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

Authors/Task Force Members: Gilbert Habib (Chairperson) (France)*, Bruno Hoen (France), Pilar Tornos (Spain), Franck Thuny (France), Bernard Prendergast (UK), Isidre Vilacosta (Spain), Philippe Moreillon (Switzerland), Manuel de Jesus Antunes (Portugal), Ulf Thilen (Sweden), John Lelakis (Greece), Maria Lengyel (Hungary), Ludwig Müller (Austria), Christoph K. Naber (Germany), Petros Nihoyannopoulos (UK), Anton Moritz (Germany), Jose Luis Zamorano (Spain)

ESC Committee for Practice Guidelines (CPG): Alec Vahanian (Chairperson) (France), Angelo Auricchio (Switzerland), Jeroen Bax (The Netherlands), Claudio Ceconi (Italy), Veronica Dean (France), Gerasimos Filippatos (Greece), Christian Funck-Brentano (France), Richard Hobbs (UK), Peter Kearney (Ireland), Theresa McDonagh (UK), Keith McGregor (France), Bogdan A. Popescu (Romania), Zeljko Reiner (Croatia), Udo Sechtem (Germany), Per Anton Sirnes (Norway), Michal Tendera (Poland), Panos Vardas (Greece), Petr Widimsky (Czech Republic)

Document Reviewers: Alec Vahanian (CPG Review Coordinator) (France), Rio Aguilar (Spain), Maria Grazia Bongiorni (Italy), Michael Borger (Germany), Eric Butchart (UK), Nicolas Danchin (France), Francois Delahaye (France), Raimund Erbel (Germany), Damian Franzen (Germany), Kate Gould (UK), Roger Hall (UK), Christian Hassager (Denmark), Keld Kjeldsen (Denmark), Richard McManus (UK), José M. Miró (Spain), Ales Mokracek (Czech Republic), Raphael Rosenhek (Austria), José A. San Román Calvar (Spain), Petar Seferovic (Serbia), Christine Selton-Suty (France), Miguel Sousa Uva (Portugal), Rita Trinchero (Italy), Guy van Camp (Belgium)

The disclosure forms of the authors and reviewers are available on the ESC website www.escardio.org/guidelines

* Corresponding author. Gilbert Habib, Service de Cardiologie, CHU La Timone, Bd Jean Moulin, 13005 Marseille, France. Tel: +33 4 91 38 63 79, Email: gilbert.habib@free.fr

The content of these European Society of Cardiology (ESC) Guidelines has been published for personal and educational use only. No commercial use is authorized. No part of the ESC Guidelines may be translated or reproduced in any form without written permission from the ESC. Permission can be obtained upon submission of a written request to Oxford University Press, the publisher of the European Heart Journal and the party authorized to handle such permissions on behalf of the ESC.

Disclaimer. The ESC Guidelines represent the views of the ESC and were arrived at after careful consideration of the available evidence at the time they were written. Health professionals are encouraged to take them fully into account when exercising their clinical judgement. The guidelines do not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patients, in consultation with that patient, and where appropriate and necessary the patient’s guardian or carer. It is also the health professional’s responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

© The European Society of Cardiology 2009. All rights reserved. For permissions please email: journals.permissions@oxfordjournals.org
Table of Contents

A. Preamble ............................................. 2371
B. Justification/scope of the problem ............. 2372
C. Epidemiology ....................................... 2372
   A changing epidemiology ......................... 2372
   Incidence of infective endocarditis ....... 2373
   Types of infective endocarditis ............... 2373
   Microbiology ...................................... 2373
D. Pathophysiology .................................. 2374
   The valve endothelium ............................. 2374
   Transient bacteraemia ............................ 2374
   Microbial pathogens and host defences .... 2374
E. Preventive measures ............................... 2375
   Evidence justifying the use of antibiotic prophylaxis for infective endocarditis in previous ESC recommendations 2375
   Reasons justifying revision of previous ESC Guidelines 2375
   Principles of the new ESC Guidelines ....... 2376
   Limitations and consequences of the new ESC Guidelines 2378
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
   Streptococcus pneumoniae, β-haemolytic streptococci (groups A, B, C, and G) .... 2384
   Nutritionally variant streptococci .......... 2384
   Staphylococcus aureus and coagulase-negative staphylococci .......... 2386
   Methicillin-resistant and vancomycin-resistant staphylococci ............ 2387
   Enterococcus 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
      Pre- and peri-operative management ....... 2394
      Surgical approach and techniques ........ 2394
      Operative mortality, morbidity, and post-operative complications .... 2394
J. Other complications of infective endocarditis
   Part 1. Neurological complications, antithrombotic therapy .......... 2395
   Part 2. Other complications (infectious aneurysms, acute renal failure, rheumatic complications, splenic abscess, myocarditis, pericarditis) ............................................. 2396
   K. Outcome after discharge and long-term prognosis ................. 2397
      Recurrences; relapses and reinfecions ............................................. 2397
      Heart failure and need for valvular surgery ....... 2398
      Long-term mortality ............................................. 2398
      Follow-up ............................................. 2398
   L. Specific situations
      Part 1. Prosthetic valve endocarditis ............................ 2398
      Part 2. Infective endocarditis on pacemakers and implantable defibrillators ......... 2400
      Part 3. Right-sided infective endocarditis .......................... 2401
      Part 4. Infective endocarditis in congenital heart disease .... 2403
      Part 5. Infective endocarditis in the elderly ....................... 2404
      Part 6. Infective endocarditis during pregnancy ................. 2404
   M. References ............................................. 2404

Abbreviations and acronyms

BCNIE blood culture-negative infective endocarditis
CD cardiac device
CDRIE cardiac device-related infective endocarditis
CHD congenital heart disease
CNS coagulase-negative staphylococci
CT computed tomography
ELISA enzyme-linked immunosorbent assay
HF heart failure
IA infectious aneurysm
ICD implantable cardioverter defibrillator
ICE International Collaboration on Endocarditis
IE infective endocarditis
IVDA intravenous drug abuser
LDI local device infection
MBC minimal bactericidal concentration
MIC minimal inhibitory concentration
MRI magnetic resonance imaging
MRSA methicillin-resistant Staphylococcus aureus
MSSA methicillin-susceptible Staphylococcus aureus
NBTE non-bacterial thrombotic endocarditis
NVE native valve endocarditis
OPAT outpatient parenteral antibiotic therapy
PBP plasma-binding protein
PCR polymerase chain reaction
PET positron emission tomography
PMP platelet microbicidal protein
PPM permanent pacemaker
PVE prosthetic valve endocarditis
TEE transoesophageal echocardiography
TTE transthoracic echocardiography
VISA vancomycin-intermediate Staphylococcus aureus
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 1  Classes of recommendations

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

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.

Several reasons justify the decision of the ESC to update the previous guidelines published in 2004. 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 intra-cardiac 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.

Unfortunately, their conclusions are not uniform, particularly in the field of prophylaxis, where conflicting recommendations have been formulated. 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. 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 disease or in patients with prosthetic valves.

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.

Newer predisposing factors have emerged—valve prostheses, degenerative valve sclerosis, intravenous drug abuse—associated with increased use of invasive procedures at risk for bacteremia, resulting in health care-associated IE. 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. 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. 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. In other African countries, the persistence of a high burden of rheumatic fever, rheumatic valvular heart diseases, and IE has also been highlighted.

In addition, significant geographical variations have been shown. The highest increase in the rate of staphylococcal IE has been reported in the USA, 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. intermedia*, and *S. constellatus*) must be distinguished since they

### Table 3: Classification and definitions of infective endocarditis

| IE according to localisation of infection and presence or absence of intracardiac material |
|９్ |
| • 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) |

<table>
<thead>
<tr>
<th>IE according to the mode of acquisition(^{27})</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Health care-associated IE</td>
</tr>
<tr>
<td>- Nosocomial:</td>
</tr>
<tr>
<td>IE developing in a patient hospitalized &gt;48 hours prior to the onset of signs / symptoms consistent with IE</td>
</tr>
<tr>
<td>- Non nosocomial:</td>
</tr>
<tr>
<td>Signs and/or symptoms of IE starting &lt;48 hours after admission in a patient with health care contact defined as:</td>
</tr>
<tr>
<td>1) home-based nursing or intravenous therapy, haemodialysis, or intravenous chemotherapy &lt;30 days before the onset of IE; or</td>
</tr>
<tr>
<td>2) hospitalized in an acute care facility &lt;90 days before the onset of IE; or</td>
</tr>
<tr>
<td>3) resident in a nursing home or long-term care facility</td>
</tr>
<tr>
<td>• Community-acquired IE</td>
</tr>
<tr>
<td>Signs and/or symptoms of IE starting &lt;48 hours after admission in a patient not fulfilling the criteria for health care-associated infection</td>
</tr>
<tr>
<td>• Intravenous drug abuse-associated IE</td>
</tr>
<tr>
<td>IE in an active injection drug user without alternative source of infection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Active IE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• IE with persistent fever and positive blood cultures or</td>
</tr>
<tr>
<td>• Active inflammatory morphology found at surgery or</td>
</tr>
<tr>
<td>• Patient still under antibiotic therapy or</td>
</tr>
<tr>
<td>• Histopathological evidence of active IE</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Relapse:</td>
</tr>
<tr>
<td>• Reinfecition:</td>
</tr>
</tbody>
</table>

Repeat episodes of IE caused by the same microorganism <6 months after the initial episode |

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 commensals 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. Conversely, CNS can also cause native valve IE, 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. 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, and to 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, 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. 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. 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.

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. 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.
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. 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. 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.

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%. 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. 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.

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. 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. 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; 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.

   (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.

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, 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 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.

   Finally, the concept of antibiotic prophylaxis efficacy itself has never been investigated in a prospective randomized controlled trial, 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. 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.
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 IE or even com-
plete cessation of antibiotic prophylaxis in any patient groups,12
the Task Force decided:

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

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 compli-
cations 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** | **Level** |
| Antibiotic prophylaxis should only be considered for patients at highest risk of IE | IIa | C |
| 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 | | |
| Antibiotic prophylaxis is no longer recommended in other forms of valvular or congenital heart disease | III | C |

*Class of recommendation.

*Level 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** | **Level** |
| A - Dental procedures: Antibiotic prophylaxis should only be considered for dental procedures requiring manipulation of the gingival or periradicular region of the teeth or perforation of the oral mucosa | IIa | C |
| Antibiotic prophylaxis is not recommended for local anesthetic injections in non-infected tissue, removal of sutures, dental X-rays, placement or adjustment of removable prosthetic or orthodontic appliances or braces | III | C |
| Prophylaxis is also not recommended following the shedding of deciduous teeth or trauma to the lips and oral mucosa | | |
| 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 transesophageal echocardiography | III | C |
| D - Skin and soft tissue*: Antibiotic prophylaxis is not recommended for any procedure | III | C |

*Class of recommendation.

*Level of evidence.

*For management when infections are present, please refer to text.
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 bacteremia 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, particularly when piercing involves the tongue, 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

<table>
<thead>
<tr>
<th>Situation</th>
<th>Antibiotic</th>
<th>Single dose 30–60 minutes before procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adults</td>
</tr>
<tr>
<td>No allergy to penicillin or ampicillin</td>
<td>Amoxicillin or ampicillin*</td>
<td>2 g p.o. or i.v.</td>
</tr>
<tr>
<td>Allergy to penicillin or ampicillin</td>
<td>Clindamycin</td>
<td>600 mg p.o. or i.v.</td>
</tr>
</tbody>
</table>

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

Alternatively cefalexin 2 g i.v. or 50 mg/kg i.v. for children, cefazolin or ceftriaxone 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. 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, though unnecessarily so since adherence to recognized guidelines affords robust legal protection.

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. 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>
<thead>
<tr>
<th>Table 7 Clinical presentation of infective endocarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>IE must be suspected in the following situations</td>
</tr>
<tr>
<td>1. New regurgitant heart murmur</td>
</tr>
<tr>
<td>2. Embolic events of unknown origin</td>
</tr>
<tr>
<td>3. Sepsis of unknown origin (especially if associated with IE causative organism)</td>
</tr>
<tr>
<td>4. Fever: the most frequent sign of IE. *</td>
</tr>
<tr>
<td>a. Intracardiac prosthetic material (e.g. prosthetic valve, pacemaker, implantable defibrillator, surgical baffle/conduit)</td>
</tr>
<tr>
<td>b. Previous history of IE</td>
</tr>
<tr>
<td>c. Previous valvular or congenital heart disease</td>
</tr>
<tr>
<td>d. Other predisposition for IE (e.g. immunocompromised state, IVDA)</td>
</tr>
<tr>
<td>e. Predisposition and recent intervention with associated bacteraemia</td>
</tr>
<tr>
<td>f. Evidence of congestive heart failure</td>
</tr>
<tr>
<td>g. New conduction disturbance</td>
</tr>
<tr>
<td>h. Positive blood cultures with typical IE causative organism or positive serology for chronic Q fever (microbiological findings may precede cardiac manifestations)</td>
</tr>
<tr>
<td>i. Vascular or immunologic phenomena: embolic event, Roth spots, splinter haemorrhages, Janeway lesions, Osler’s nodes</td>
</tr>
<tr>
<td>j. Focal or non-specific neurological symptoms and signs</td>
</tr>
<tr>
<td>k. Evidence of pulmonary embolism/infiltration (right-sided IE)</td>
</tr>
<tr>
<td>l. Peripheral abscesses (renal, splenic, cerebral, vertebral) of unknown cause</td>
</tr>
</tbody>
</table>

*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.
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. 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. However, these lack specificity and have not been integrated into current diagnostic criteria.

Atypical presentation is common in elderly or immunocompromised patients, 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.

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 yield (Figure 1). An exception is the patient with *S. aureus*
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 fibroelastoma).

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. 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. 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). 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](image-url)  
**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>
<thead>
<tr>
<th>Pathogen</th>
<th>Diagnostic procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brucella spp.</td>
<td>Blood cultures; serology; culture, immunohistology and PCR of surgical material</td>
</tr>
<tr>
<td>Coxiella burnetii</td>
<td>Serology (IgG phase 1 &gt; 1.800); tissue culture, immunohistology and PCR of surgical material</td>
</tr>
<tr>
<td>Bartonella spp.</td>
<td>Blood cultures; serology; culture, immunohistology and PCR of surgical material</td>
</tr>
<tr>
<td>Tropheryma whippelii</td>
<td>Histology and PCR of surgical material</td>
</tr>
<tr>
<td>Mycoplasma spp.</td>
<td>Serology; culture, immunohistology and PCR of surgical material</td>
</tr>
<tr>
<td>Legionella spp.</td>
<td>Blood cultures; serology; culture, immunohistology and PCR of surgical material</td>
</tr>
</tbody>
</table>

PCR = polymerase chain reaction.
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.

**4. Molecular biology techniques**

The polymerase chain reaction (PCR) allows rapid and reliable detection of fastidious and non-culturable agents in patients with IE. The technique has been validated using valve tissue from patients undergoing surgery for IE. 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. Improvements (including the availability of real-time PCR and a wider range of comparator gene sequences) and availability of other emerging technologies 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, 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, 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 1).

---

**Table 11 Modified Duke criteria for the diagnosis of infective endocarditis (adapted from Li et al.**

<table>
<thead>
<tr>
<th><strong>MAJOR CRITERIA</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood cultures positive for IE:</td>
</tr>
<tr>
<td>• Typical microorganisms consistent with IE from two separate blood cultures: <em>Coxiella burnetii</em>, <em>Bartonella</em> species, or Community-acquired enterococci, in the absence of a primary focus;</td>
</tr>
<tr>
<td>• Microorganisms consistent with IE from persistently positive blood cultures: All of three or a majority of ≥ 4 separate cultures of blood (with first and last sample drawn at least 1 h apart)</td>
</tr>
<tr>
<td>• Single positive blood culture for <em>Coxiella burnetii</em> or phase I IgG antibody titer &gt; 1 : 800</td>
</tr>
<tr>
<td>Evidence of endocardial involvement</td>
</tr>
<tr>
<td>• Echocardiography positive for IE</td>
</tr>
<tr>
<td>• Vegetation - Abscess - New partial dehiscence of prosthetic valve</td>
</tr>
<tr>
<td>• New valvular regurgitation</td>
</tr>
<tr>
<td><strong>MINOR CRITERIA</strong></td>
</tr>
<tr>
<td>• Predisposition: predisposing heart condition, injection drug use</td>
</tr>
<tr>
<td>• Fever: temperature &gt; 38°C</td>
</tr>
<tr>
<td>• Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysms, intracranial hemorrhages, conjunctival hemorrhages, Janeway lesions</td>
</tr>
<tr>
<td>• Immunologic phenomena: glomerulonephritis, Osler’s nodes, Roth’s spots, rheumatoid factor</td>
</tr>
<tr>
<td>• Microbiological evidence: positive blood culture but does not meet a major criterion or serological evidence of active infection with organism consistent with IE</td>
</tr>
</tbody>
</table>

**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

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 heart (particularly in IVDS).

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%, 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 intermediate outcome who will benefit from closer follow-up and a more aggressive treatment strategy (eg, 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. 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. When three of these factors are present, the risk reaches 79%. 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.

Nowadays, ~50% of patients undergo surgery during hospitalization. In those patients who need urgent surgery, persistent infection and renal failure are predictors of mortality. Predictably, patients with an indication for surgery who cannot proceed due to prohibitive surgical risk have the worst prognosis.

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.
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, 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 1.3,7,10–12 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.13,14 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 (>98%) and penetrates slowly into vegetations.116 However, only limited retrospective studies have assessed its efficacy in streptococcal IE and enterococcal 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.7,10,11 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\textsuperscript{a}

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

\textsuperscript{a}See text for other streptococcal species.
\textsuperscript{b}Preferred in patients \textgreater;65 years or with impaired renal function.
\textsuperscript{c}6-week therapy in PVE.
\textsuperscript{d}Or ampicillin, same dosages as amoxicillin.
\textsuperscript{e}Preferred for outpatient therapy.
\textsuperscript{f}Paediatric doses should not exceed adult doses.
\textsuperscript{g}Only if non complicated native valve IE.
\textsuperscript{h}Renal function and serum gentamicin concentrations should be monitored once a week. When given in a single daily dose, pre-dose (trough) concentrations should be \textless;1 mg/L and post-dose (peak; 1 h after injection) serum concentrations should be \textless;10–12 mg/L.\textsuperscript{112}
\textsuperscript{i}Serum 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.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage and route</th>
<th>Duration (weeks)</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Native valves</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methicillin-susceptible staphylococci:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Flu)cloxacillin or Oxacillin with Gentamicin</td>
<td>12 g/day i.v. in 4–6 doses</td>
<td></td>
<td>4–6</td>
</tr>
<tr>
<td></td>
<td>3 mg/kg/day i.v. or i.m. in 2 or 3 doses</td>
<td></td>
<td>3–5 days</td>
</tr>
<tr>
<td>Penicillin-allergic patients or methicillin-resistant staphylococci:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin with Gentamicin</td>
<td>30 mg/kg/day i.v. in 2 doses</td>
<td></td>
<td>4–6</td>
</tr>
<tr>
<td></td>
<td>3 mg/kg/day i.v. or i.m. in 2 or 3 doses</td>
<td></td>
<td>3–5 days</td>
</tr>
<tr>
<td>Prosthetic valves</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methicillin-susceptible staphylococci:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Flu)cloxacillin, or Oxacillin with Rifampin and Gentamicin</td>
<td>12 g/day i.v. in 4–6 doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1200 mg/day i.v. or orally in 2 doses</td>
<td></td>
<td>4–6</td>
</tr>
<tr>
<td></td>
<td>3 mg/kg/day i.v. or i.m. in 2 or 3 doses</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Penicillin-allergic patients and methicillin-resistant staphylococci:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin with Rifampin and Gentamicin</td>
<td>30 mg/kg/day i.v. in 2 doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1200 mg/day i.v. or orally in 2 doses</td>
<td></td>
<td>4–6</td>
</tr>
<tr>
<td></td>
<td>3 mg/kg/day i.v. or i.m. in 2 or 3 doses</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

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

*bPediatric 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.136,137 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.*

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
aminoglycoside in *S. aureus* IE is not formally demonstrated. 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%) 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 prostheses (in combination with quinolones) and in the prevention of re-infection of vascular prostheses. 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.

**Methicillin-resistant and vancomycin-resistant staphylococci**

MRSA produce low-affinity plasma-binding protein (PBPs) 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. 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. Observational studies suggest that daptomycin might also be considered in left-sided IE and may overcome methicillin and vancomycin resistance. However, definitive studies are missing. Importantly, daptomycin needs to be administered in appropriate doses to avoid further resistance. Other choices include newer β-lactams with relatively good PBPs affinity, quinupristin – dalfopristin, linezolid, daptomycin, and tigecycline. Again, these situations require the expertise of 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 PBP2A modification and sometimes β-lactamases), and vancomycin.

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. 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*. 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, 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–dalfopristin, 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.

**2. Non-HACEK species**

The International Collaboration on Endocarditis (ICE) reported non-HACEK Gram-negative bacteria in 49/2761 (1.8%) of IE cases. 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. Treatment options are summarized in Table 16.
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. 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. 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. 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 15 Antibiotic treatment of infective endocarditis due to Enterococcus spp.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage and route</th>
<th>Duration (weeks)</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-lactam and gentamicin susceptible strain (for resistant isolates see</strong></td>
<td><strong>Beta-lactam and gentamicin susceptible strain (for resistant isolates see</strong></td>
<td><strong>Beta-lactam and gentamicin susceptible strain (for resistant isolates see</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Amoxicillin with Gentamicin</strong></td>
<td>200 mg/kg/day i.v. in 4–6 doses</td>
<td>4–6</td>
<td><strong>I B</strong></td>
</tr>
<tr>
<td><strong>Ampicillin with Gentamicin</strong></td>
<td>200 mg/kg/day i.v. in 4–6 doses</td>
<td>4–6</td>
<td><strong>I B</strong></td>
</tr>
<tr>
<td><strong>Vancomycin with Gentamicin</strong></td>
<td>30 mg/kg/day i.v. in 2 doses</td>
<td>6</td>
<td><strong>I C</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage and route</th>
<th>Duration (weeks)</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-lactam and gentamicin susceptible strain (for resistant isolates see</strong></td>
<td><strong>Beta-lactam and gentamicin susceptible strain (for resistant isolates see</strong></td>
<td><strong>Beta-lactam and gentamicin susceptible strain (for resistant isolates see</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Amoxicillin with Gentamicin</strong></td>
<td>200 mg/kg/day i.v. in 4–6 doses</td>
<td>4–6</td>
<td><strong>I B</strong></td>
</tr>
<tr>
<td><strong>Ampicillin with Gentamicin</strong></td>
<td>200 mg/kg/day i.v. in 4–6 doses</td>
<td>4–6</td>
<td><strong>I B</strong></td>
</tr>
<tr>
<td><strong>Vancomycin with Gentamicin</strong></td>
<td>30 mg/kg/day i.v. in 2 doses</td>
<td>6</td>
<td><strong>I C</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage and route</th>
<th>Duration (weeks)</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-lactam and gentamicin susceptible strain (for resistant isolates see</strong></td>
<td><strong>Beta-lactam and gentamicin susceptible strain (for resistant isolates see</strong></td>
<td><strong>Beta-lactam and gentamicin susceptible strain (for resistant isolates see</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Amoxicillin with Gentamicin</strong></td>
<td>200 mg/kg/day i.v. in 4–6 doses</td>
<td>4–6</td>
<td><strong>I B</strong></td>
</tr>
<tr>
<td><strong>Ampicillin with Gentamicin</strong></td>
<td>200 mg/kg/day i.v. in 4–6 doses</td>
<td>4–6</td>
<td><strong>I B</strong></td>
</tr>
<tr>
<td><strong>Vancomycin with Gentamicin</strong></td>
<td>30 mg/kg/day i.v. in 2 doses</td>
<td>6</td>
<td><strong>I C</strong></td>
</tr>
</tbody>
</table>

**Notes:**
- High level resistance to gentamicin (MIC > 500 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
- (Ia, 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.
- Multiresistance to aminoglycosides, β-lactams, and vancomycin: suggested alternatives are (i) linezolid 2 × 600 mg/day i.v. or orally for ≥ 8 weeks (IIa, C) (monitor haematological toxicity); (ii) quinupristin–dalfopristin 3 × 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).
- 6-week therapy recommended for patients with >3 months symptoms and in PVE.
- *Paediatric doses should not exceed adult doses.
- In β-lactam allergic patients. Monitor serum vancomycin concentrations as indicated in Table 13.
Outpatient parenteral antibiotic therapy for infective endocarditis

Outpatient parenteral antibiotic therapy (OPAT) is used in >250 000 patients/year in the USA. 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. 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.

---

**Table 16 Antibiotic treatment of blood culture-negative infective endocarditis**

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

Adapted from Brouqui and Raoult. Due 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. Addition of streptomycin (15 mg/kg/24 h in two doses) for the first few weeks is optional. Doxycycline plus hydroxychloroquine (with monitoring of serum hydroxychloroquine levels) is superior to doxycycline alone and to doxycycline + fluoroquinolone. Several 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). Newer fluoroquinolones are more potent than ciprofloxacin against intracellular pathogens such as *Mycoplasma spp.*, *Legionella spp.*, and *Chlamydia spp.* Treatment 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.

---

ESC Guidelines 2019
**Table 17** Proposed antibiotic regimens for initial empirical treatment of infective endocarditis. (before or without pathogen identification)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage and route</th>
<th>Duration (weeks)</th>
<th>Level of evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Native valves</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin-Sulbactam, or</td>
<td>12 g/day i.v. in 4 doses</td>
<td>4–6</td>
<td>IIb C</td>
<td>Patients with blood-culture negative IE should be treated in consultation with an infectious disease specialist.</td>
</tr>
<tr>
<td>+ Amoxicillin-Clavulinate, with</td>
<td>12 g/day i.v. in 4 doses</td>
<td>4–6</td>
<td>IIb C</td>
<td></td>
</tr>
<tr>
<td>Gentamicin¹</td>
<td>3 mg/kg/day i.v. or i.m. in 2 or 3 doses.</td>
<td>4–6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin¹ with Gentamicin¹</td>
<td>30 mg/kg/day i.v. in 2 doses</td>
<td>4–6</td>
<td>IIb C</td>
<td>For patients unable to tolerate β-lactams.</td>
</tr>
<tr>
<td>+ Gentamicin¹ with Ciprofloxacin</td>
<td>1000 mg/day orally in 2 doses or 800 mg/day i.v. in 2 doses</td>
<td>4–6</td>
<td></td>
<td>Ciprofloxacin is not uniformly active on Bartonella spp. Addition of doxycycline (see Table 16) is an option if Bartonella spp. is likely.</td>
</tr>
<tr>
<td><strong>Prosthetic valves (early, &lt; 12 months post surgery)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin¹ with</td>
<td>30 mg/kg/day i.v. in 2 doses</td>
<td>6</td>
<td>IIb C</td>
<td>If no clinical response, surgery and maybe extension of the antibiotic spectrum to gram-negative pathogens must be considered.</td>
</tr>
<tr>
<td>Gentamicin¹ with Rifampin</td>
<td>3 mg/kg/day i.v. or i.m. in 2 or 3 doses.</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1200 mg/day orally in 2 doses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prosthetic valves (late, &gt; 12 months post surgery)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same as for native valves</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ 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

<table>
<thead>
<tr>
<th>Phase of treatment</th>
<th>Guidelines for use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Critical phase (weeks 0–2)</strong></td>
<td>Complications occur during this phase. Preferred inpatient treatment during this phase. Consider OPAT if oral streptococcal, patient stable, no complications.</td>
</tr>
<tr>
<td><strong>Continuation phase (beyond week 2)</strong></td>
<td>Consider OPAT if medically stable. Do not consider OPAT if heart failure, concerning echocardiographic features, neurological signs, or renal impairment.</td>
</tr>
<tr>
<td>Essential for OPAT</td>
<td>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.</td>
</tr>
</tbody>
</table>

Adapted from Andrews and von Reyn.¹³⁹
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. 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. 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.

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.

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.

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. 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. 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** | **Level** |
| **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 |

*Class of recommendation.

*Level 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.
The most characteristic lesion leading to HF in NVE is valve destruction causing acute regurgitation, 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 infection 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. 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.

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

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 IE and is the principal indication for urgent surgery. 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.

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 surgery 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. 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).

Perivalvular abscess is more common in aortic IE (10–40% in native valve IE) and very frequent in PVE (56–100%). In mitral IE, perivalvular abscesses are usually located posteriorly or laterally. In aortic IE, perivalvular extension occurs most frequently in the mitral–aortic intervalvular fibrosa. 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. In one study, the most important risk factors for perivalvular complications were prosthetic valve, aortic location, and infection with CNS.

Pseudoaneurysms and fistulae are severe complications of IE and frequently associated with very severe valvular and perivalvular damage. The frequency of fistula formation in IE has been reported to be 1.6%, S. aureus being the most commonly associated organism (46%). Despite high rates of surgery in this population (87%), hospital mortality remains high (41%). 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.

Perivalvular extension should be suspected in cases with persistently 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%. (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.
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 (spleenic, vertebral, cerebral, or renal) and other causes of fever have been excluded.

Signs of locally uncontrolled infection

These include increasing vegetable size, abscess formation, false aneurysms or the creation of fistulae. 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. 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 favorable early response to antibiotics is not achieved.

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

Embolic events are a frequent and life-threatening complication of IE related to the migration of 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. Conversely, embolic 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. 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 embolic risk is very high in IE, with embolic events occurring in 20–50% of patients. However, the risk of new events (occurring after initiation of antibiotic therapy) is only 6–2% in patients receiving appropriate antimicrobial therapy. A recent study from the ICE group 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, although prediction remains difficult in the individual patient. Several factors are associated with increased risk of embolism, including the size and mobility of vegetations, the location of the vegetation on the mitral valve, the increasing or decreasing size of the vegetation under antibiotic therapy, particular microorganisms (staphylococci), previous embolism, multivalvular IE, and biological markers. Among these, the size and mobility of the vegetations are the most potent independent predictors of a new embolic event. Patients with vegetations length >10 mm are at higher risk of embolism, and this risk is even higher in patients with very large (>15 mm) and mobile vegetations, especially in staphylococcal IE affecting the mitral valve.

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, 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. The best means to reduce the risk of an embolic event is the prompt institution of appropriate antibiotic therapy. Whilst promising, the addition of antiplatelet therapy did not reduce the risk of embolism in the only published randomized study.

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, 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. 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. 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.

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 Disease 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.224,225,227,228 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.35,237 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. Neurological complications are 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. They are associated with an excess mortality, particularly in the case of stroke. 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. The risk of post-operative neurological deterioration is low after a silent cerebral embolism or transient ischaemic attack, 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. 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. Conversely, in cases with intracranial haemorrhage, neurological prognosis is worse and surgery must be postponed for at least 1 month. If urgent cardiac surgery is needed, close cooperation with the neurosurgical team is mandatory. Table 20 and Figure 3

Table 20 Management of neurological complications

<table>
<thead>
<tr>
<th>Recommendations: neurological complications</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>After a silent cerebral embolism or transient ischaemic attack, surgery is recommended without delay if an indication remains</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Following intracranial haemorrhage, surgery must be postponed for at least one month</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Neurosurgery or endovascular therapy are indicated for very large, enlarging, or ruptured intracranial aneurysm</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>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</td>
<td>IIA</td>
<td>B</td>
</tr>
<tr>
<td>Intracranial aneurysm should be looked for in any patient with IE and neurological symptoms - CT or MR angiography should be considered for diagnosis</td>
<td>IIA</td>
<td>B</td>
</tr>
<tr>
<td>Conventional angiography should be considered when non-invasive techniques are negative and the suspicion of intracranial aneurysm remains</td>
<td>IIA</td>
<td>B</td>
</tr>
</tbody>
</table>

*Class of recommendation.

*Level of evidence.

CT = computed tomography; MR = magnetic resonance.
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

### Table 21  Management of antithrombotic therapy in infective endocarditis

<table>
<thead>
<tr>
<th>Recommendations: antithrombotic therapy</th>
<th>Classa</th>
<th>Levelb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interruption of antiplatelet therapy is only recommended in the presence of major bleeding</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In ischaemic stroke without cerebral haemorrhage, replacement of oral anticoagulant therapy by unfractioned heparin for 2 weeks is indicated with a close monitoring of activated partial thromboplastin or the activated cephalin clotting time</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>In intracranial haemorrhage, interruption of all anticoagulation is recommended</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>In patients with intracranial haemorrhage and a mechanical valve, unfractioned heparin should be reinitiated as soon as possible (with close monitoring of activated partial thromboplastin or activated cephalin clotting time) following multidisciplinary discussion</td>
<td>IIA</td>
<td>C</td>
</tr>
<tr>
<td>In the absence of stroke, replacement of oral anticoagulant therapy by unfractioned heparin during 2 weeks may be considered in case of <em>S. aureus</em> IE with a close monitoring of activated partial thromboplastin or the activated cephalin clotting time</td>
<td>IIB</td>
<td>C</td>
</tr>
</tbody>
</table>

*aClass of recommendation.  
bLevel of evidence.*

An intracranial location is most frequent, and the reported frequency of 2–4% is probably an underestimate since some IAs are clinically silent.257 Clinical presentation is highly variable (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. 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. 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.

**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. Myocardial involvement is best assessed using TTE. Pericarditis may be associated with an abscess, myocarditis, or bacteraemia often as a result of S. aureus infection. Purulent periocarditis is rare and may necessitate surgical drainage. 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.

**Recurrences: relapses and reinfections**

The risk of recurrence amongst survivors of IE varies between 2.7 and 22.5%. In a recent large series with mean 5-year follow-up, the rate of recurrence in non-IVDAs was 1.3% per patient-year. 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. In contrast, ‘reinfection’ is primarily used to describe infection with a different microorganism. 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. 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. For these purposes, storage of endocarditis isolates for at least 1 year is recommended.

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, and prophylactic measures should be very strict. Reinfection is more

<table>
<thead>
<tr>
<th>Table 22</th>
<th>Factors associated with an increased rate of relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Inadequate antibiotic treatment (agent, dose, duration)</td>
<td></td>
</tr>
<tr>
<td>- Polymicrobial infection in an IVDA</td>
<td></td>
</tr>
<tr>
<td>- Empirical antimicrobial therapy for culture negative IE</td>
<td></td>
</tr>
<tr>
<td>- Periannular extension</td>
<td></td>
</tr>
<tr>
<td>- Prosthetic valve endocarditis</td>
<td></td>
</tr>
<tr>
<td>- Persistent metastatic foci of infection (abscesses)</td>
<td></td>
</tr>
<tr>
<td>- Resistance to conventional antibiotic regimens</td>
<td></td>
</tr>
<tr>
<td>- Positive valve culture</td>
<td></td>
</tr>
<tr>
<td>- Persistence of fever at the seventh postoperative day</td>
<td></td>
</tr>
</tbody>
</table>
frequent in IVDAs (especially in the year after the initial episode), in PVE, and in those with multiple risk factors for IE. Patients with reinfection are at higher risk of death and need for valve replacement. The type of valve implanted has no effect on the risk of recurrent IE. Aortic valve and root replacement with a prosthetic conduit yields results comparable with those of homograft root replacement.

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. 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.

Long-term mortality
Long-term survival is 60–90% at 10 years. Information concerning longer follow-up is scarce. A survival at 15–20 years of ~50% has been reported. 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. In a recent series, IE was the cause of the late mortality in only 6.5% of patients who died.

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 at 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 prostheses—an incidence of 0.3–1.2% per patient-year. It accounts for 10–30% of all cases of IE and affects mechanical and bioprosthetic valves equally. PVE was observed in 16% of cases in the French Survey, in 26% of cases in the Euro Heart Survey, and in 20% of 2670 patients with definite IE in the ICE Prospective Cohort Study. 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. However, this is an artificial distinction. What is important is 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.

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. 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. Although TEE is mandatory in suspected PVE (Figure 1), its diagnostic value is lower than in NVE. A negative echocardiogram is frequently observed in PVE 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%, but are less useful in PVE, because of their lower sensitivity in this setting.

**Prognosis and treatment**

A very high in-hospital mortality rate of 20–40% has been reported in PVE. 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, 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 conduit can be used.

Although surgical treatment is frequently necessary in PVE, the best therapeutic option is still debated. 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, similar to patients with NVE. Similar data have been reported by others. 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 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. Conversely, patients with uncomplicated non-staphylococcal and non-fungal late PVE can be managed conservatively. 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)

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

*a*Class of recommendation.

*b*Level of evidence.

*aEmergency 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. 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. 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. Overall incidence lies between that of NVE in the general population and that of PVE. 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. 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, 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. 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.

The main mechanism of CDRIE is contamination by local bacterial flora at the time of device implantation. Then, the infection can spread along the electrode to the endocardium and the electrode tip. The consequence may be formation of vegetations, which can be found anywhere from the subclavian vein to the superior vena cava, 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.

Diagnosis

CDRIE is one of the most difficult forms of IE to diagnose. Clinical presentation is frequently misleading, with predominant respiratory or rheumatological symptoms, 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 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. Blood cultures are positive in 77% of cases of CDRIE. Staphylococci are the most frequent pathogens, S. aureus being predominant in the acute forms of PPM infection.

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

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. 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. However, in the case of definite CDRIE, medical therapy alone has been associated with high mortality and risk of recurrence. For this reason, CD removal is recommended in all cases of proven CDRIE and should also be considered when CRDIE is only suspected, in the case of occult infection without any other apparent source than the device.

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. However, these episodes are frequently asymptomatic, and percutaneous extraction remains the recommended method even in cases of large vegetations, since overall risks are even higher with surgical extraction.

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

In patients with NVE or PVE and an apparently non-infected PPM, device extraction may be considered.

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

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-morbidities.

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. Although it may occur in patients with a PPM, ICD, central venous catheter, or CHD, this situation is most frequently observed in IVDAs. The exact incidence of IE in IVDAs is unknown, but some recent data show an increasing number of hospitalizations for intravenous drug abuse-related IE. This disease occurs more frequently in IVDAs who are HIV seropositive, particularly those with advanced immunosuppression. 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 IVDAs. Whilst the tricuspid valve is the usual site of infection in IVDAs, pulmonary and eustachian valve infection may also be observed, and left-sided IE is not
unusual in this group. Staphylococcus aureus is the dominant organism (60–90%), 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. 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. However, TEE is more sensitive in the detection of pulmonary vegetations 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%. 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. In HIV-infected patients, a CD4 count of <200 cells/μL has a high prognostic value.

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. 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. If the patient is a pentazocine addict, an antipseudomonas agent should be added. If an IVDA uses brown heroin dissolved in lemon juice, Candida spp. (not C. albicans) should be considered and antifungal treatment added. More conventionally, in IVDAs with underlying valve lesions and/or left-sided involvement, antibiotic treatment should include cover against streptococci and enterococci. 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 penicillins or vancomycin are superior to glycopeptide-containing regimens.

   There are also consistent data showing that a 2-week treatment may be sufficient and that the addition of an aminoglycoside may be unnecessary. 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

   ✓ 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/μm³) 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;
   (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;
   (c) therapy with antibiotics other than penicillinase-resistant penicillins;
   (d) IVDA with severe immunosuppression (CD4 count <200 cells/μL) with or without AIDS;
   (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. For organisms other than MSSA, therapy in IVDAs does not differ from that in non-addicts.

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;
   (c) Tricuspid valve vegetations >20 mm which persist after recurrent pulmonary emboli with or without concomitant right HF.

   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, 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.

   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; and (3) if valve replacement is
unavoidable, excision of the tricuspid valve with prosthetic valve replacement. 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. Cryopreserved mitral homografts have been used for management of persistent tricuspid endocarditis. 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). The reported proportion of CHD in patients with IE varies, probably due to selection bias, between 2 and 18%, with a consistent minor male dominance.

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.

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

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. However, a negative study does not exclude the diagnosis.

Primary prevention is vital. 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 is not satisfactorily spread in the population with CHD. 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. 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. 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. The relative incidence of IE affecting the elderly was 26% in the Euro Heart Surveys and 33% of patients were older than 67 years in a French registry. 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. Previous reports have shown, though not consistently, that IE in advanced age is associated with poor prognosis and with a high complication rate. 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.

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, and have been associated with colonic disease, multiple valve involvement, and high embolic risk. Enterococcal IE has also been shown to be more frequent in older patients. Fever is less frequent 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. In some studies, the vegetations in the elderly have been reported to be smaller and to carry a lower embolic risk. Negative blood cultures were recently observed in 16.7% of elderly patients with IE.

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

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. The incidence of IE during pregnancy has been reported to be 0.006%. 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 3%, most deaths relating to HF or an embolic event, while foetal mortality is 29%. 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.
13. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD,  
16. Tleyjeh IM, Abdel-Latif A, Rahbi H, Scott CG, Bailey KR, Steckelberg JM,  
20. Nkomo VT. Epidemiology and prevention of valvular heart diseases and infective  
heart disease: a report of the American College of Cardiology/American Heart  
Association Task Force on Practice Guidelines (Writing Committee to revise the  
1998 guidelines for the management of patients with valvular heart disease).  
Endorsed by the Society for Cardiovascular Angiography and Interventions, and  
21. Fowler VG Jr, Miro JM, Hoen B, Cabell CH, Abrutyn E, Corey GR,  
22. Fowler VG Jr, Miro JM, Hoen B, Cabell CH, Abrutyn E, Corey GR,  
23. Ribera E, Miro JM, Cortes E, Cruceta A, Merce J, Marco F, Planes A, Pare JC,  
24. Wu F, Green C, Bell L, Veugelers P, Newell J, Duan H, Hsu Y, Bode C,  
25. Okell CC, Elliott SD. Bacteraemia and oral sepsis: with special reference to the  
26. van der Meer JT, Thompson J, Valkenburg HA, Michel MF. Changing profile of  
endocarditis: results of a 10-year multicentric retrospective study. Int J Infect  
Current profile of left-sided native valve endocarditis caused by coagulase- 
32. Richardson DC, Buurrows LL, Rabinovich S, Buitia D, David TE, Conty JM.  
Tropheryma whipelli as a cause of verruciform xanthoma: an emerging  
disease: a report of the American College of Cardiology/American Heart  
Association Task Force on Practice Guidelines (Writing Committee to revise the  
1998 guidelines for the management of patients with valvular heart disease).  
Endorsed by the Society for Cardiovascular Angiography and Interventions, and  
Age-related prevalence of cardiac valvular abnormalities warranting infectious  
34. Fowler YA, Hafliger JA, Pironi L, Franciosi P, Widmer E, Entenza JM, Sinha B,  
Herrmann M, Francioli P, Vaudaux P, Moreillon P. Fibronectin binding  
Jr. Native valve endocarditis due to coagulase-negative staphylococci: report  
of 99 episodes from the International Collaboration on Endocarditis Merged  
Current profile of left-sided native valve endocarditis caused by coagulase- 


222. Pavie A. Heart transplantation for end-stage valvular disease: indications and heart transplantation for end-stage valvular disease: indications and...


