception is the patient with *S. aureus*

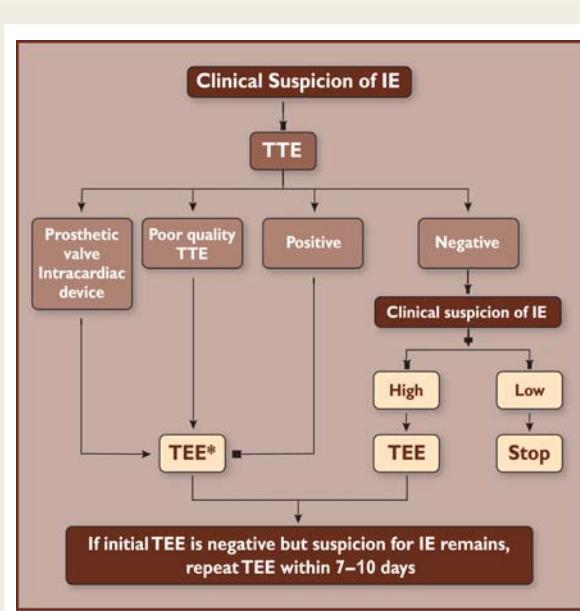


Figure 1 Indications for echocardiography in suspected infective endocarditis. IE = infective endocarditis; TEE = transoesophageal echocardiography; TTE = transthoracic echocardiography. *TEE is not mandatory in isolated right-sided native valve IE with good quality TTE examination and unequivocal echocardiographic findings.

Table 9 Anatomic and echocardiographic definitions

	Surgery/necropsy	Echocardiography
Vegetation	Infected mass attached to an endocardial structure, or on implanted intracardiac material	Oscillating or non oscillating intracardiac mass on valve or other endocardial structures, or on implanted intracardiac material
Abscess	Perivalvular cavity with necrosis and purulent material not communicating with the cardiovascular lumen	Thickened, non-homogeneous perivalvular area with echodense or echolucent appearance
Pseudoaneurysm	Perivalvular cavity communicating with the cardiovascular lumen	Pulsatile perivalvular echo-free space, with colour-Doppler flow detected
Perforation	Interruption of endocardial tissue continuity	Interruption of endocardial tissue continuity traversed by colour-Doppler flow
Fistula	Communication between two neighbouring cavities through a perforation	Colour-Doppler communication between two neighbouring cavities through a perforation
Valve aneurysm	Saccular outpouching of valvular tissue	Saccular bulging of valvular tissue
Dehiscence of a prosthetic valve	Dehiscence of the prosthesis	Paravalvular regurgitation identified by TTE/TEE, with or without rocking motion of the prosthesis

bacteraemia where routine echocardiography is justified in view of the frequency of IE in this setting and of the virulence of this organism, and its devastating effects once intracardiac infection is established.^{13,72}

Three echocardiographic findings are major criteria in the diagnosis of IE: vegetation, abscess, and new dehiscence of a prosthetic valve (see Table 9 for anatomical and echocardiographic definitions).

The sensitivity of TTE ranges from 40 to 63% and that of TEE from 90 to 100%.⁷³ However, diagnosis may be particularly challenging in IE affecting intracardiac devices, even with use of TEE. Identification of vegetations may be difficult in the presence of pre-existing severe lesions (mitral valve prolapse, degenerative calcified lesions, prosthetic valves), if vegetations are very small (<2 mm), not yet present (or already embolized), and in non-vegetant IE. Appearances resembling vegetations may be seen in degenerative or myxomatous valve disease, systemic lupus (inflammatory Libman–Sacks lesions), and rheumatoid disease, primary antiphospholipid syndrome, valvular thrombus, advanced malignancy (marantic endocarditis), chordal rupture, and in association with small intracardiac tumours (typically fibroelastomata).

Similarly, small abscesses may be difficult to identify, particularly at the earliest stage of disease, in the post-operative period, and in the presence of a prosthetic device (especially in the mitral position).⁷⁴

In cases with an initially negative examination, repeat TTE/TEE must be performed 7–10 days later if the clinical level of suspicion is still high, or even earlier in case of *S. aureus* infection. Additional echocardiographic study is seldom helpful, with little additional information derived after the second or third assessment.⁷⁵ However, follow-up echocardiography to monitor complications and response to treatment is mandatory (Table 8).

Other advances in imaging technology have had minimal impact in routine clinical practice. The use of harmonic imaging has

improved study quality,⁷⁶ while the roles of three-dimensional echocardiography and other alternative modes of imaging [computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and radionuclide scanning] have yet to be evaluated in IE. Multislice CT has recently been shown to give good results in the evaluation of IE-associated valvular abnormalities, as compared with TEE, particularly for the assessment of the perivalvular extent of abscesses and pseudoaneurysms.⁷⁷

Microbiological diagnosis

1. Blood cultures

Positive blood cultures remain the cornerstones of diagnosis and provide live bacteria for susceptibility testing. Three sets (including at least one aerobic and one anaerobic), each containing 10 mL of blood obtained from a peripheral vein using meticulous sterile technique, is virtually always sufficient to identify the usual microorganisms—the diagnostic yield of repeated sampling thereafter is low.⁷⁸ Sampling from central venous catheters should be avoided in view of the high risk of contaminants (false positives, typically staphylococcal) and misleading findings. The need for culture prior to antibiotic administration is self-evident, although surveys of contemporary practice reveal frequent violations of this rule.^{79,80} In IE, bacteraemia is almost constant, which has two implications: (1) there is no rationale for delaying blood sampling to coincide with peaks of fever; and (2) virtually all blood cultures (or a majority of them) are positive. As a result, a single positive blood culture should be regarded cautiously for establishing the diagnosis of IE, especially for potentially ‘contaminants’ such as CNS or corynebacteria.

Although IE caused by anaerobes is uncommon, cultures should be incubated in both aerobic and anaerobic atmospheres to detect organisms such as *Bacteroides* or *Clostridium* species. When cultures remain negative at 5 days, subculture onto chocolate agar plates may

allow identification of a fastidious organism. Prolonged culture is associated with rising likelihood of contamination, and alternative techniques (or an alternative diagnosis) should be considered at this stage.⁸¹ A proposed scheme for the identification of microorganisms in culture-positive and culture-negative IE is provided in Figure 2.

2. Culture-negative infective endocarditis and atypical organisms

Blood-culture negative IE (BCNIE) occurs in 2.5–31% of all cases of IE, often delaying diagnosis and the initiation of treatment, with profound impact on clinical outcome.⁸² BCNIE arises most commonly as a consequence of prior antibiotic administration, underlying the need for withdrawing antibiotics and repeat blood

cultures in this situation. An increasingly common scenario is infection by fastidious organisms with limited proliferation under conventional culture conditions, or requiring specialized tools for identification (see Section C).⁸³ These organisms may be particularly common in IE affecting patients with prosthetic valves, indwelling venous lines, pacemakers, renal failure, and immunocompromised states (Table 10). Early consultation with an infectious disease specialist is recommended.

3. Histological/immunological techniques

Pathological examination of resected valvular tissue or embolic fragments remains the gold standard for the diagnosis of IE and may also guide antimicrobial treatment if the causative agent can be identified

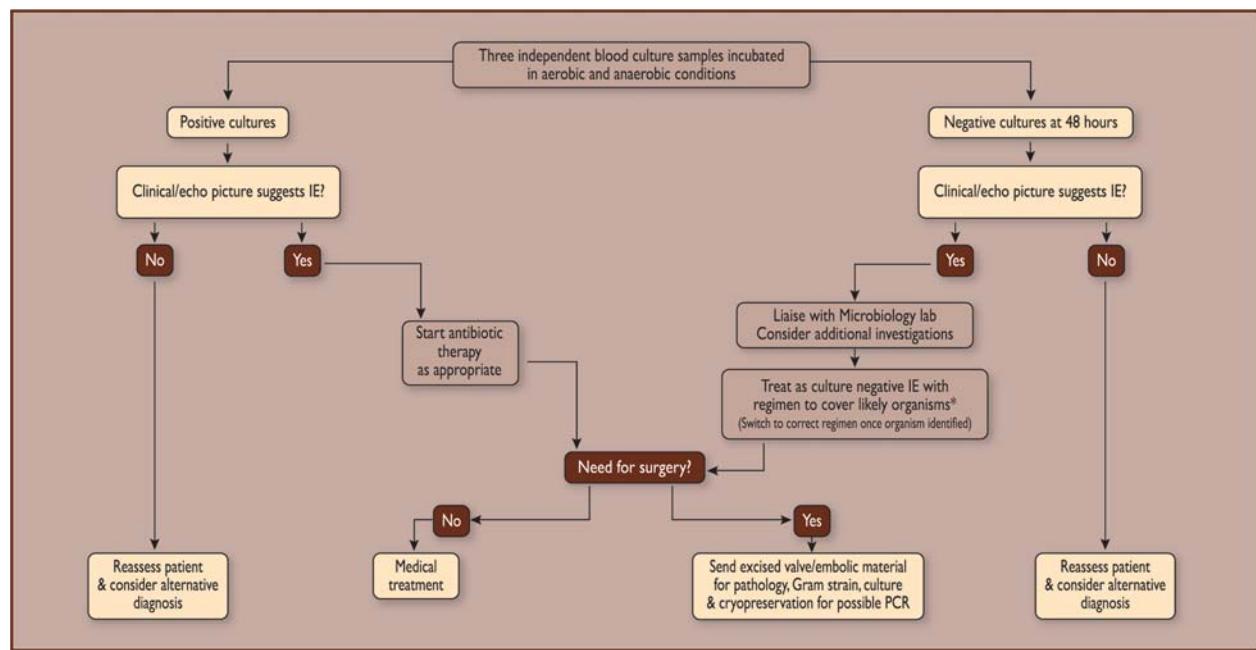


Figure 2 Microbiological diagnosis in culture-positive and culture-negative infective endocarditis. IE = infective endocarditis; PCR = polymerase chain reaction. *If the organism remains unidentified and the patient is stable, consider antibiotic withdrawal and repeat blood cultures.

Table 10 Investigation of rare causes of culture-negative infective endocarditis

Pathogen	Diagnostic procedure
<i>Brucella</i> spp.	Blood cultures; serology; culture, immunohistology and PCR of surgical material
<i>Coxiella burnetii</i>	Serology (IgG phase 1 > 1:800); tissue culture, immunohistology and PCR of surgical material
<i>Bartonella</i> spp.	Blood cultures; serology; culture, immunohistology and PCR of surgical material
<i>Tropheryma whipplei</i>	Histology and PCR of surgical material
<i>Mycoplasma</i> spp.	Serology; culture, immunohistology and PCR of surgical material
<i>Legionella</i> spp.	Blood cultures; serology; culture, immunohistology and PCR of surgical material

PCR = polymerase chain reaction.

Table II Modified Duke criteria for the diagnosis of infective endocarditis (adapted from Li et al.⁹⁴)

MAJOR CRITERIA	
Blood cultures positive for IE:	
<ul style="list-style-type: none"> • Typical microorganisms consistent with IE from two separate blood cultures: <i>Viridans streptococci, Streptococcus bovis, HACEK group, Staphylococcus aureus</i>; or Community-acquired enterococci, in the absence of a primary focus; <i>or</i> • Microorganisms consistent with IE from persistently positive blood cultures: At least two positive blood cultures of blood samples drawn > 12 h apart; or All of three or a majority of ≥ 4 separate cultures of blood (with first and last sample drawn at least 1 h apart) <i>or</i> • Single positive blood culture for <i>Coxiella burnetii</i> or phase I IgG antibody titer > 1 : 800 	
Evidence of endocardial involvement	
<ul style="list-style-type: none"> • Echocardiography positive for IE Vegetation - Abscess - New partial dehiscence of prosthetic valve • New valvular regurgitation 	
MINOR CRITERIA	
<ul style="list-style-type: none"> • Predisposition: predisposing heart condition, injection drug use • Fever: temperature > 38°C • Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhages, conjunctival haemorrhages, Janeway lesions • Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor • Microbiological evidence: positive blood culture but does not meet a major criterion or serological evidence of active infection with organism consistent with IE 	
Diagnosis of IE is definite in the presence of 2 major criteria, or 1 major and 3 minor criteria, or 5 minor criteria	Diagnosis of IE is possible in the presence of 1 major and 1 minor criteria, or 3 minor criteria

Adapted from Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG, Jr., Ryan T, Bashore T, Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000;30:633–638.

by means of special stains or immunohistological techniques. Electron microscopy has high sensitivity and may help to characterize new microorganisms, but is time consuming and expensive. *Coxiella burnetii* and *Bartonella* species may be easily detected by serological testing using indirect immunofluorescence or enzyme-linked immunosorbent assay (ELISA), and recent data demonstrate similar utility for staphylococci.⁸⁴ Immunological analysis of urine may allow detection of microorganism degradation products, and ELISA detection of *Legionella* species has been described using this technique. Incorporation of these methods into accepted diagnostic criteria awaits prospective validation.

4. Molecular biology techniques

The polymerase chain reaction (PCR) allows rapid and reliable detection of fastidious and non-culturable agents in patients with IE.⁸⁵ The technique has been validated using valve tissue from patients undergoing surgery for IE.⁸⁶ Although there are several advantages, including extreme sensitivity, inherent limitations include the lack of reliable application to whole blood samples, risk of contamination, false negatives due to the presence of PCR inhibitors in clinical samples, inability to provide information concerning bacterial sensitivity to antimicrobial agents, and persistent positivity despite clinical remission. The presence of a positive

PCR at the time of pathological examination of the excised valve is not synonymous with treatment failure unless valve cultures are positive. Indeed, positive PCR can persist for months after successful eradication of infection.^{87,88} Improvements (including the availability of real-time PCR and a wider range of comparator gene sequences)⁸⁹ and availability of other emerging technologies⁹⁰ will address many of these deficiencies, but results still require careful specialist interpretation. Although PCR positivity has been proposed as a major diagnostic criterion for IE,⁹¹ the technique seems unlikely to supersede blood cultures as a prime diagnostic tool. PCR of excised valve tissue or embolic material should be performed in patients with negative blood cultures who undergo valve surgery or embolectomy.

Diagnostic criteria and their limitations

The Duke criteria,⁹² based upon clinical, echocardiographic, and microbiological findings provide high sensitivity and specificity (~80% overall) for the diagnosis of IE. Recent amendments recognize the role of Q-fever (a worldwide zoonosis caused by *Coxiella burnetii*), increasing prevalence of staphylococcal infection, and widespread use of TEE, and the resultant so-called modified Duke criteria are now recommended for diagnostic classification (Table 11).^{93,94}

However, it should be kept in mind that these modifications await formal validation and that the original criteria were initially developed to define cases of IE for epidemiological studies and clinical trials. Clear deficiencies remain and clinical judgement remains essential, especially in settings where sensitivity of the modified criteria is diminished, e.g. when blood cultures are negative, when infection affects a prosthetic valve or pacemaker lead, and when IE affects the right heart⁹⁵ (particularly in IVDAs).

In summary, echocardiography and blood cultures are the cornerstone of diagnosis of IE. TTE must be performed first, but both TTE and TEE should ultimately be performed in the majority of cases of suspected or definite IE. The Duke criteria are useful for the classification of IE but do not replace clinical judgement.

G. Prognostic assessment at admission

The in-hospital mortality rate of patients with IE varies from 9.6 to 26%,^{14,68,96–102} but differs considerably from patient to patient. Quick identification of patients at highest risk of death may offer the opportunity to change the course of the disease and improve prognosis. It will also allow identification of patients with the worst immediate outcome who will benefit from closer follow-up and a more aggressive treatment strategy (e.g. urgent surgery).

Prognosis in IE is influenced by four main factors: patient characteristics, the presence or absence of cardiac and non-cardiac complications, the infecting organism, and echocardiographic findings (Table 12). The risk of patients with left-sided IE has been formally

assessed according to these variables.^{96,97} Patients with heart failure (HF), periannular complications, and/or *S. aureus* infection are at highest risk of death and need for surgery in the active phase of the disease.⁹⁶ When three of these factors are present, the risk reaches 79%.⁹⁶ Therefore, these patients should be followed up closely and referred to tertiary care centres with surgical facilities. A high degree of co-morbidity, insulin-dependent diabetes, depressed left ventricular function, and the presence of stroke are also predictors of poor in-hospital outcome.^{97–99,102–104} Nowadays, ~50% of patients undergo surgery during hospitalization.^{14,100,105,106} In those patients who need urgent surgery, persistent infection and renal failure are predictors of mortality.¹⁰⁷ Predictably, patients with an indication for surgery who cannot proceed due to prohibitive surgical risk have the worst prognosis.¹⁵

In summary, prognostic assessment at admission can be performed using simple clinical, microbiological, and echocardiographic parameters, and should be used to choose the best therapeutic option.

H. Antimicrobial therapy: principles and methods

General principles

Successful treatment of IE relies on microbe eradication by antimicrobial drugs. Surgery contributes by removing infected material and draining abscesses. Host defences are of little help. This explains why bactericidal regimens are more effective than bacteriostatic therapy, both in animal experiments and in humans.^{108,109}

Table 12 Predictors of poor outcome in patients with IE

Patient characteristics
<ul style="list-style-type: none"> • Older age • Prosthetic valve IE • Insulin-dependent diabetes mellitus • Comorbidity (e.g. frailty, previous cardiovascular, renal or pulmonary disease)
Presence of complications of IE
<ul style="list-style-type: none"> • Heart failure • Renal failure • Stroke • Septic shock • Periannular complications
Microorganism
<ul style="list-style-type: none"> • <i>S. aureus</i> • Fungi • Gram-negative bacilli
Echocardiographic findings
<ul style="list-style-type: none"> • Periannular complications • Severe left-sided valve regurgitation • Low left ventricular ejection fraction • Pulmonary hypertension • Large vegetations • Severe prosthetic dysfunction • Premature mitral valve closure and other signs of elevated diastolic pressures

Aminoglycosides synergize with cell wall inhibitors (i.e. β -lactams and glycopeptides) for bactericidal activity and are useful to shorten the duration of therapy (e.g. oral streptococci) and eradicate problematic organisms (e.g. *Enterococcus* spp.).

One major hindrance to drug-induced killing is bacterial antibiotic tolerance. Tolerant microbes are not resistant, i.e. they are still susceptible to growth inhibition by the drug, but escape drug-induced killing and may resume growth after treatment discontinuation. Slow-growing and dormant microbes display phenotypic tolerance towards most antimicrobials (except rifampin to some extent). They are present in vegetations and biofilms, e.g. in prosthetic valve endocarditis (PVE), and justify the need for prolonged therapy (6 weeks) to sterilize infected heart valves fully. Some bacteria carry mutations rendering them tolerant during both active growth and stationary (dormant) phases. Bactericidal drug combinations are preferred to monotherapy against tolerant organisms.

Drug treatment of PVE should last longer (at least 6 weeks) than that of native valve endocarditis (NVE) (2–6 weeks), but is otherwise similar, except for staphylococcal PVE where the regimen should include rifampin whenever the strain is susceptible.

In NVE needing valve replacement by a prosthesis during antibiotic therapy, the post-operative antibiotic regimen should be that recommended for NVE, not for PVE. In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery. After surgery, a new full course of treatment should only start if valve cultures are positive,^{109a} the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate.

Penicillin-susceptible oral streptococci and group D streptococci

Recommended regimens against susceptible streptococci (penicillin MIC ≤ 0.125 mg/L) are summarized in Table 13.^{3,7,110–112} Cure rate is expected to be $>95\%$. In non-complicated cases, short-term 2-week therapy can be administered by combining penicillin or ceftriaxone with gentamicin or netilmicin.^{113,114} The latter two studies demonstrated that gentamicin and netilmicin can be given once daily in patients with IE due to susceptible streptococci and normal renal function. Ceftriaxone alone or combined with gentamicin or netilmicin given once a day is particularly convenient for outpatient therapy.^{113–115} Patients allergic to β -lactams should receive vancomycin. Teicoplanin has been proposed as an alternative³ and requires loading doses (6 mg/kg/12 h for 3 days) followed by 6–10 mg/kg/day. Loading is critical because the drug is highly bound to serum proteins ($\geq 98\%$) and penetrates slowly into vegetations.¹¹⁶ However, only limited retrospective studies have assessed its efficacy in streptococcal¹¹⁷ and enterococcal¹¹⁸ IE.

Penicillin-resistant oral streptococci and group D streptococci

Penicillin-resistant oral streptococci are classified as relatively resistant (MIC 0.125–2 mg/L) and fully-resistant (MIC >2 mg/L). However, some guidelines consider a MIC >0.5 mg/L as fully resistant.^{3,7,110} Such resistant streptococci are increasing. Recent large strain collections report $>30\%$ of relatively and fully

resistant *S. mitis* and *S. oralis*.^{118,119} Conversely, $>99\%$ of group D streptococci remain penicillin susceptible. Treatment guidelines for penicillin-resistant streptococcal IE rely on retrospective series. Compiling four of them, 47/60 (78%) patients were treated with penicillin G or ceftriaxone mostly combined with aminoglycosides, and some with either clindamycin or aminoglycosides alone.^{120–123} Most penicillin MICs were ≥ 1 mg/L. Fifty patients (83%) were cured and 10 (17%) died. Death was not related to resistance, but to patients' underlying conditions.¹²² Treatment outcome was similar in PVE and NVE.¹²¹ Hence, antibiotic therapy for penicillin-resistant and penicillin-susceptible oral streptococci is qualitatively similar (Table 13). However, in penicillin-resistant cases aminoglycoside treatment may be prolonged to 3–4 weeks and short-term therapy regimens are not recommended. Little experience exists with highly resistant isolates (MIC >4 mg/L)—vancomycin might be preferred in such circumstances.

Streptococcus pneumoniae, β -haemolytic streptococci (groups A, B, C, and G)

IE due to *S. pneumoniae* has become rare since the introduction of antibiotics. It is associated with meningitis in up to 30% of cases,¹²⁴ which requires special consideration in cases with penicillin resistance. Treatment of penicillin-susceptible strains (MIC ≤ 0.1 mg/L) is similar to that of oral streptococci (Table 13), except for the use of short-term 2-week therapy, which has not been formally investigated. The same holds true for penicillin-resistant strains (MIC >1 mg/L) without meningitis. In cases with meningitis, penicillin must be avoided because it poorly penetrates the cerebrospinal fluid, and should be replaced with ceftriaxone or cefotaxime alone or in combination with vancomycin.¹²⁵

IE due to group A, B, C, or G streptococci—including the *S. milleri* group (*S. constellatus*, *S. anginosus*, and *S. intermedius*)—is relatively rare.¹²⁶ Group A streptococci are uniformly susceptible to β -lactams, whereas other serogroups may display resistance. IE due to group B streptococci was once associated with the peripartum period, but now occurs in other adults, especially the elderly. Group B, C, and G streptococci and *S. milleri* produce abscesses and thus may require adjunctive surgery.¹²⁶ Mortality of Group B PVE is very high and cardiac surgery is recommended.¹²⁷ Antibiotic treatment is similar to that of oral streptococci (Table 13), except that short-term therapy is not recommended.

Nutritionally variant streptococci

They produce IE with a protracted course, which is associated with higher rates of complications and treatment failure (up to 40%),¹²⁸ possibly due to delayed diagnosis and treatment. One recent study reported on eight cases of successful treatment with penicillin G or ceftriaxone plus gentamicin.¹²⁹ Seven patients had large vegetations (>10 mm) and underwent surgery. Antibiotic recommendations include penicillin G, ceftriaxone or vancomycin for 6 weeks, combined with an aminoglycoside for at least the first 2 weeks.

Table 13 Antibiotic treatment of infective endocarditis due to oral streptococci and group D streptococci^a

Antibiotic	Dosage and route	Duration (weeks)	Level of evidence
Strains fully susceptible to penicillin (MIC <0.125 mg/L)			
Standard treatment			
Penicillin G ^b or Amoxicillin ^d or Ceftriaxone ^e	12–18 million U/day i.v. in 6 doses 100–200 mg/kg/day i.v. in 4–6 doses 2 g/day i.v. or i.m. in 1 dose <i>Paediatric doses:</i> ^f Penicillin G 200,000 U/kg/day i.v. in 4–6 divided doses. Amoxicillin 300 mg/kg/day i.v. in 4–6 equally divided doses. Ceftriaxone 100 mg/kg/day i.v. or i.m. in 1 dose.	4 ^c	I B
Two-week treatment^(g)			
Penicillin G or Amoxicillin ^d or Ceftriaxone ^e <i>with</i> Gentamicin ^h or Netilmicin	12–18 million U/day i.v. in 6 doses 100–200 mg/kg/day i.v. in 4–6 doses 2 g/day i.v. or i.m. in 1 dose 3 mg/kg/day i.v. or i.m. in 1 dose 4–5 mg/kg/day i.v. in 1 dose <i>Paediatric doses:</i> ^f Penicillin, amoxicillin and ceftriaxone as above. Gentamicin 3 mg/kg/day i.v. or i.m. in 1 dose or in 3 equally divided doses.	2	I B
In beta-lactam allergic patients			
Vancomycin ⁱ	30 mg/kg/day i.v. in 2 doses <i>Paediatric doses:</i> ^f Vancomycin 40 mg/kg/day i.v. in 2–3 equally divided doses.	4 ^c	I C
Strains relatively resistant to penicillin (MIC 0.125–2 mg/L)			
Standard treatment			
Penicillin G or Amoxicillin ^d <i>with</i> Gentamicin ^h	24 million U/day i.v. in 6 doses 200 mg/kg/day i.v. in 4–6 doses 3 mg/kg/day i.v. or i.m. in 1 dose	4 ^c 4 ^c 2	I B I B I B
In beta-lactam allergic patients			
Vancomycin ⁱ <i>with</i> Gentamicin ^h	30 mg/kg/day i.v. in 2 doses <i>Paediatric doses:</i> ^f As above. 3 mg/kg/day i.v. or i.m. in 1 dose	4 ^c 2	I C I C

^aSee text for other streptococcal species.^bPreferred in patients >65 years or with impaired renal function.^c6-week therapy in PVE.^dOr ampicillin, same dosages as amoxicillin.^ePreferred for outpatient therapy.^fPaediatric doses should not exceed adult doses.^gOnly if non complicated native valve IE.^hRenal function and serum gentamicin concentrations should be monitored once a week. When given in a single daily dose, pre-dose (trough) concentrations should be <1 mg/L and post-dose (peak; 1 h after injection) serum concentrations should be ~10–12 mg/L.¹¹²ⁱSerum vancomycin concentrations should achieve 10–15 mg/L at pre-dose (trough) level and 30–45 mg/L at post-dose level (peak; 1 h after infusion is completed).

Staphylococcus aureus and coagulase-negative staphylococci

Staphylococcus aureus is usually responsible for acute and destructive IE, whereas CNS produce more protracted valve infections

(except *S. lugdunensis* and some cases of *S. capitis*).^{130,131} Table 14 summarizes treatment recommendations for methicillin-susceptible and methicillin-resistant *S. aureus* and CNS in both native and prosthetic valve IE. Of note, the benefit of additional

Table 14 Antibiotic treatment of infective endocarditis due to *Staphylococcus* spp.

Antibiotic	Dosage and route	Duration (weeks)	Level of evidence
Native valves			
Methicillin-susceptible staphylococci:			
(Flu)cloxacillin or Oxacillin with Gentamicin ^a	12 g/day i.v. in 4–6 doses 3 mg/kg/day i.v. or i.m. in 2 or 3 doses <i>Paediatric doses:</i> ^b Oxacillin or (Flu)cloxacillin 200 mg /kg/day i.v. in 4–6 equally divided doses. Gentamicin 3 mg/kg/day i.v. or i.m. in 3 equally divided doses.	4–6 3–5 days	I B
Penicillin-allergic patients or methicillin-resistant staphylococci:			
Vancomycin ^c with Gentamicin ^a	30 mg/kg/day i.v. in 2 doses 3 mg/kg/day i.v. or i.m. in 2 or 3 doses <i>Paediatric doses:</i> ^b Vancomycin 40 mg/kg/day i.v. in 2–3 equally divided doses.	4–6 3–5 days	I B
Prosthetic valves			
Methicillin-susceptible staphylococci:			
(Flu)cloxacillin, or Oxacillin with Rifampin ^d and Gentamicin ^e	12 g /day i.v. in 4–6 doses 1200 mg/day i.v. or orally in 2 doses 3 mg/kg/day i.v. or i.m. in 2 or 3 doses <i>Paediatric doses:</i> ^b Oxacillin and (Flu)cloxacillin as above. Rifampin 20 mg/kg/day i.v. or orally in 3 equally divided doses.	≥ 6 ≥ 6 2	I B
Penicillin-allergic patients and methicillin-resistant staphylococci:			
Vancomycin ^c with Rifampin ^d and Gentamicin ^e	30 mg/kg/day i.v. in 2 doses 1200 mg/day i.v. or orally in 2 doses 3 mg/kg/day i.v. or i.m. in 2 or 3 doses <i>Paediatric doses:</i> ^b As above.	≥ 6 ≥ 6 2	I B

^aThe clinical benefit of gentamicin addition has not been formally demonstrated. Its use is associated with increased toxicity and is therefore optional.

^bPaediatric doses should not exceed adult doses.

^cSerum vancomycin concentrations should achieve 25–30 mg/L at pre-dose (trough) levels.

^dRifampin increases the hepatic metabolism of warfarin and other drugs. Rifampin is believed to play a special role in prosthetic device infection because it helps eradicate bacteria attached to foreign material.¹³⁵ Rifampin should always be used in combination with another effective antistaphylococcal drug, to minimize the risk of resistant mutant selection.

^eAlthough the clinical benefit of gentamicin has not been demonstrated, it remains recommended for PVE. Renal function and serum gentamicin concentrations should be monitored once/week (twice/week in patients with renal failure). When given in three divided doses, pre-dose (trough) concentrations should be <1 mg/L and post-dose (peak; 1 h after injection) concentrations should be between 3–4 mg/L.¹¹²

aminoglycoside in *S. aureus* IE is not formally demonstrated.^{132,133} It is optional for the first 3–5 days of therapy in NVE, and recommended for the first 2 weeks in PVE. Short-term (2 week) and oral treatment have been proposed for uncomplicated right-sided IE (see also Section L), but these regimens are invalid for left-sided IE.

Staphylococcus aureus PVE carries a very high risk of mortality (>45%)¹³⁴ and often requires early valve replacement. Other differences in comparison with NVE include the overall duration of therapy, prolonged additional use of aminoglycosides, and the addition of rifampin. Use of the latter is based on its success in treatment of infected orthopaedic prostheses¹³⁵ (in combination with quinolones) and in the prevention of re-infection of vascular prostheses.¹³⁶ Although the level of evidence is poor, adding rifampin in the treatment of staphylococcal PVE is standard practice, although treatment may be associated with microbial resistance, hepatotoxicity, and drug interactions.¹³⁷

Methicillin-resistant and vancomycin-resistant staphylococci

MRSA produce low-affinity plasma-binding protein (PBP) 2A, which confers cross-resistance to most β-lactams. They are usually resistant to multiple antibiotics, leaving only vancomycin to treat severe infections. However, vancomycin-intermediate *S. aureus* (VISA) (MIC 4–16 mg/L) and hetero-VISA (MIC ≤2 mg/L, but with subpopulations growing at higher concentrations) have emerged worldwide, and are associated with IE treatment failures.¹³⁸ Moreover, some highly vancomycin-resistant *S. aureus* have been isolated from infected patients in recent years, requiring new approaches to treatment. New lipo-peptide daptomycin (6 mg/kg/day i.v.) was recently approved for *S. aureus* bacteraemia and right-sided IE.¹³⁹ Observational studies suggest that daptomycin might also be considered in left-sided IE and may overcome methicillin and vancomycin resistance.¹⁴⁰ However, definitive studies are missing. Importantly, daptomycin needs to be administered in appropriate doses to avoid further resistance.^{139,141} Other choices include newer β-lactams with relatively good PBP2A affinity, quinupristin–dalforpristin with or without β-lactams,^{142,143} β-lactams plus oxazolidinones,¹⁴⁴ and β-lactams plus vancomycin.¹⁴⁵ Such cases warrant collaborative management with an infectious diseases specialist.

Enterococcus spp.

Enterococcal IE is primarily caused by *Enterococcus faecalis* (90% of cases) and, more rarely, by *Enterococcus faecium* or other species. They pose two major problems. First, enterococci are highly tolerant to antibiotic-induced killing, and eradication requires prolonged administration (up to 6 weeks) of synergistic bactericidal combinations of cell wall inhibitors with aminoglycosides (Table 15). Secondly, they may be resistant to multiple drugs, including aminoglycosides, β-lactams (via PBP5 modification and sometimes β-lactamases), and vancomycin.¹⁴⁶

Fully penicillin-susceptible strains (penicillin MIC ≤8 mg/L) are treated with penicillin G or ampicillin (or amoxicillin) combined with gentamicin. Ampicillin (or amoxicillin) might be preferred

since MICs are 2–4 times lower. Prolonged courses of gentamicin require regular monitoring of serum drug levels and renal and vestibular function. One study reported success with short-course administration of aminoglycosides (2–3 weeks) in 74 (81%) of 91 episodes of enterococcal IE.¹⁴⁷ This option might be considered in cases where prolonged treatment is limited by toxicity.

High-level gentamicin resistance is frequent in both *E. faecalis* and *E. faecium*.¹⁴⁶ An aminoglycoside MIC >500 mg/L is associated with loss of bactericidal synergism with cell wall inhibitors, and aminoglycosides should not be used in such conditions. Streptomycin may remain active in such cases and is a useful alternative. A further recently described option against gentamicin-resistant *E. faecalis* is the combination of ampicillin and ceftriaxone,¹⁴⁸ which synergize by inhibiting complementary PBPs. Otherwise, more prolonged courses of β-lactams or vancomycin should be considered.

β-Lactam and vancomycin resistance are mainly observed in *E. faecium*. Since dual resistance is rare, β-lactam might be used against vancomycin-resistant strains and vice versa. Varying results have been reported with quinupristin–dalforpristin, linezolid, daptomycin, and tigecycline. Again, these situations require the expertise of an infectious diseases specialist.

Gram-negative bacteria

1. HACEK-related species

HACEK Gram-negative bacilli are fastidious organisms needing specialized investigations (see also Section C). Because they grow slowly, standard MIC tests may be difficult to interpret. Some HACEK group bacilli produce β-lactamases, and ampicillin is therefore no longer the first-line option. Conversely, they are susceptible to ceftriaxone, other third-generation cephalosporins, and quinolones—the standard treatment is ceftriaxone 2 g/day for 4 weeks. If they do not produce β-lactamase, intravenous ampicillin (12 g/day i.v. in four or six doses) plus gentamicin (3 mg/kg/day divided in two or three doses) for 4 weeks is an option. Ciprofloxacin (2 × 400 mg/day i.v. or 1000 mg/day orally) is a less well validated option.^{149,150}

2. Non-HACEK species

The International Collaboration on Endocarditis (ICE) reported non-HACEK Gram-negative bacteria in 49/2761 (1.8%) of IE cases.¹⁵¹ Recommended treatment is early surgery plus long-term (≥6 weeks) therapy with bactericidal combinations of β-lactams and aminoglycosides, sometimes with additional quinolones or cotrimoxazole. *In vitro* bactericidal tests and monitoring of serum antibiotic concentrations may be helpful. Because of their rarity and severity, these conditions should be managed with the input of an infectious diseases specialist.

Blood culture-negative infective endocarditis

The main causes of BCNIE are summarized in Section F.¹⁵² Treatment options are summarized in Table 16.¹⁵³

Table 15 Antibiotic treatment of infective endocarditis due to *Enterococcus* spp.

Antibiotic	Dosage and route	Duration (weeks)	Level of evidence
Beta-lactam and gentamicin susceptible strain (for resistant isolates see^{a,b,c})			
Amoxicillin with Gentamicin ^e	200 mg/kg/day i.v. in 4–6 doses 3 mg/kg/day i.v. or i.m. in 2 or 3 doses. <i>Paediatric doses:</i> ^f Amoxicillin 300 mg/kg/day i.v. in 4–6 equally divided doses. Gentamicin 3 mg/kg/day i.v. or i.m. in 3 equally divided doses.	4–6 ^d 4–6	I B
OR			
Ampicillin with Gentamicin ^e	200 mg/kg/day i.v. in 4–6 doses 3 mg/kg/day i.v. or i.m. in 2 or 3 doses <i>Paediatric doses:</i> ^f Ampicillin 300 mg/kg/day i.v. in 4–6 equally divided doses. Gentamicin as above.	4–6 ^d 4–6	I B
OR			
Vancomycin ^g with Gentamicin ^e	30 mg/kg/day i.v. in 2 doses 3 mg/kg/day i.v. or i.m. in 2 or 3 doses <i>Paediatric doses:</i> ^f Vancomycin 40 mg/kg/day i.v. in 2–3 equally divided doses. Gentamicin as above.	6 6	I C

^aHigh level resistance to gentamicin ($\text{MIC} > 500 \text{ mg/L}$): if susceptible to streptomycin, replace gentamicin with streptomycin 15 mg/kg/day in two equally divided doses (I, A). Otherwise, use more prolonged course of β -lactam therapy. The combination of ampicillin with ceftriaxone was recently suggested for gentamicin-resistant *E. faecalis*.¹⁴⁸ (IIa, B).

^b β -Lactam resistance: (i) if due to β -lactamase production, replace ampicillin with ampicillin–sulbactam or amoxicillin with amoxicillin–clavulanate (I, C); (ii) if due to PBPS alteration, use vancomycin-based regimens.

^cMultiresistance to aminoglycosides, β -lactams, and vancomycin: suggested alternatives are (i) linezolid 2 \times 600 mg/day i.v. or orally for ≥ 8 weeks (IIa, C) (monitor haematological toxicity), (ii) quinupristin–dalfopristin 3 \times 7.5 mg/kg/day for ≥ 8 weeks (IIa, C), (iii) β -lactam combinations including imipenem plus ampicillin or ceftriaxone plus ampicillin for ≥ 8 weeks (IIb, C).

^d6-week therapy recommended for patients with >3 months symptoms and in PVE.

^eMonitor serum levels of aminoglycosides and renal function as indicated in Table 13.

^fPaediatric doses should not exceed adult doses.

^gIn β -lactam allergic patients. Monitor serum vancomycin concentrations as indicated in Table 13.

Fungi

Fungi are most frequently observed in PVE and in IE affecting IVDAs and immunocompromised patients. *Candida* and *Aspergillus* spp. predominate, the latter resulting in BCNIE. Mortality is very high (>50%), and treatment necessitates dual antifungal administration and valve replacement.¹⁵⁴ Most cases are treated with various forms of amphotericin B with or without azoles, although recent case reports describe successful therapy with the new echinocandin caspofungin.^{155,156} Suppressive treatment with oral azoles is often maintained long term and sometimes for life.

Empirical therapy

Treatment of IE should be started promptly. Three sets of blood cultures should be drawn at 30 min intervals before initiation of

antibiotics.¹⁵⁷ The initial choice of empirical treatment depends on several considerations:

- (i) whether the patient has received prior antibiotic therapy or not
- (ii) whether the infection affects a native valve or a prosthesis (and, if so, when surgery was performed (early vs. late PVE) and
- (iii) knowledge of local epidemiology, especially for antibiotic resistance and specific genuine culture-negative pathogens (Table 16).

Suggested regimens are summarized in Table 17. NVE and late PVE regimens should cover staphylococci, streptococci, HACEK species, and *Bartonella* spp. Early PVE regimens should cover methicillin-resistant staphylococci and ideally non-HACEK Gram-negative pathogens.

Table 16 Antibiotic treatment of blood culture-negative infective endocarditis

Pathogens	Proposed therapy ^a	Treatment outcome
<i>Brucella</i> spp.	Doxycycline (200 mg/24h) plus Cotrimoxazole (960 mg/12h) plus Rifampin (300–600 mg/24h) for ≥ 3 months ^b orally	Treatment success defined as an antibody titre <1:60
<i>Coxiella burnetii</i> (agent of Q fever)	Doxycycline (200 mg/24h) plus Hydroxychloroquine (200–600 mg/24h) ^c orally <i>or</i> Doxycycline (200 mg/24h) plus Quinolone (Ofloxacin, 400 mg/24h) orally (> 18 months treatment)	Treatment success defined as anti-phase I IgG titre <1:200, and IgA and IgM titres <1:50
<i>Bartonella</i> spp.	Ceftriaxone (2 g/24h) or Ampicillin (or Amoxicillin) (12 g/24h) i.v. <i>or</i> Doxycycline (200 mg/24h) orally for 6 weeks <i>plus</i> Gentamicin (3 mg/24h) or Netilmicin intravenously (for 3 weeks) ^d	Treatment success expected in ≥ 90%
<i>Legionella</i> spp.	Erythromycin (3 g/24h) i.v. for 2 weeks, then orally for 4 weeks, <i>plus</i> Rifampin (300–1200 mg/24h) or Ciprofloxacin (1.5 g/24h) orally for 6 weeks	Optimal treatment unknown. Because of high susceptibility, quinolones should probably be included.
<i>Mycoplasma</i> spp.	Newer fluoroquinolones ^e (> 6 months treatment)	Optimal treatment unknown
<i>Tropheryma whipplei</i> ^f (agent of Whipple's disease)	Cotrimoxazole Penicillin G (1.2 MU/24h) and Streptomycin (1 g/24h) i.v. for 2 weeks, then Cotrimoxazole orally for 1 year <i>or</i> Doxycycline (200 mg/24h) plus Hydroxychloroquine (200–600 mg/24h) ^c orally for ≥ 18 months	Long-term treatment, optimal duration unknown.

Adapted from Brouqui and Raoult.¹⁵³

^aDue to the lack of large series, optimal duration of treatment of IE due to these pathogens is unknown. The presented durations are based on selected case reports.

^bAddition of streptomycin (15 mg/kg/24 h in two doses) for the first few weeks is optional.

^cDoxycycline plus hydroxychloroquine (with monitoring of serum hydroxychloroquine levels) is superior to doxycycline alone and to doxycycline + fluoroquinolone.

^dSeveral therapeutic regimens were reported, including aminopenicillins and cephalosporins combined with aminoglycosides, doxycycline, vancomycin, and quinolones. Dosages are as for streptococcal and enterococcal IE (Tables 13 and 15).^{383,384}

^eNewer fluoroquinolones are more potent than ciprofloxacin against intracellular pathogens such as *Mycoplasma* spp., *Legionella* spp., and *Chlamydia* spp.

^fTreatment of Whipple IE remains highly empirical. Successes have been reported with long-term (>1 year) cotrimoxazole therapy. γ -Interferon plays a protective role in intracellular infections and has been proposed as adjuvant therapy in Whipple's disease.^{385,386}

Outpatient parenteral antibiotic therapy for infective endocarditis

Outpatient parenteral antibiotic therapy (OPAT) is used in >250 000 patients/year in the USA.¹⁵⁸ For IE, it should be used to consolidate antimicrobial therapy once critical infection-related complications are under control (e.g. perivalvular abscesses, acute heart failure, septic emboli, and stroke). Two different phases may be separated during the course of antibiotic therapy—a first critical phase (the first 2 weeks of therapy), during which OPAT has a restricted indication, and a second continuation phase

(beyond 2 weeks therapy) where OPAT may be feasible. Table 18 summarizes the salient questions to address when considering OPAT for IE.¹⁵⁹ Logistic issues are critical and require patient and staff education to enforce compliance, monitoring of efficacy and adverse effects, paramedic and social support, and easy access to medical advice. If problems arise, the patient should be directed towards informed medical staff familiar with the case and not an anonymous emergency department. Under these conditions, OPAT performs equally well independently of the pathogen and clinical context.^{160,161}

Table 17 Proposed antibiotic regimens for initial empirical treatment of infective endocarditis. (before or without pathogen identification)

Antibiotic	Dosage and route	Duration (weeks)	Level of evidence	Comments
Native valves				
Ampicillin-Sulbactam, or Amoxicillin-Clavulanate, <i>with</i> Gentamicin ^a	12 g/day i.v. in 4 doses 12 g/day i.v. in 4 doses 3 mg/kg/day i.v. or i.m. in 2 or 3 doses.	4–6 4–6 4–6	IIb C IIb C	Patients with blood-culture negative IE should be treated in consultation with an infectious disease specialist.
Vancomycin ^b <i>with</i> Gentamicin ^a <i>with</i> Ciprofloxacin	30 mg/kg/day i.v. in 2 doses 3 mg/kg/day i.v. or i.m. in 2 or 3 doses. 1000 mg/day orally in 2 doses or 800 mg/day i.v. in 2 doses	4–6 4–6 4–6	IIb C	For patients unable to tolerate β -lactams. Ciprofloxacin is not uniformly active on <i>Bartonella</i> spp. Addition of doxycycline (see Table 16) is an option if <i>Bartonella</i> spp. is likely.
Prosthetic valves (early, < 12 months post surgery)				
Vancomycin ^b <i>with</i> Gentamicin ^a <i>with</i> Rifampin	30 mg/kg/day i.v. in 2 doses 3 mg/kg/day i.v. or i.m. in 2 or 3 doses. 1200 mg/day orally in 2 doses	6 2	IIb C	If no clinical response, surgery and maybe extension of the antibiotic spectrum to gram-negative pathogens must be considered.
Prosthetic valves (late, \geq 12 months post surgery)				
Same as for native valves				

^{a,b}Monitoring of gentamicin and vancomycin dosages is as in Table 13 and Table 14.

Table 18 Criteria which determine suitability of outpatient parenteral antibiotic therapy (OPAT) for infective endocarditis

Phase of treatment	Guidelines for use
Critical phase (weeks 0–2)	Complications occur during this phase. Preferred inpatient treatment during this phase. <u>Consider OPAT</u> : if oral streptococci, patient stable, no complications.
Continuation phase (beyond week 2)	<u>Consider OPAT</u> : if medically stable. <u>Do not consider OPAT</u> : if heart failure, concerning echocardiographic features, neurological signs, or renal impairment
Essential for OPAT	Educate patient and staff. Regular post discharge evaluation (nurses 1/day, physician in charge 1–2/week). Prefer physician-directed program, not home-infusion model.

Adapted from Andrews and von Reyn.¹⁵⁹

I. Complications and indications for surgery in left-sided native valve infective endocarditis

Part 1. Indications and optimal timing of surgery

Surgical treatment is used in approximately half of patients with IE because of severe complications.⁷⁹ Reasons to consider early surgery in the active phase, i.e. while the patient is still receiving antibiotic treatment, are to avoid progressive HF and irreversible structural damage caused by severe infection and to prevent systemic embolism.^{798,162–165} On the other hand, surgical therapy during the active phase of the disease is associated with significant risk. Surgery is justified in patients with high-risk features which make the possibility of cure with antibiotic treatment unlikely and who do not have co-morbid conditions or complications which make the prospect of recovery remote. Age per se is not a contraindication to surgery.¹⁶⁶

Early consultation with a cardiac surgeon is recommended in order to determine the best therapeutic approach. Identification

of patients requiring early surgery is frequently difficult. Each case must be individualized and all factors associated with increased risk identified at the time of diagnosis. Frequently, the need for surgery will be determined by a combination of several high-risk features.¹⁶⁵

In some cases, surgery needs to be performed on an emergency (within 24 h) or urgent (within a few days) basis, irrespective of the duration of antibiotic treatment. In other cases, surgery can be postponed to allow 1 or 2 weeks of antibiotic treatment under careful clinical and echocardiographic observation before an elective surgical procedure is performed.^{165,167}

The three main indications for early surgery in IE are HF, uncontrolled infection, and prevention of embolic events (Table 19).

Heart failure

1. Heart failure in infective endocarditis

HF is the most frequent complication of IE and represents the most frequent indication for surgery in IE.⁷⁹ HF is observed in 50–60% of cases overall and is more often present when IE affects the aortic (29%) rather than the mitral (20%) valve.⁷ HF can be caused by severe aortic or mitral insufficiency, intracardiac

Table 19 Indications and timing of surgery in left-sided native valve infective endocarditis

Recommendations: Indications for surgery	Timing*	Class ^a	Level ^b
A - HEART FAILURE			
Aortic or mitral IE with severe acute regurgitation or valve obstruction causing refractory pulmonary oedema or cardiogenic shock	Emergency	I	B
Aortic or mitral IE with fistula into a cardiac chamber or pericardium causing refractory pulmonary oedema or shock	Emergency	I	B
Aortic or mitral IE with severe acute regurgitation or valve obstruction and persisting heart failure or echocardiographic signs of poor haemodynamic tolerance (early mitral closure or pulmonary hypertension)	Urgent	I	B
Aortic or mitral IE with severe regurgitation and no HF	Elective	IIa	B
B - UNCONTROLLED INFECTION			
Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	Urgent	I	B
Persisting fever and positive blood cultures > 7–10 days	Urgent	I	B
Infection caused by fungi or multiresistant organisms	Urgent/elective	I	B
C - PREVENTION OF EMBOLISM			
Aortic or mitral IE with large vegetations (> 10 mm) following one or more embolic episodes despite appropriate antibiotic therapy	Urgent	I	B
Aortic or mitral IE with large vegetations (> 10 mm) and other predictors of complicated course (heart failure, persistent infection, abscess)	Urgent	I	C
Isolated very large vegetations (> 15 mm) [#]	Urgent	IIb	C

^aClass of recommendation.

^bLevel of evidence.

*Emergency surgery: surgery performed within 24 h, urgent surgery: within a few days, elective surgery: after at least 1 or 2 weeks of antibiotic therapy.

[#]Surgery may be preferred if procedure preserving the native valve is feasible.

fistulae, or, more rarely, by valve obstruction, when a large vegetation partially obstructs the valve orifice.

The most characteristic lesion leading to HF in NVE is valve destruction causing acute regurgitation,⁹² which may occur as a result of mitral chordal rupture, leaflet rupture (flail leaflet), leaflet perforation, or interference of the vegetation mass with leaflet closure. A special situation is secondary infection¹⁶⁸ of the anterior mitral leaflet associated with primary aortic IE with aortic regurgitation. Resultant aneurysm formation on the atrial aspect of the mitral leaflet may later lead to mitral perforation.

Clinical presentation of HF may include severe dyspnoea, pulmonary oedema, and cardiogenic shock. In addition to clinical findings, TTE is of crucial importance for initial evaluation and follow-up. In IE with acute regurgitation, regurgitant flow velocities are frequently low with a short deceleration time since pressures in the left atrium (mitral regurgitation) or left ventricle (aortic regurgitation) equalize rapidly. Chamber size is usually normal. Valve perforation, secondary mitral lesions, and aneurysms are best assessed using TEE.^{169,170} The suspicion of valve obstruction is raised by an elevated transvalvular gradient on TTE. Echocardiography is also of more general value for haemodynamic assessment of valvular dysfunction, measurement of pulmonary artery pressure, and assessment and monitoring of left ventricular systolic function and left and right heart filling pressures.^{171,172} Brain natriuretic peptide (NT-proBNP) has potential use in the diagnosis and monitoring of HF in IE.¹⁷³

HF may progress from mild to severe during treatment, and two-thirds of these cases occur during the active phase of the disease.⁷ Moderate-to-severe HF is the most important predictor of in-hospital and 6-month mortality.^{7,68,98,174,175}

2. Indications and timing of surgery in the presence of heart failure in infective endocarditis (Table 19)

The presence of HF indicates surgery in the majority of patients with IE⁷ and is the principal indication for urgent surgery.^{107,165} Surgery is indicated in patients with HF caused by severe aortic or mitral insufficiency, intracardiac fistulae, or by valve obstruction caused by vegetations. Surgery is also indicated in patients with severe acute aortic or mitral regurgitation without clinical HF but with echocardiographic signs of elevated left ventricular end-diastolic pressure (premature closure of the mitral valve), high left atrial pressure, or moderate or severe pulmonary hypertension.

Surgery must be performed on an emergency basis, irrespective of the status of infection, when patients are in persistent pulmonary oedema or cardiogenic shock despite medical therapy. It must be performed on an urgent basis when HF is less severe. In patients with well tolerated severe valvular insufficiency and no other reasons for surgery, medical management with antibiotics is recommended under strict clinical and echocardiographic observation. Surgery should be subsequently considered after healing of IE, depending on tolerance of the valve lesion and according to the recommendations of the ESC Guidelines on the Management of Valvular Heart Disease.¹⁷⁶

In summary, HF is the most frequent and severe complication of IE. Unless severe co-morbidity exists,

the presence of HF indicates early surgery in patients with NVE.

Uncontrolled infection

Uncontrolled infection is the second most frequent cause for surgery⁷⁹ and encompasses persisting infection (>7–10 days), infection due to resistant organisms, and locally uncontrolled infection.

1. Persisting infection

Persisting fever is a frequent problem observed during treatment of IE. Usually, temperature normalizes within 5–10 days under specific antibiotic therapy. Persisting fever may be related to several reasons, including inadequate antibiotic therapy, resistant organisms, infected lines, locally uncontrolled infection, embolic complications or extracardiac site of infection, and adverse reaction to antibiotics.³ Management of persisting fever includes replacement of intravenous lines, repeat laboratory measurements, blood cultures and echocardiography, and research for intracardiac or extracardiac focus of infection.

2. Perivalvular extension in infective endocarditis

Perivalvular extension of IE is the most frequent cause of uncontrolled infection and is associated with poor prognosis and high likelihood of need for surgery. Perivalvular complications include abscess formation, pseudoaneurysms, and fistulae (Table 9).^{177,178}

Perivalvular abscess is more common in aortic IE (10–40% in native valve IE)^{3,179–181} and very frequent in PVE (56–100%).^{3,7} In mitral IE, perivalvular abscesses are usually located posteriorly or laterally.¹⁸² In aortic IE, perivalvular extension occurs most frequently in the mitral–aortic intervalvular fibrosa.¹⁸³ Serial echocardiographic studies have shown that abscess formation is a dynamic process, starting with aortic root wall thickening and extending to the development of fistulae.¹⁸⁴ In one study, the most important risk factors for perivalvular complications were prosthetic valve, aortic location, and infection with CNS.¹⁸¹

Pseudoaneurysms and fistulae are severe complications of IE and frequently associated with very severe valvular and perivalvular damage.^{185–188} The frequency of fistula formation in IE has been reported to be 1.6%, *S. aureus* being the most commonly associated organism (46%).¹⁸⁸ Despite high rates of surgery in this population (87%), hospital mortality remains high (41%).^{186–188} Other complications due to major extension of infection are less frequent and may include ventricular septal defect, third degree atrioventricular block, and acute coronary syndrome.^{177,178,189}

Perivalvular extension should be suspected in cases with persistent unexplained fever or new atrioventricular block. An ECG should therefore be performed frequently during follow-up, particularly in aortic IE. TEE is the technique of choice for the diagnosis and follow-up of all perivalvular complications, while the sensitivity of TTE is <50%^{179–183} (see Section F). Indeed, perivalvular extension is frequently discovered on a systematic TEE. However, small abscesses can be missed, even using TEE, particularly those in a mitral location when there is co-existent annular calcification.⁷⁴

3. Indications and timing of surgery in the presence of uncontrolled infection in infective endocarditis (Table 19)

Persistent infection

In some cases of IE, antibiotics alone are insufficient to eradicate the infection. Surgery is indicated when fever and positive blood cultures persist for several days (>7–10 days) despite an appropriate antibiotic regimen and when extracardiac abscesses (splenic, vertebral, cerebral, or renal) and other causes of fever have been excluded.

Signs of locally uncontrolled infection

These include increasing vegetation size, abscess formation, false aneurysms or the creation of fistulae.^{186,190,191} Persistent fever is also usually present, and surgery is recommended as soon as possible. Rarely, when there are no other reasons for surgery and fever is easily controlled with antibiotics, small abscesses or false aneurysms can be treated conservatively under close clinical and echocardiographic follow-up.

Infection by microorganisms infrequently cured by antimicrobial therapy
Surgery is indicated in fungal IE.^{154,155} Surgery is indicated in IE due to multiresistant organisms, e.g. MRSA or vancomycin-resistant enterococci, and also in the rare infections caused by Gram-negative bacteria. In NVE caused by *S. aureus*, surgery is indicated if a favourable early response to antibiotics is not achieved.^{134,192,193}

In summary, uncontrolled infection is most frequently related to perivalvular extension or ‘difficult-to-treat’ organisms. Unless severe co-morbidity exists, the presence of locally uncontrolled infection indicates early surgery in patients with NVE.

Prevention of systemic embolism

1. Embolic events in infective endocarditis

Emolic events are a frequent and life-threatening complication of IE related to the migration of cardiac vegetations. The brain and spleen are the most frequent sites of embolism in left-sided IE, while pulmonary embolism is frequent in native right-sided and pacemaker lead IE. Stroke is a severe complication and is associated with increased morbidity and mortality.¹⁹⁴ Conversely, emolic events may be totally silent in ~20% of patients with IE, especially those affecting the splenic or cerebral circulation, and can be diagnosed by non-invasive imaging.¹⁹⁵ Thus, systematic abdominal and cerebral CT scan may be helpful. However, contrast media should be used with caution in patients with renal failure or haemodynamic instability because of the risk of worsening renal impairment in combination with antibiotic nephrotoxicity.

Overall emolic risk is very high in IE, with emolic events occurring in 20–50% of patients.^{195–203} However, the risk of new events (occurring after initiation of antibiotic therapy) is only 6–21%.^{68,196,200} A recent study from the ICE group²⁰⁴ demonstrated that the incidence of stroke in patients receiving appropriate antimicrobial therapy was 4.8/1000 patient days in the first week of therapy, falling to 1.7/1000 patient days in the second week and further thereafter.

2. Predicting the risk of embolism

Echocardiography plays a key role in predicting embolic events,^{68,200–205} although prediction remains difficult in the individual patient. Several factors are associated with increased risk of embolism, including the size and mobility of vegetations,^{68,195,199–207} the location of the vegetation on the mitral valve,^{199–203} the increasing or decreasing size of the vegetation under antibiotic therapy,^{200,207} particular microorganisms (staphylococci,²⁰⁰ *Streptococcus bovis*,^{16,208} *Candida* spp.), previous embolism,²⁰⁰ multivalvular IE,¹⁹⁹ and biological markers.²⁰⁹ Among these, the size and mobility of the vegetations are the most potent independent predictors of a new embolic event.⁶⁸ Patients with vegetations length >10 mm are at higher risk of embolism,^{68,195,203} and this risk is even higher in patients with very large (>15 mm) and mobile vegetations, especially in staphylococcal IE affecting the mitral valve.²⁰⁰

It must be re-emphasized that the risk of new embolism is highest during the first days following initiation of antibiotic therapy and rapidly decreases thereafter, particularly beyond 2 weeks,^{196,200,204,210} although some risk persists indefinitely whilst vegetations remain present. For this reason, the benefits of surgery to prevent embolism are greatest during the first week of antibiotic therapy, when embolic risk peaks.

3. Indications and timing of surgery to prevent embolism in infective endocarditis (Table 19)

Avoiding embolic events is difficult since the majority occur before admission.¹⁹⁵ The best means to reduce the risk of an embolic event is the prompt institution of appropriate antibiotic therapy.¹⁹⁵ Whilst promising,^{211,212} the addition of antiplatelet therapy did not reduce the risk of embolism in the only published randomized study.²¹³

The exact role of early surgery in preventing embolic events remains controversial. In the Euro Heart Survey, vegetation size was one of the reasons for surgery in 54% of patients with NVE and in 25% of those with PVE,⁷⁹ but was rarely the only reason. The value of early surgery in this situation has never been proven. Thus, the decision to operate early for prevention of embolism must take into account the presence of previous embolic events, other complications of IE, the size and mobility of the vegetation, the likelihood of conservative surgery, and the duration of antibiotic therapy.¹⁶⁵ The overall benefits of surgery should be weighed against the operative risk and must consider the clinical status and co-morbidity of the patient.

The main indications and timing of surgery to prevent embolism in NVE are given in Table 19. Surgery is indicated in patients with large vegetations (>10 mm) following one or more clinical or silent embolic events despite appropriate antibiotic therapy.⁶⁸ In the absence of embolism, surgery is indicated in patients with large vegetations (>10 mm), and other predictors of a complicated course (HF, persistent infection despite appropriate antibiotic therapy, abscess), particularly if the vegetation is located on the mitral valve. In these situations, the presence of a large vegetation favours earlier surgery. Surgery may be considered in patients with very large (>15 mm) isolated vegetations on the aortic or mitral valve, although this decision is more difficult and must be very carefully individualized, according to the probability of conservative surgery.⁶⁸

Surgery undertaken for the prevention of embolism must be performed very early, during the first few days following initiation

of antibiotic therapy (urgent surgery), as the risk of embolism is highest at this time.^{68,200}

In summary, embolism is very frequent in IE, complicating 20–50% of cases of IE, falling to 6–21% after initiation of antibiotic therapy. The risk of embolism is the highest during the first 2 weeks of antibiotic therapy and is clearly related to the size and mobility of the vegetation. Risk is increased with large (>10 mm) vegetations and particularly high with very mobile and larger (>15 mm) vegetations. The decision to operate on early to prevent embolism is always difficult and specific for the individual patient. Governing factors include size and mobility of the vegetation, previous embolism, type of microorganism, and duration of antibiotic therapy.

Part 2. Principles, methods, and immediate results of surgery

Pre- and peri-operative management

1. Coronary angiography

Coronary angiography is recommended according to the ESC Guidelines on the Management of Valvular Heart Disease¹⁷⁶ in men >40 years, in post-menopausal women, and in patients with at least one cardiovascular risk factor or a history of coronary artery disease. Exceptions arise when there are large aortic vegetations which may be dislodged during catheterization, or when emergency surgery is necessary. In these situations, high-resolution CT may be used to rule out significant coronary artery disease.¹⁷⁶

2. Extracardiac infection

If a primary focus of infection likely to be responsible for IE has been identified, it must be eradicated prior to cardiac surgical intervention, unless valve surgery is urgent.

3. Intra-operative echocardiography

Intra-operative TEE is most useful to determine the exact location and extent of infection, to guide surgery, assess the result, and help in early post-operative follow-up.²¹⁴

Surgical approach and techniques

The two primary objectives of surgery are total removal of infected tissues and reconstruction of cardiac morphology, including repair or replacement of the affected valve(s).

Where infection is confined to the valve cusps or leaflets, any method to repair or replace the valve may be used. However, valve repair is favoured whenever possible, particularly when IE affects the mitral or tricuspid valve.^{215,216} Perforations in a single valve cusp or leaflet may be repaired with an autologous glutaraldehyde-treated or bovine pericardial patch.

In complex cases with locally uncontrolled infection, total excision of infected and devitalized tissue should be followed by valve replacement and repair of associated defects to secure valve fixation. Mechanical and biological prostheses have similar operative mortality.²¹⁷ Therefore, the Task Force does not favour any specific valve substitute but recommends a tailored approach for each individual patient and clinical situation. The use of foreign

material should be kept to a minimum. Small abscesses can be closed directly, but larger cavities should be allowed to drain into the pericardium or the circulation.

In mitral valve IE, successful valve repair can be achieved by experienced teams in up to 80% of patients, although such excellent results may not be matched in non-specialist centres.²¹⁸ Residual mitral regurgitation should be assessed using intra-operative TEE. Mitral subannular, annular, or supraannular tissue defects are preferably repaired with autologous or bovine pericardium, a prosthetic valve then being secured to the reconstructed/reinforced annulus, if necessary. The choice of technique depends on the vertical extension of the lesion/tissue defect.^{219–221} The use of mitral valve homografts and pulmonary autografts (Ross procedure) has been suggested,^{222,223} but their application is limited by poor availability and difficulty of the surgical technique.

In aortic IE, replacement of the aortic valve using a mechanical or biological prosthesis is the technique of choice. The use of cryopreserved or sterilized homografts has been suggested to reduce the risk of persistent or recurrent infection.^{224,225} However, mechanical prostheses and xenografts compare favourably, with improved durability.^{226–228} Homografts or stentless xenografts may be preferred in PVE or in cases where there is extensive aortic root destruction with aorto-ventricular discontinuity.^{224,225,227,229} In experienced hands, the Ross procedure may be used in children or adolescents to facilitate growth and in young adults for extended durability.^{230,231}

A monoblock aorto-mitral homograft has been suggested as a surgical option for extensive bivalvular IE.²³² Cardiac transplantation may be considered in extreme cases where repeated operative procedures have failed to eradicate persistent or recurrent PVE.²³³

Operative mortality, morbidity, and post-operative complications

Peri-operative mortality and morbidity vary according to the type of infective agent, the extent of destruction of cardiac structures, the degree of left ventricular dysfunction, and the patient's haemodynamic condition at the time of surgery. Currently, operative mortality in IE lies between 5 and 15%.^{234–239} When surgery must be performed within the first week of antimicrobial therapy, a recent study showed that in-hospital mortality is 15%, with risks of recurrence and non-infective post-operative valvular dysfunction of 12 and 7%, respectively.²³⁹ In less complex cases, where disease is limited to the valve structures alone allowing complete excision of infected tissue, mortality should be similar to routine valve surgery. The cause of death is often multifactorial, but the main reasons are multiorgan failure, HF, intractable sepsis, coagulopathy, and stroke.²³⁷

Immediate post-operative complications are relatively common. Among the most frequent are severe coagulopathy requiring treatment with clotting factors, re-exploration of the chest for bleeding or tamponade, acute renal failure requiring haemodialysis, stroke, low cardiac output syndrome, pneumonia, and atrioventricular block following radical resection of an aortic root abscess with need for pacemaker implantation.^{235,237} A pre-operative ECG demonstrating left bundle branch block predicts the need for a post-operative permanent pacemaker.¹⁰⁴

J. Other complications of infective endocarditis

Part 1. Neurological complications, antithrombotic therapy

Neurological complications

Neurological events develop in 20–40% of all patients with IE and are mainly the consequence of vegetation embolism.^{194,240,241} The clinical spectrum of these complications is wide, including ischaemic or haemorrhagic stroke, transient ischaemic attack, silent cerebral embolism, symptomatic or asymptomatic infectious aneurysm, brain abscess, meningitis, toxic encephalopathy, and seizure. *Staphylococcus aureus* causes higher overall rates of neurological complications.^{194,240} They are associated with an excess mortality, particularly in the case of stroke.^{98,194} Rapid diagnosis and initiation of appropriate antibiotics are of major importance to prevent a first or recurrent neurological complication. A neurologist/neurosurgeon should always be involved in the management of these patients.

After a neurological event, most patients still have at least one indication for cardiac surgery.¹⁹⁴ The risk of post-operative neurological deterioration is low after a silent cerebral embolism or transient ischaemic attack,¹⁹⁴ and surgery is recommended without delay if an indication remains. After an ischaemic stroke, cardiac surgery is not contraindicated unless the neurological prognosis is judged to poor (Figure 3). Evidence regarding the optimal time interval between stroke and cardiac surgery is conflicting because of lack of controlled studies.^{194,242–246} If cerebral haemorrhage has been excluded by cranial CT and neurological damage is not severe (i.e. coma), surgery indicated for HF, uncontrolled infection, abscess, or persistent high embolic risk should not be delayed

and can be performed with a relatively low neurological risk (3–6%) and good probability of complete neurological recovery.^{246,247} Conversely, in cases with intracranial haemorrhage, neurological prognosis is worse and surgery must be postponed for at least 1 month.²⁴² If urgent cardiac surgery is needed, close cooperation with the neurosurgical team is mandatory. Table 20 and Figure 3

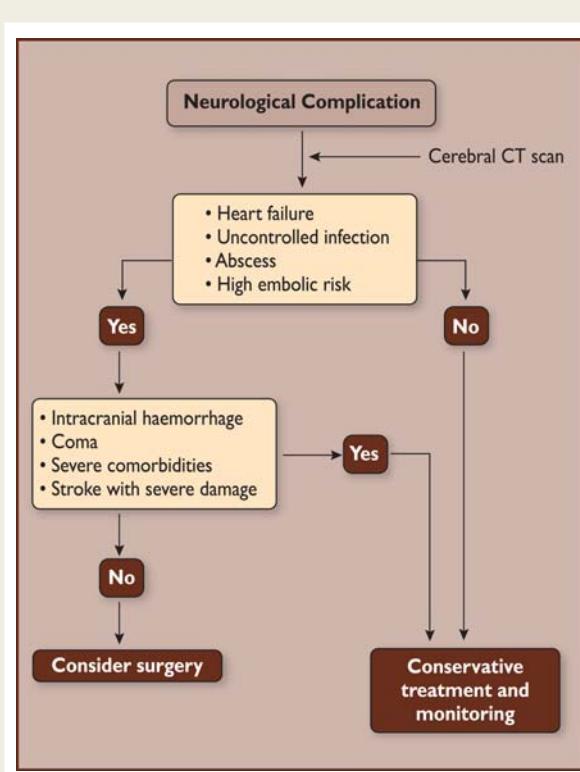


Figure 3 Therapeutic strategy for patients with infective endocarditis and neurological complications.

Table 20 Management of neurological complications

Recommendations: neurological complications	Class ^a	Level ^b
After a silent cerebral embolism or transient ischaemic attack, surgery is recommended without delay if an indication remains	I	B
Following intracranial haemorrhage, surgery must be postponed for at least one month	I	C
Neurosurgery or endovascular therapy are indicated for very large, enlarging, or ruptured intracranial aneurysm	I	C
After a stroke, surgery indicated for heart failure, uncontrolled infection, abscess, or persistent high embolic risk should not be delayed. Surgery should be considered as long as coma is absent and cerebral haemorrhage has been excluded by cranial CT	IIa	B
Intracranial aneurysm should be looked for in any patient with IE and neurological symptoms - CT or MR angiography should be considered for diagnosis	IIa	B
Conventional angiography should be considered when non-invasive techniques are negative and the suspicion of intracranial aneurysm remains	IIa	B

^aClass of recommendation.

^bLevel of evidence.

CT = computed tomography; MR = magnetic resonance.

Table 21 Management of antithrombotic therapy in infective endocarditis

Recommendations: antithrombotic therapy	Class ^a	Level ^b
Interruption of antiplatelet therapy is only recommended in the presence of major bleeding	I	B
In ischaemic stroke without cerebral haemorrhage, replacement of oral anticoagulant therapy by unfractionned heparin for 2 weeks is indicated with a close monitoring of activated partial thromboplastin or the activated cephalin clotting time	I	C
In intracranial haemorrhage, interruption of all anticoagulation is recommended	I	C
In patients with intracranial haemorrhage and a mechanical valve, unfractionated heparin should be reinitiated as soon as possible (with close monitoring of activated partial thromboplastin or activated cephalin clotting time) following multidisciplinary discussion	IIa	C
In the absence of stroke, replacement of oral anticoagulant therapy by unfractionned heparin during 2 weeks may be considered in case of <i>S.aureus</i> IE with a close monitoring of activated partial thromboplastin or the activated cephalin clotting time	IIb	C

^aClass of recommendation.^bLevel of evidence.

summarize the recommended management of neurological complications in IE.

In summary, neurological events develop in 20–40% of all patients with IE and are mainly the consequence of embolism. Stroke is associated with excess mortality. Rapid diagnosis and initiation of appropriate antibiotics are of major importance to prevent a first or recurrent neurological complication. After a first neurological event, most patients still have an indication for surgery which is generally not contraindicated.

Antithrombotic therapy

There is no indication for the initiation of antithrombotic drugs (thrombolytic drugs, anticoagulant or antiplatelet therapy) during the active phase of IE. In patients already taking oral anticoagulants, there is a risk of intracranial haemorrhage which seems to be highest in patients with *S. aureus* PVE and those with a previous neurological event.²⁴⁸ The recommendations for the management of the anticoagulant therapy are based on low level of evidence (Table 21).

Although initial experimental studies showed a beneficial impact of aspirin therapy on the risk of an embolic event in *S.aureus* IE,^{249–251} no strong evidence exists on its beneficial effect in clinical practice because of conflicting data.^{212,213,252} Besides, some studies showed a non-significant increase of major bleeding episodes.^{213,252}

Part 2. Other complications (infectious aneurysms, acute renal failure, rheumatic complications, splenic abscess, myocarditis, pericarditis)

Infectious aneurysms

Infectious (mycotic) aneurysms (IAs) result from septic arterial embolism to the intraluminal space or vasa vasorum, or

from subsequent spread of infection through the intimal vessels.^{253,254}

An intracranial location is most frequent, and the reported frequency of 2–4% is probably an underestimate since some IAs are clinically silent.²⁵⁵ Clinical presentation is highly variable²⁵⁶ (focal neurological deficit, headache, confusion, seizures) and imaging should be performed to detect intracranial IAs in any case of IE with neurological symptoms. CT and magnetic resonance angiography both reliably diagnose IAs with high sensitivity and specificity.^{257,258} However, conventional angiography remains the gold standard and should be performed when non-invasive techniques are negative and suspicion remains. No randomized trials exist to guide management, and therapy must be tailored to the individual patient. Ruptured IAs have a very poor prognosis, but no predictors of this complication have been identified to date. Since many unruptured IAs may resolve during antibiotic treatment,²⁵⁹ serial imaging is required. In cases with large, enlarging, or ruptured IAs, neurosurgery or endovascular therapy is indicated.^{255,260} The choice between these options will depend on the presence and size of the haematoma, and the experience of the medical team.

Acute renal failure

Acute renal failure is a common complication of IE which occurs in ~30% of patients and predicts poor prognosis.²⁶¹ Causes are often multifactorial:²⁶²

- Immune complex and vasculitic glomerulonephritis
- Renal infarction
- Haemodynamic impairment in cases with HF or severe sepsis, or after cardiac surgery
- Antibiotic toxicity (acute interstitial nephritis), notably related to aminoglycosides, vancomycin (synergistic toxicity with aminoglycosides), and even high dose penicillin
- Nephrotoxicity of contrast agents used for imaging purposes.

Haemodialysis may be required in some patients,²⁶³ but acute renal failure is often reversible. To prevent this complication, antibiotic

doses should be adjusted for creatinine clearance with careful monitoring of serum levels (aminoglycosides and vancomycin). Imaging with nephrotoxic contrast agents should be avoided in those with haemodynamic impairment or previous renal insufficiency.

Rheumatic complications

Musculoskeletal symptoms (arthralgia, myalgia, back pain) are frequent during IE, and rheumatic complications may be the first manifestations of the disease. Peripheral arthritis occurs in ~14% and spondylodiscitis in 3–15% of cases.^{264–266} In one study, IE was diagnosed in 30.8% of patients with pyogenic spondylodiscitis and was more common in cases of streptococcal infection and predisposing heart conditions.²⁶⁷ MRI or CT of the spine should be performed in IE patients with back pain. Conversely, echocardiography may be performed in patients with a definite diagnosis of pyogenic spondylodiscitis and underlying cardiac conditions predisposing to endocarditis. Prolonged antibiotic therapy is generally required in definite spondylodiscitis.

Splenic abscess

Although splenic emboli are common, splenic abscess is rare. Persistent or recurrent fever and bacteraemia suggest the diagnosis, and these patients should be evaluated by abdominal CT, MRI, or ultrasound. Treatment consists of appropriate antibiotic regimens. Splenectomy may be considered for splenic rupture or large abscesses which respond poorly to antibiotics alone, and should be performed before valvular surgery unless the latter is urgent. Percutaneous drainage is an alternative for high-risk surgical candidates.^{268,269}

Myocarditis, pericarditis

Cardiac failure may also be due to myocarditis which is frequently associated with abscess formation. Regional myocardial infarction may be caused by coronary embolism or compression. Ventricular arrhythmias may indicate myocardial involvement and imply a poor prognosis.³ Myocardial involvement is best assessed using TTE.³

Pericarditis may be associated with an abscess, myocarditis, or bacteraemia often as a result of *S. aureus* infection. Purulent pericarditis is rare and may necessitate surgical drainage.^{270,271} Rarely, ruptured pseudoaneurysms or fistulae may communicate with the pericardium, with dramatic and often fatal consequences.

K. Outcome after discharge and long-term prognosis

Late complications occurring after the initial infection contribute to the poor prognosis of IE. Following in-hospital treatment, the main complications include recurrence of infection, HF, need for valve surgery, and death.^{272,273}

Recurrences: relapses and reinfections

The risk of recurrence amongst survivors of IE varies between 2.7 and 22.5%.^{57,105,235–237,273–275} In a recent large series with mean 5-year follow-up, the rate of recurrence in non-IVDAs was 1.3% per patient-year.²⁷²

Although not systematically differentiated in the literature, there are two types of recurrence: relapse and reinfection. The term 'relapse' refers to a repeat episode of IE caused by the same microorganism as the previous episode.⁵⁶ In contrast, 'reinfection' is primarily used to describe infection with a different microorganism.⁵⁶ When the same species is isolated during a subsequent episode of IE, there is often uncertainty as to whether the repeat infection is a relapse of the initial infection or a new infection (reinfection). In these cases, molecular methods including strain-typing techniques should be employed.^{3,56} When these techniques or the identity of both isolates are unavailable, the timing of the second episode of IE may be used to distinguish relapse from reinfection. Thus, although variable, the time between episodes is usually shorter for relapse than for reinfection—in broad terms, an episode of IE caused by the same species within 6 months of the initial episode represents relapse, whereas later events suggest reinfection.^{56,275} For these purposes, storage of endocarditis isolates for at least 1 year is recommended.^{3,56}

Factors associated with an increased rate of relapse are listed in Table 22. Relapses are most often due to insufficient duration of original treatment, suboptimal choice of initial antibiotics, and a persistent focus of infection (e.g. periprosthetic abscess). When the duration of therapy has been insufficient or the choice of antibiotic incorrect, relapse should be treated for a further 4–6 weeks depending on the causative microorganism and its susceptibility (remembering that resistance may develop in the meantime).

Patients with previous IE are at risk of reinfection,²⁷⁴ and prophylactic measures should be very strict. Reinfection is more

Table 22 Factors associated with an increased rate of relapse

- Inadequate antibiotic treatment (agent, dose, duration)
- Resistant microorganisms, e.g. *Brucella* spp., *Legionella* spp., *Chlamydia* spp., *Mycoplasma* spp., *Mycobacterium* spp., *Bartonella* spp., *Coxiella Burnetii*, fungi
- Polymicrobial infection in an IVDA
- Empirical antimicrobial therapy for culture negative IE
- Perianular extension
- Prosthetic valve endocarditis
- Persistent metastatic foci of infection (abscesses)
- Resistance to conventional antibiotic regimens
- Positive valve culture
- Persistence of fever at the seventh postoperative day

frequent in IVDAs (especially in the year after the initial episode),^{236,276} in PVE,^{57,235,275,277} in patients undergoing chronic dialysis,²⁷³ and in those with multiple risk factors for IE.³ Patients with reinfection are at higher risk of death and need for valve replacement.²⁷⁵

The type of valve implanted has no effect on the risk of recurrent IE.^{57,237} Aortic valve and root replacement with a prosthetic conduit yields results comparable with those of homograft root replacement.^{225,278}

Heart failure and need for valvular surgery

Progressive HF can occur as a consequence of valve destruction, even when infection is healed. After completion of treatment, recommendations for surgery follow conventional guidelines.¹⁷⁶ As a consequence of increasing rates of operation during the active phase of the infection, the need for late valve surgery is low, ranging from 3 to 7% in the most recent series.^{272,273}

Long-term mortality

Long-term survival is 60–90% at 10 years.^{101,105,235,236,273,274} Information concerning longer follow-up is scarce. A survival at 15–20 years of ~50% has been reported.^{235,236,273} Following the in-hospital phase, principal factors which determine long-term mortality are age, co-morbidity, and HF, particularly when surgery has not been performed, suggesting that long-term mortality is related to the underlying conditions rather than IE itself.^{272,273} In a recent series, IE was the cause of the late mortality in only 6.5% of patients who died.²⁷²

Follow-up

Patients should be educated about the signs and symptoms of IE after discharge. They should be aware that recurrence can occur in IE and that new onset of fever, chills, or other signs of infection mandate immediate evaluation, including the procurement of blood cultures before empirical use of antibiotics.

Preventive measures should be applied in these patients who are a high risk group (see Section E).

To monitor the development of secondary HF, an initial clinical evaluation and baseline TTE should be performed at the completion of antimicrobial therapy and repeated serially, particularly during the first year of follow-up. There is no evidence base to guide the optimal monitoring of these patients, but the Task Force recommend clinical evaluation, blood samples (white cell count, C-reactive protein) and TTE at 1, 3, 6, and 12 months during the first year following completion of treatment.

In summary, relapse and reinfection are rare following IE, but may be caused by inadequate initial antibiotic therapy, resistant microorganisms, persistent focus of infection, or intravenous drug abuse. After discharge, patients with IE must be informed of the risk of recurrence and educated about how to diagnose and prevent a new episode of IE.

L. Specific situations

Part 1. Prosthetic valve endocarditis

PVE is the most severe form of IE and occurs in 1–6% of patients with valve prostheses²⁷⁹—an incidence of 0.3–1.2% per patient-year.^{1,3,106,188,253,280–284} It accounts for 10–30% of all cases of IE²⁸⁰ and affects mechanical and bioprosthetic valves equally. PVE was observed in 16% of cases in the French Survey,¹⁴ in 26% of cases in the Euro Heart Survey,⁷⁹ and in 20% of 2670 patients with definite IE in the ICE Prospective Cohort Study.¹⁰⁶ PVE is still associated with difficulties in diagnosis, determination of the optimal therapeutic strategy, and poor prognosis.

Definition and pathophysiology

Early PVE is defined as occurring within 1 year of surgery, and late PVE beyond 1 year, because of significant differences between the microbiological profiles observed before and after this time point.^{3,284} However, this is an artificial distinction. What is important is not the time from the surgical procedure to the onset of IE, but whether IE is acquired peri-operatively or not and which microorganism is involved. A recent large prospective multicentre international registry found that 37% of PVE were associated with nosocomial infection or non-nosocomial health care-associated infections in outpatients with extensive health care contact.¹⁰⁶

The pathogenesis of PVE differs according to both the type of contamination and the type of prosthetic valve. In cases with peri-operative contamination, the infection usually involves the junction between the sewing ring and the annulus, leading to perivalvular abscess, dehiscence, pseudoaneurysms, and fistulae.^{1,281,282} In late PVE, the same and other mechanisms may exist. For example, in late bioprosthetic PVE, infection is frequently located on the leaflets of the prosthesis, leading to vegetations, cusp rupture, and perforation.

The consequence of PVE is usually new prosthetic regurgitation. Less frequently, large vegetations may cause prosthetic valve obstruction, which can be diagnosed by fluoroscopy and/or TEE.

Diagnosis

Diagnosis is more difficult in PVE than in NVE. Clinical presentation is frequently atypical, particularly in the early post-operative period, in which fever and inflammatory syndromes are common in the absence of IE. As in NVE, diagnosis of PVE is mainly based on the results of echocardiography and blood cultures. However, both are more frequently negative in PVE.²⁸⁵ Although TEE is mandatory in suspected PVE (Figure 1), its diagnostic value is lower than in NVE. A negative echocardiogram is frequently observed in PVE² and does not exclude the diagnosis. Similarly, blood cultures are more frequently negative in PVE, as compared with NVE.

In PVE, staphylococcal and fungal infections are more frequent and streptococcal infection less frequent than in NVE. Staphylococci, fungi, and Gram-negative bacilli are the main causes of early PVE, while the microbiology of late PVE mirrors that of NVE, with staphylococci, oral streptococci, *Streptococcus bovis*, and enterococci being the most frequent organisms, more probably due to community-acquired infections.

The Duke criteria have been shown to be helpful for the diagnosis of NVE, with a sensitivity of 70–80%,^{92,285} but are less useful in PVE, because of their lower sensitivity in this setting.^{286,287}

Prognosis and treatment

A very high in-hospital mortality rate of 20–40% has been reported in PVE.^{279,280} As in NVE, prognostic assessment is of crucial importance in PVE, since it allows identification of high-risk subgroups of patients in whom an aggressive strategy may be necessary. Several factors have been associated with poor prognosis in PVE,^{134,263,288–290} including age, staphylococcal infection, early PVE, HF, stroke, and intracardiac abscess. Among these, complicated PVE and staphylococcal infection are the most powerful markers, and these patients need aggressive management.

Antimicrobial therapy for PVE is similar to that for NVE. An exception is *S. aureus* PVE, which requires a more prolonged antibiotic regimen (particularly aminoglycosides) and frequent use of rifampin (see Section H).

Surgery for PVE follows the general principles outlined for NVE. By definition, most cases referred for surgery represent uncontrolled PVE and are treated accordingly. Radical debridement in these cases means removal of all foreign material, including the original prosthesis, and any calcium remaining from previous surgery. Homografts, stentless xenografts, or autografts may be

considered in aortic PVE, and homograft or xenograft root replacement is indicated for any abnormality of the aortic root that distorts the aortic sinuses. Alternatively, a valved Dacron conduit²⁷⁸ can be used.

Although surgical treatment is frequently necessary in PVE, the best therapeutic option is still debated.^{13,283,291–295} Although surgery is generally considered the best option when PVE causes severe prosthetic dysfunction or HF, it was performed in only 50% of patients with PVE in the Euro Heart Survey,⁷⁹ similar to patients with NVE. Similar data have been reported by others.^{106,283} Although no evidence-based data exist, a surgical strategy is recommended for PVE in high-risk subgroups identified by prognostic assessment, i.e. PVE complicated by HF, severe prosthetic dysfunction, abscess, or persistent fever. Similarly, early surgery is frequently needed in early staphylococcal PVE^{134,290} or PVE caused by fungi or other highly resistant organisms. The need for surgery should be considered in all cases of early PVE, since most are caused by staphylococci or other aggressive organisms.^{283,291} Conversely, patients with uncomplicated non-staphylococcal and non-fungal late PVE can be managed conservatively.^{288,294,295} However, patients who are initially treated medically require close follow-up, because of the risk of late events. Table 23 summarizes the main indications and proposed timing of surgery in PVE.

Table 23 Indications and timing of surgery in prosthetic valve infective endocarditis (PVE)

Indications for surgery in PVE	Timing*	Class ^a	Level ^b
A - HEART FAILURE			
PVE with severe prosthetic dysfunction (dehiscence or obstruction) causing refractory pulmonary oedema or cardiogenic shock	Emergency	I	B
PVE with fistula into a cardiac chamber or pericardium causing refractory pulmonary oedema or shock	Emergency	I	B
PVE with severe prosthetic dysfunction and persisting heart failure	Urgent	I	B
Severe prosthetic dehiscence without HF	Elective	I	B
B - UNCONTROLLED INFECTION			
Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	Urgent	I	B
PVE caused by fungi or multiresistant organisms	Urgent/elective	I	B
PVE with persisting fever and positive blood cultures > 7–10 days	Urgent	I	B
PVE caused by staphylococci or gram negative bacteria (most cases of early PVE)	Urgent/elective	IIa	C
C - PREVENTION OF EMBOLISM			
PVE with recurrent emboli despite appropriate antibiotic treatment	Urgent	I	B
PVE with large vegetations (> 10 mm) and other predictors of complicated course (heart failure, persistent infection, abscess)	Urgent	I	C
PVE with isolated very large vegetations (> 15 mm)	Urgent	IIb	C

^aClass of recommendation.

^bLevel of evidence.

*Emergency surgery is surgery performed within 24 h, urgent surgery: within a few days, elective surgery: after at least 1 or 2 weeks of antibiotic therapy.

In summary, PVE represents 20% of all cases of IE with increasing incidence. Diagnosis is more difficult than in NVE. Complicated PVE, staphylococcal PVE, and early PVE are associated with worse prognosis, if treated without surgery, and must be managed aggressively. Patients with non-complicated, non-staphylococcal late PVE can be managed conservatively with close follow-up.

Part 2. Infective endocarditis on pacemakers and implantable defibrillators

Infection of cardiac devices (CDs), including permanent pacemakers (PPMs) and implantable cardioverter defibrillators (ICDs), is a severe disease associated with high mortality.²⁹⁶ The rising number of patients with an implanted CD explains the increasing frequency of IE in these patients. The reported incidence of PPM infection varies widely among studies.²⁹⁷ A recent population-based study found an incidence of CD infection of 1.9 per 1000 device-years and a higher probability of infection after ICD as compared with PPM.²⁹⁸ Overall incidence lies between that of NVE in the general population and that of PVE.^{297,299} Both diagnosis and therapeutic strategy are particularly difficult in these patients.

Definition and pathophysiology of cardiac device infections.

A distinction should be made between local device infection (LDI) and cardiac device-related IE (CDRIE). LDI is defined as an infection limited to the pocket of the CD and is clinically suspected in the presence of local signs of inflammation at the generator pocket, including erythema, warmth, fluctuance, wound dehiscence, erosion, tenderness, or purulent drainage.³⁰⁰ CDRIE is defined as an infection extending to the electrode leads, cardiac valve leaflets, or endocardial surface. However, differentiating LDI and CDRIE is frequently difficult. In one study,³⁰¹ culture of intravascular lead segments was positive in 72% of 50 patients with manifestations strictly limited to the implantation site. However, the possibility of intra-operative contamination of the lead tip cannot be excluded in these patients.³⁰² It has recently been proposed that positive lead cultures can be used as a sign of CDRIE only in the absence of pocket infection or when the leads were removed using a remote incision from the pocket or surgical extraction.³⁰²

The main mechanism of CDRIE is contamination by local bacteriological flora at the time of device implantation.³⁰³ Then, the infection can spread along the electrode to the endocardium and the electrode tip.²⁹⁷ The consequence may be formation of vegetations, which can be found anywhere from the subclavian vein to the superior vena cava,³ on the electrode lead, on the tricuspid valve, but also on the mural endocardium of the right atrium and right ventricle. Septic pulmonary embolism is a very frequent complication of CDRIE. Other possible mechanisms of CDRIE include haematogenous seeding from a distant focus of infection. Several factors have been associated with CD infections, including fever within 24 h before implantation, use of temporary pacing before

implantation, and early reimplantation. Antibiotic prophylaxis is protective in this indication.³⁰⁴

Diagnosis

CDRIE is one of the most difficult forms of IE to diagnose. Clinical presentation is frequently misleading, with predominant respiratory or rheumatological symptoms,³⁰⁵ as well as local signs of infection. CDRIE must be suspected in the presence of unexplained fever in a patient with a CD. Fever is frequently blunted, particularly in elderly patients.

As in other forms of IE, echocardiography and blood cultures are the cornerstone of diagnosis. Echocardiography plays a key role in CDRIE and is helpful for the diagnosis of both lead vegetation and tricuspid involvement, quantification of tricuspid regurgitation, sizing of vegetations, and follow-up after lead extraction. Although TEE has superior sensitivity and specificity to TTE,^{305–308} and is cost-effective, it is recommended to perform both in suspected CDRIE. However, both TTE and TEE may be falsely negative in CDRIE, and a normal echographic examination does not rule out CDRIE. Preliminary experience with intracardiac echocardiography has recently been reported.³⁰⁹ Blood cultures are positive in 77% of cases of CDRIE.³⁰² Staphylococci are the most frequent pathogens, *S. aureus* being predominant in the acute forms of PPM infection.³⁰⁵

The Duke criteria are difficult to apply in these patients because of lower sensitivity. Modifications of Duke criteria have been proposed,^{302,305} to include local signs of infection and pulmonary embolism as major criteria.³⁰⁵

Finally, lung CT and lung scintigraphy are both useful to detect pulmonary septic embolism.

Treatment (Table 24)

In the majority of patients, CDRIE must be treated by prolonged antibiotic therapy associated with device removal.^{296,302,310}

Antimicrobial therapy for PPM infections should be individualized and based on culture and susceptibility results if possible. Duration of therapy should be 4–6 weeks in most cases. Attempts to treat these patients with antibiotic alone have been proposed in the case of negative TEE.³¹¹ However, in the case of definite CDRIE, medical therapy alone has been associated with high mortality and risk of recurrence.^{296,302} For this reason, CD removal is recommended in all cases of proven CDRIE and should also be considered when CDRIE is only suspected, in the case of occult infection without any other apparent source than the device.³¹²

CD extraction can be performed percutaneously without need for surgical intervention in the majority of patients. However, percutaneous extraction may be more difficult when the CD has been implanted for several years. Pulmonary embolism as a result of vegetation displacement during extraction occurs frequently, particularly when vegetations are large.^{305,313} However, these episodes are frequently asymptomatic, and percutaneous extraction remains the recommended method even in cases of large vegetations,^{296,302,313} since overall risks are even higher with surgical extraction.³⁰⁵

Some authors recommend surgery to be performed in patients with very large vegetations,^{302,314} when percutaneous extraction is technically impossible, or when severe tricuspid valve IE is associated. When performed, surgery requires good exposure under

Table 24 Cardiac device-related infective endocarditis (CDRIE): treatment and prevention

Recommendations: IE on pacemakers and implantable defibrillators	Class ^a	Level ^b
A - PRINCIPLES OF TREATMENT:		
Prolonged antibiotic therapy and device removal are recommended in definite CDRIE	I	B
Device removal should be considered when CDRIE is suspected on the basis of occult infection without other apparent source of infection	IIa	C
In patients with native or prosthetic valve endocarditis and an intracardiac device with no evidence of associated device infection, device extraction may be considered	IIb	C
B - MODE OF DEVICE REMOVAL:		
Percutaneous extraction is recommended in most patients with CDRIE, even those with large (> 10 mm) vegetations	I	B
Surgical extraction should be considered if percutaneous extraction is incomplete or impossible or when there is associated severe destructive tricuspid IE	IIa	C
Surgical extraction may be considered in patients with very large (> 25 mm) vegetations	IIb	C
C - REIMPLANTATION:		
After device extraction, reassessment of the need for reimplantation is recommended	I	B
When indicated, reimplantation should be postponed if possible to allow a few days or weeks of antibiotic therapy	IIa	B
Temporary pacing is not recommended	III	C
D - PROPHYLAXIS		
Routine antibiotic prophylaxis is recommended before device implantation	I	B

^aClass of recommendation.^bLevel of evidence.

extracorporeal circulation to allow complete removal of all foreign material. Excision of all infected contact lesions at the level of the tricuspid valve, right atrium, right ventricular free wall, and distal superior vena cava is essential. However, mortality associated with surgical removal is high³¹⁵ in these frequently elderly patients with associated co-morbidities.

There is no clear recommendation concerning the optimal timing and site of reimplantation, and this decision must be adapted to the individual patient. Immediate reimplantation should be avoided owing to the risk of new infection. Temporary pacing is not recommended because it has been shown to be a risk factor for subsequent CD infection.³⁰⁴ If reimplantation is performed, a new transvenous system is usually implanted on the contralateral side. If immediate reimplantation is necessary, epicardial implantation is a possible alternative. In other patients, reimplantation can be postponed for a few days or weeks, with reduced infectious risk. Finally, reassessment may lead to the conclusion that reimplantation is unnecessary in a number of patients.^{300,306,310,316} In patients with NVE or PVE and an apparently non-infected PPM, device extraction may be considered.³¹⁷

Although there are no large controlled studies on this topic, antibiotic prophylaxis is usually recommended before implantation.³¹⁸

In summary, CDRIE is one of the most difficult forms of IE to diagnose, and must be suspected in the presence of

frequently misleading symptoms, particularly in elderly patients. Prognosis is poor, not least because of its frequent occurrence in elderly patients with associated co-morbidity. In the majority of patients, CDRIE must be treated by prolonged antibiotic therapy and device removal.

Part 3. Right-sided infective endocarditis

Epidemiology

Right-sided IE accounts for 5–10% of cases of IE.^{14,319,320} Although it may occur in patients with a PPM, ICD, central venous catheter, or CHD, this situation is most frequently observed in IVDA. The exact incidence of IE in IVDA is unknown, but some recent data show an increasing number of hospitalizations for intravenous drug abuse-related IE.³²¹ This disease occurs more frequently in IVDA who are HIV seropositive, particularly those with advanced immunosuppression.^{320,322} Damage to the right-sided valves from injected particulate matter associated with poor injection hygiene, contaminated drug solutions, and abnormalities of immune function are some of the pathophysiological hypotheses underlying right-sided IE in IVDA.³²³ Whilst the tricuspid valve is the usual site of infection in IVDA, pulmonary and eustachian valve infection may also be observed, and left-sided IE is not

unusual in this group.^{324–326} *Staphylococcus aureus* is the dominant organism (60–90%),³²⁷ and *Pseudomonas aeruginosa*, other Gram-negative organisms, fungi, enterococci, streptococci, and polymicrobial infections also occur less frequently.

Diagnosis and complications

The usual manifestations of right-sided IE are persistent fever, bacteraemia, and multiple septic pulmonary emboli, which may manifest with chest pain, cough, or haemoptysis. When systemic emboli occur, paradoxical embolism or associated left-sided IE should be considered. Pulmonary septic emboli may be complicated by pulmonary infarction, abscess, pneumothorax, and purulent pulmonary effusion.^{327,328} Right HF is rare, but can be caused by the increase of pulmonary pressures or severe right-sided valvular regurgitation or obstruction.

TTE usually allows assessment of tricuspid involvement because of the anterior location of this valve and usual large vegetations.^{329–331} However, TEE is more sensitive in the detection of pulmonary vegetations³³² and abscesses (particularly those adjacent to the membranous septum), and associated left-sided involvement.

Prognosis and treatment

Prognosis of right-sided NVE is relatively good, with an in-hospital mortality rate <10%.^{333–335} Vegetation length >20 mm and fungal aetiology were the main predictors of death in a recent large retrospective cohort of right-sided IE in IVDAs.³³⁵ In HIV-infected patients, a CD4 count of <200 cells/ μ L has a high prognostic value.^{320,322}

1. Antimicrobial therapy

On admission, the choice of initial empiric antimicrobial therapy depends on the suspected microorganism, the type of drug and solvent used by the addict, and the location of cardiac involvement.^{333,334} In right-sided NVE, *S. aureus* must always be covered, particularly in IVDAs or venous catheter-related infection. Treatment will include either penicillinase-resistant penicillins or vancomycin, depending on the local prevalence of MRSA.^{336,337} If the patient is a pentazocine addict, an antipseudomonas agent should be added.³³⁸ If an IVDA uses brown heroin dissolved in lemon juice, *Candida* spp. (not *C. albicans*) should be considered and antifungal treatment added.³³⁹ More conventionally, in IVDAs with underlying valve lesions and/or left-sided involvement, antibiotic treatment should include cover against streptococci and enterococci.^{333,334} Once the causative organisms have been isolated, therapy has to be adjusted.

In IVDAs, the standard therapy for IE due to MSSA is appropriate, with clear data demonstrating that penicillinase-resistant penicillin regimens are superior to glycopeptide-containing regimens.^{340,341}

There are also consistent data showing that a 2-week treatment may be sufficient^{341–343} and that the addition of an aminoglycoside may be unnecessary.³⁴¹ Two-week treatment with oxacillin (or cloxacillin) with or without gentamicin is possible if all the following criteria are fulfilled:

- ✓ Methicillin-susceptible *S. aureus* **and**
- ✓ Good response to treatment **and**

- ✓ Absence of metastatic sites of infection or empyema **and**
- ✓ Absence of cardiac and extracardiac complications **and**
- ✓ Absence of associated prosthetic valve or left-sided valve infection **and**
- ✓ < 20 mm vegetation **and**
- ✓ Absence of severe immunosuppression (<200 CD4 cells/mm³) with or without AIDS.

Because of limited bactericidal activity, poor penetration into vegetations, and increased drug clearance in IVDAs, glycopeptides should not be used in a 2-week treatment.

The standard 4–6 week regimen must be used in the following situations:

- (a) slow clinical or microbiological response (>96 h) to antibiotic therapy;^{343,344}
- (b) right-sided IE complicated by right HF, vegetations >20 mm, acute respiratory failure, septic metastatic foci outside the lungs (including empyema), or extracardiac complications, e.g. acute renal failure;^{344,345}
- (c) therapy with antibiotics other than penicillinase-resistant penicillins;^{342,343,346,347}
- (d) IVDA with severe immunosuppression (CD4 count <200 cells/ μ L) with or without AIDS;^{348,349}
- (e) associated left-sided IE.

Right-sided *S. aureus* IE in IVDAs may also be successfully treated with oral ciprofloxacin (750 mg b.i.d.) plus rifampicin (300 mg b.i.d.) provided that the strain is fully susceptible to both drugs and patient adherence is monitored carefully.³⁵⁰ For organisms other than MSSA, therapy in IVDAs does not differ from that in non-addicts.^{344,351}

2. Surgery

Surgical treatment should generally be avoided in right-sided native IE, but should be considered in the following situations (Table 25):

- (a) right HF secondary to severe tricuspid regurgitation with poor response to diuretic therapy;
- (b) IE caused by organisms which are difficult to eradicate (e.g. persistent fungi), or bacteraemia for at least 7 days (e.g. *S. aureus*, *P. aeruginosa*) despite adequate antimicrobial therapy;³⁵²
- (c) Tricuspid valve vegetations >20 mm which persist after recurrent pulmonary emboli with or without concomitant right HF.^{335,345}

Indications for surgery and the peri-operative approach in IVDAS are the same as for non-addicts but should be more conservative overall since IVDAS have a much higher incidence of recurrent IE,^{352,353} usually due to continued drug abuse. Although the full implications of HIV infection for the medical and surgical therapy of IE in IVDAS are not yet fully known, a 2-week course of antimicrobial therapy is unsuitable. Cardiac surgery in HIV-infected IVDAS with IE does not worsen the prognosis of either the IE or the HIV.^{354,355}

Current strategies for surgery of tricuspid valve IE should be based on the following three principles: (1) debridement of the infected area or 'vegetectomy'; (2) valve repair whenever possible, avoiding artificial material;³⁵⁶ and (3) if valve replacement is

Table 25 Indications for surgical treatment of right-sided infective endocarditis

Recommendations: right-sided infective endocarditis	Class ^a	Level ^b
Surgical treatment should be considered in the following scenarios: <ul style="list-style-type: none"> • Microorganisms difficult to eradicate (e.g. persistent fungi) or bacteraemia for > 7 days (e.g. <i>S. aureus</i>, <i>P. aeruginosa</i>) despite adequate antimicrobial therapy or • Persistent tricuspid valve vegetations > 20 mm after recurrent pulmonary emboli with or without concomitant right heart failure or • Right HF secondary to severe tricuspid regurgitation with poor response to diuretic therapy 	IIa	C

^aClass of recommendation.^bLevel of evidence.

unavoidable, excision of the tricuspid valve with prosthetic valve replacement.³⁵⁷ Valvectomy without prosthetic replacement has been advocated, but may be associated with severe post-operative right HF, particularly in patients with elevated pulmonary arterial pressure, e.g. after multiple pulmonary emboli. It may be performed in extreme cases, but the valve should be subsequently replaced once cure of infection has been achieved.³⁵⁸ Cryopreserved mitral homografts have been used for management of persistent tricuspid endocarditis.^{359,360} Pulmonary valve replacement is best avoided—if judged necessary, use of a pulmonary homograft (or, if unavailable, a xenograft valve) is preferred.

In summary, right-sided IE is most frequently observed in IVDAs and CHD. Diagnostic features include respiratory symptoms and fever. TTE is of major value in these patients. Despite relatively low in-hospital mortality, right-sided IE has a high risk of recurrence in IVDAs and a conservative approach to surgery is recommended in this group.

Part 4. Infective endocarditis in congenital heart disease

The population of children and adults with CHD is expanding, and this is the major substrate for IE in younger patients. However, our knowledge of IE in this setting is limited since systematic studies are few and often retrospective, and selection bias associated with studies from highly specialized centres hampers universal application.

The reported incidence of IE in CHD is 15–140 times higher than that in the general population (the highest estimate originating from a highly specialized unit).^{361,362} The reported proportion of CHD in patients with IE varies, probably due to selection bias, between 2 and 18%,^{363–365} with a consistent minor male dominance.^{58,362,366}

Some simple lesions, such as secundum atrial septal defect and pulmonary valve disease, carry a low risk of IE. However, CHD often consists of multiple cardiac lesions, each contributing to the total risk of IE. For example, the incidence of IE is considerably higher in patients with a ventricular septal defect when there is associated aortic regurgitation.³⁶⁷

The distribution of causative organisms does not differ from the pattern found in acquired heart disease, streptococci and staphylococci being the most common strains.^{58,362,366}

The principal symptoms, complications, and basis for diagnosis do not differ from IE in general. However, right-sided IE is more frequent in CHD than in acquired cardiac disease. The superiority of TEE over TTE has not been systematically studied in this setting. However, complex anatomy and the presence of artificial material may reduce the rate of detection of vegetations and other features of IE, thus favouring the addition of TEE, particularly in the adult group.³⁶² However, a negative study does not exclude the diagnosis.

Treatment of IE in CHD follows general principles. Cardiac surgery is appropriate when medical therapy fails, when serious haemodynamic complications arise, and when there is a high risk of devastating septic embolism.

IE in CHD carries a mortality of 4–10%.^{58,62,362,366} This better prognosis in comparison with acquired heart disease may reflect the higher proportion of right heart IE.

Primary prevention is vital.³⁶⁸ The importance of good oral, dental, and skin hygiene has already been emphasized, and antibiotic prophylaxis is indicated in high-risk groups as defined in Section E. However, there is also an educational problem, and awareness of the risk of IE and need for preventive measures are not satisfactorily spread in the population with CHD.³⁶⁹ Cosmetic piercing, at least involving the tongue and mucous membranes, should be discouraged in this group.

Surgical repair of CHD often reduces the risk of IE, provided there is no residual lesion.^{364,370} However, in other cases when artificial valve substitutes are implanted, the procedure may increase the overall risk of IE. There are no scientific data justifying cardiac surgery or percutaneous interventions (e.g. closure of a patent ductus arteriosus) with the sole purpose of eliminating the risk of IE.³⁷¹ Cardiac repair as a secondary preventive measure to reduce the risk of recurrent IE has been described but not systematically studied.

In summary, IE in CHD is rare and more frequently affects the right heart. Complex anatomy makes echocardiographic assessment difficult. Prognosis is better than in other forms of IE, with a mortality rate <10%. Preventive measures and patient education are of particular importance in this population.

Part 5. Infective endocarditis in the elderly

IE in the elderly (>70 years) is increasingly frequent and associated with specific features.³⁷² The relative incidence of IE affecting the elderly was 26% in the Euro Heart Survey,³⁷³ and 33% of patients were older than 67 years in a French registry.⁸⁰ In the French surveys, the incidence of IE increased between 1991 and 1999 among patients >50 years old and peaked at 145 cases per million between 70 and 80 years of age.¹⁴

Previous reports have shown, though not consistently, that IE in advanced age is associated with poor prognosis and with a high complication rate.^{166,372,374,375} This more severe clinical course has been related to insidious initial symptoms and delayed diagnosis in elderly people, and to a higher incidence of more aggressive pathogens in this cohort.^{166,374,375}

A gastrointestinal source of infection has been described more commonly in elderly patients. Group D streptococci (*S. bovis*) are an increasingly frequent cause of IE, especially in the elderly,^{208,376} and have been associated with colonic disease, multiple valve involvement, and high embolic risk.²⁰⁸ Enterococcal IE has also been shown to be more frequent in older patients.³⁷⁷

Fever is less frequent³⁷⁴ and anaemia more common in elderly patients, probably related to the high proportion of *S. bovis* IE, in which colonic lesions are frequent and may cause occult bleeding.²⁰⁸ In some studies, the vegetations in the elderly have been

reported to be smaller³⁷⁵ and to carry a lower embolic risk.³⁷² Negative blood cultures were recently observed in 16.7% of elderly patients with IE.⁶⁹

Finally, older age has been associated with poor prognosis in the majority of recent studies.^{166,372,374,375} Fewer elderly patients are treated by surgery, probably in relation to a higher operative risk related to advanced age and frequent co-morbidity.³⁷⁸ However, surgical treatment appears as a reasonable option in the elderly, with the same indications as for younger patients.³⁷⁹

Part 6. Infective endocarditis during pregnancy

A challenge for the physician during pregnancy in the cardiac patient is the changing cardiovascular physiology which can mimic cardiac disease and confuse the clinical picture.^{380,381}

The incidence of IE during pregnancy has been reported to be 0.006%.³⁸² Therefore, IE in pregnancy is extremely rare, and is either a complication of a pre-existing cardiac lesion or the result of intravenous drug abuse. Maternal mortality approaches 33%, most deaths relating to HF or an embolic event, while foetal mortality is 29%.³⁸² Close attention should be paid to any pregnant woman with unexplained fever and a cardiac murmur. Rapid detection of IE and appropriate treatment is important in reducing the risk of both maternal and foetal mortality.³⁸²



The CME Text 'Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009)' is accredited by the European Board for Accreditation in Cardiology (EBAC). EBAC works according to the quality standards of the European Accreditation Council for Continuing Medical Education (EACCME), which is an institution of the European Union of Medical Specialists (UEMS). In compliance with EBAC/EACCME guidelines, all authors participating in this programme have disclosed potential conflicts of interest that might cause a bias in the article. The Organizing Committee is responsible for ensuring that all potential conflicts of interest relevant to the programme are declared to the participants prior to the CME activities.

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