



ESC Guidelines

# Guidelines on Prevention, Diagnosis and Treatment of Infective Endocarditis

## Full Text

### The Task Force on Infective Endocarditis of the European Society of Cardiology

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## Preamble

Guidelines and Expert Consensus documents aim to present all the relevant evidence on a particular issue in order to help physicians to weigh the benefits and risks of a particular diagnostic or therapeutic procedure. They should be helpful in everyday clinical decision-making.

A great number of Guidelines and Expert Consensus Documents have been issued in recent years by different organisations, the European Society of Cardiology (ESC) and by other related societies. By means of links to web sites of National Societies several hundred guidelines are available. This profusion can put at stake the authority and validity of guidelines, which can only be guaranteed if they have been developed by an unquestionable decision-making process. This is one of the reasons why the ESC and others have issued recommendations for formulating and issuing Guidelines and Expert Consensus Documents.

In spite of the fact that standards for issuing good quality Guidelines and Expert Consensus Documents are well defined, recent surveys of Guidelines and Expert Consensus Documents published in peer-reviewed journals between 1985 and 1998 have shown that methodological standards were not complied within the vast majority of cases. It is, therefore, of great importance that guidelines and recommendations are presented in formats that are easily interpreted. Subsequently, their

implementation programmes must also be well conducted. Attempts have been made to determine whether guidelines improve the quality of clinical practice and the utilisation of health resources.

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 of these Guidelines and Expert Consensus Documents or statements.

## Introduction

The European Society of Cardiology Task Force on Infective Endocarditis was formed to prepare recommendations regarding adequate diagnosis, treatment and prevention of Infective Endocarditis (IE). The advice of additional experts (see Appendix A) was obtained whenever the core group felt that additional specific knowledge was mandatory. The document was read by all members of the Task Force twice, redrafted and approved by the Board of the European Society of Cardiology in 2003.

To end up with a readable paper, including a maximum of information and covering the majority of issues frequently associated with IE, the text has been condensed to essential information accompanied by key references to allow for the information. The text is thus not a substitute for textbooks.

The term 'bacterial endocarditis' has been replaced by 'infective endocarditis' (IE) since fungi are also involved as causative pathogens.

If untreated, IE is a fatal disease. Major diagnostic (first of all echocardiography) and therapeutic progress (mainly surgery during active IE) have contributed to some prognostic improvement during the last decades. If the diagnosis is delayed or appropriate therapeutic measures postponed, mortality is still high. Differences in morbidity and mortality recently reported point to the importance of an early and proper diagnosis and adequate treatment. In this respect, it is of utmost importance that

- IE, although relatively uncommon, is considered early in every patient with fever or septicaemia and cardiac murmurs;
- echocardiography is applied without delay in suspected IE;
- in suspected and definite IE, cardiologists, microbiologists and cardiac surgeons cooperate closely.

### Level of evidence

The Task Force has attempted to classify the usefulness or efficacy of the recommended diagnostic and therapeutic approach and the level of evidence on which these recommendations are based (see 'Recommendations for Task Force Creation and Report Production' [www.escardio.org](http://www.escardio.org))

| Strength of recommendation | Definition   |
|----------------------------|--|
| Class I                    | Evidence and/or general agreement that a given treatment or a diagnostic approach is beneficial, useful and effective        |
| Class II                   | Conflicting evidence and/or a divergence of opinions about the usefulness/efficacy of a treatment or a diagnostic measure    |
| IIa                        | Weight of evidence/opinion is in favour of usefulness/efficacy   |
| IIb                        | Usefulness/efficacy is less well established by evidence/opinion   |
| Class III                  | Evidence or general agreement that the treatment/diagnostic measure is not useful/effective and in some cases may be harmful |

The strength of evidence will be ranked according to three levels:

| Level of evidence | Available evidence   |
|-------------------|--|
| A                 | At least two randomized trials supporting the recommendation   |
| B                 | Single randomized trial and/or a meta-analysis of non-randomized studies supporting the recommendation |
| C                 | Consensus opinion of experts based on trials and clinical experience                                   |

## Definitions, terminology and incidence

### Definition

Infective endocarditis (IE) is an endovascular microbial infection of cardiovascular structures (e.g., native valves, ventricular or atrial endocardium) including endarteritis of the large intrathoracic vessels (e.g., in a patent ductus arteriosus, arterio-venous shunts, coarctation of the aorta) or of intracardiac foreign bodies (e.g., prosthetic valves, pacemaker or ICD leads, surgically created conduits) facing the bloodstream. Although clinical relevance and therapeutic considerations may be very similar, infections of lines placed inside the heart but not connected to endocardial structures should be classified as 'polymer-associated infections' rather than IE.

The early characteristic lesion of IE is a variably sized vegetation containing platelets, erythrocytes, fibrin, inflammatory cells, and microorganisms. However, destruction, ulceration, or abscess formation may be alterations first seen with echocardiography.

## Classification and terminology

In contrast to older classifications distinguishing between acute, subacute and chronic IE, the present classification refers to (a), activity of the disease and recurrence; (b), diagnostic status; (c), pathogenesis; (d), anatomical site; and (e), microbiology.

a With respect to activity, differentiation between active and healed IE is especially important for patients undergoing surgery. Active IE is present if positive blood cultures and fever are present at the time of surgery, or positive cultures are obtained at surgery, or active inflammatory morphology is found intraoperatively, or surgery has been performed before completion of a full course of antibiotic therapy.<sup>1</sup> More recently, it has been recommended to call IE active if the diagnosis has been established two months or less before surgery.<sup>2</sup>

IE is recurrent if it develops after eradication of a previous IE, while in persistent IE, the infection has never been truly eradicated. It can be difficult or even impossible to differentiate between the two unless another episode of IE is caused by a different organism. Endocarditis developing more than one year after operation is usually considered recurrent.<sup>2</sup> Recurrent IE is a dreaded complication with high mortality.<sup>3</sup>

b The diagnosis of IE is established (definite IE) if during septicaemia or systemic infection involvement of the endocardium can be demonstrated, preferably by multiplane transoesophageal echocardiography (TEE). If IE is strongly suspected clinically (see Section 4.4) but involvement of the endocardium has not been proven so far, endocarditis should be classified as 'suspected' to express a more or less high suspicion of IE. If IE is only a potential differential diagnosis in febrile patients, a situation which is of special importance when applying the Duke criteria, one should describe this as 'possible' IE.

c Native (NVE), prosthetic valve endocarditis (PVE) and IE in intravenous drug abuse (IE in IVDA) differ with respect to pathology. PVE should be classified as an infection more likely to have been acquired perioperatively and thus being nosocomial (early PVE), or more likely to have been community-acquired (late PVE).<sup>4,5</sup> Because of significant differences in the microbiology of PVE observed within one year of operation and later, the cut-off between early and late PVE should be at one year.<sup>4-9</sup>

d Due to the differences in clinical manifestation and prognosis, IE involving structures of the left and the right heart should be distinguished and referred to as right heart or left heart IE, respectively. If the anatomical site of the infection has been identified properly, e.g., by transoesophageal echocardiography, it should be part of the definition (e.g., mitral, aortic, mural).

e When the causative organism has been identified, it should be included in the terminology, as it provides crucial information regarding clinical presentation, treatment and prognosis.<sup>10-12</sup> As long as cultures,

serological tests, histological and/or molecular biological methods (e.g., broad-spectrum polymerase chain reaction (PCR)) have remained negative, this information should also be included in the terminology (e.g., culture, serology, histologically, PCR-negative or -positive IE). If all techniques have been applied and were negative, the term 'microbiologically negative' is considered appropriate.

f Classification referring to the population involved (e.g. IE in addicts, in patients with congenital heart disease, neonates, children, in the elderly; nosocomial NVE) is helpful for epidemiological purposes and clinical management.

An increasing frequency of IE in neonates has been observed recently,<sup>13,14</sup> and IE in the elderly may present with fewer symptoms but has a worse prognosis than IE in younger age groups.<sup>10</sup> Nosocomial NVE should be defined as occurring more than 72 h after admission to a hospital or as directly related to a procedure performed in hospital within the preceding six months of admission.<sup>15</sup> Nosocomial IE comprises 5–29% of all cases of IE<sup>12</sup> and may carry a mortality up to 40–56%. The most frequent pathogen is *Staphylococcus aureus*.<sup>12,15</sup> In intravenous drug abusers, the prevalence of IE is approximately 60 times higher than in an age-matched population.

Terminology recommended by the Task Force should give information on the above mentioned subsets (a)–(d) (see Table 1).

## Incidence

As IE is not subject to registration and prospective studies on its incidence are rare and contradictory (1.9 to 6.2 annual infections per 100 000 population),<sup>16-19</sup> there is considerable uncertainty about the present incidence of the disease. In countries with a low incidence of rheumatic fever, IE in the paediatric group is rare (0.3 per 100 000 and year).<sup>16</sup>

## Prevention of infective endocarditis

### Misconceptions, evidence and efficacy

The relation between preexisting cardiac diseases, occurrence of bacteraemia, and onset of IE was first recognized in 1923.<sup>20</sup> The relationship between transient bacteraemia (often due to viridans streptococci after dental extraction) and bacterial endocarditis in patients predisposed by rheumatic heart disease was observed in 1944<sup>21</sup> and forms the basis for the use of antibiotics to prevent IE in patients undergoing dental treatment or other procedures that may cause bacteraemia. However, since the time prophylaxis has been employed, the incidence of IE has not decreased significantly.

This apparent discrepancy might be due to several reasons: Bacteraemias do not occur only after major procedures such as dental extraction, tonsillectomy, and bronchoscopy but also after more common events, such

**Table 1** Terminology for infective endocarditis (IE). Examples: active mitral valve IE due to *Enterococcus faecalis*; healed recurrent prosthetic aortic valve endocarditis due to *Staphylococcus epidermidis*; suspected culture-negative late prosthetic mitral valve endocarditis

|                            | Activity         | Recurrence             | Diagnostic terminology | Pathology  | Anatomical site                         | Microbiology  |
|----------------------------|------------------|------------------------|------------------------|--|---|---|
| First episode <sup>a</sup> | Active<br>healed | Relapsing<br>recurrent |                        |  | Mitral aortic<br>tricuspid mural<br>etc | Microorganism<br>culture-negative,<br>serologically negative,<br>PCR negative,<br>histologically negative |
| Definite <sup>a</sup>      |                  |                        | Suspected<br>Possible  |  |   |   |
| Native <sup>a</sup>        |                  |                        |                        | Early prosthetic<br>Late prosthetic<br>IVDA <sup>b</sup> |   |   |

<sup>a</sup>If the columns 'recurrence', 'diagnostic terminology', and/or 'pathology' are without text, they signify the first episode of IE (not relapsing or recurrent), 'definite' IE (not suspected or possible) and involvement of a native cardiac valve.

<sup>b</sup>Intravenous drug abuse.

as toothbrushing and chewing gum.<sup>22</sup> Furthermore, common bacterial infections, especially upper respiratory tract infections, may result in short-lasting but significant bacteraemias.<sup>23</sup> Another possible reason for the unchanged incidence is that antibiotic prophylaxis may not be effective in preventing bacterial endocarditis if the amount of bacteraemia in terms of colony-forming units (CFU) is very large. Although effectiveness of antibiotic prophylaxis has never been proven unequivocally in man,<sup>24,25</sup> there is convincing evidence from clinical practice and experimental animal models that antibiotics can be effective to prevent IE.<sup>26–31</sup> Various antibiotic regimens have been compared in their ability to prevent experimental endocarditis.<sup>32,33</sup> Although these studies have been criticized, they can be used to compare the efficacy of various antibiotics and, thus, they form important grounds on which the Committee on Prevention of Bacterial Endocarditis of the American Heart Association based its recommendations in 1955 and 1972.<sup>34–36</sup> As an indirect assessment of the efficacy of antibiotic prophylaxis in preventing bacterial endocarditis after dental extraction, the incidence of post-extraction bacteraemia under antibiotic prophylaxis has been used. Results of such studies are inconsistent, but several investigators have demonstrated the occurrence of early post-extraction bacteraemia under antibiotic prophylaxis.<sup>37,38</sup> However, these bacteraemias do not reflect failure of prophylaxis because killing of microorganisms and the use of bactericidal dosages of antibiotics are not necessary to prevent IE,<sup>25,29,30</sup> as it is more likely that antibiotics work through modulation of adhesion of microorganisms.<sup>39</sup> In less controlled series of patients with prosthetic heart valves, prophylaxis has been associated with a significant reduction of PVE cases.<sup>31</sup>

Eradication of microorganisms may become more difficult after adhesion to the endocardium, and even more if prosthetic material is involved.<sup>40,41</sup> For prophylactic reasons, antibiotics should, therefore, be given

before bacteraemia is expected in order to reduce the capacity of the microorganism to adhere and to multiply. If antibiotic prophylaxis has not been given prior to this event, antibiotics may help for late clearance if they are administered intravenously within 2–3 h afterwards.

It should be noted that

- a a widespread use of antibiotics in cases of minor 'respiratory' viral infections has no rationale and might affect the patient's own bacterial flora;
- b antibiotic prevention of recurrent rheumatic fever attacks should not be confused with prevention of bacterial endocarditis.

## Pathogenesis and pathology of native and prosthetic valve endocarditis

### Pathogenesis

Sterile (micro-) thrombi attached to damaged endocardium are considered the primary nidi for bacterial adhesion. Haemodynamic (mechanical stress) and immunological processes seem to play an important role in endocardial damage.<sup>42,43</sup> The site of predilection in IE is the area of valve line closure where altered haemodynamics due to preexisting valve damage may predispose to endothelial damage. Entry of microorganisms into the circulation due to focal infection or trauma may convert thrombotic, non-bacterial endocarditis into IE. The potential of microorganisms to adhere to non-bacterial thrombotic vegetations plays a major role and fibronectin, a glycoprotein that is a major surface constituent of mammalian cells, has been identified as an important factor in this process.<sup>43</sup> Decreased host defence mechanisms play an additional role (see Section 3.4). After adhesion, microorganisms can grow and induce further thrombus formation and neutrophil chemotaxis. Most gram-positive bacteria are resistant to the bactericidal activity of serum, whereas gram-negative ones are not. Beside their capacity to adhere, this is a second reason

why gram-positive bacteria are found significantly more often than gram-negative ones as causative organisms of IE.

#### Pathology of native valve endocarditis

The pathology of NVE may be local (cardiac) including valvular and perivalvular destruction or distal (non-cardiac) due to detachment of septic vegetations with embolism, metastatic infection and septicaemia. As far as non-cardiac complications are concerned, they differ whether IE is right- or left-sided, and whether emboli from vegetations are septic or non-infected. Right-sided endocarditis may be complicated by pulmonary artery embolism and infarction, pneumonia and lung abscesses. Left-sided endocarditis may be complicated by systemic embolism with cerebral, myocardial, kidney, splenic, intestinal infarcts and/or abscesses. With an incidence ranging from 22 to 43% embolic events belong to the most common extracardiac complications associated with IE.<sup>44</sup>

Metastatic infection may lead to meningitis, myocarditis and pyelonephritis. Septicaemia may stimulate disseminated intravascular coagulation. Deposition of circulating immune complexes accounts for diffuse or focal glomerulonephritis. 'Mycotic aneurysms' may involve both large to medium sized arteries and small vessels Osler's nodes are expressions of an immunologically mediated necrotising small vessel vasculitis.

Cardiac complications of IE occur at the valves themselves or in the perivalvular region. Vegetations are usually attached to atrial aspects of atrio-ventricular valves and to ventricular sides of semilunar valves, predominantly at the valve closure line. Cusp rupture with loss of substance accounts for tearing, fraying, perforation and bulging, especially if staphylococci are the causative microorganisms. Acute valve incompetence with subsequent congestive heart failure is the most frequent cardiac complication. Local spread of the infection includes extension to the aortic wall, which may result in sinus of Valsalva aneurysms, ring abscesses, pseudoaneurysms, tunnels and fistulas to the surrounding cardiac chambers (right and left atria, right and left ventricles) and the pericardial cavity, with cardiac rupture and tamponade. Extension of IE from the aorta to the mitral valve occurs through mitral-aortic fibrous continuity or direct contact of vegetations attached to the aortic cusps with the anterior mitral leaflet (satellite infection, mitral kissing vegetation) with or without mitral leaflet perforation. Involvement of the conduction system may account for atrio-ventricular block. In IE of atrio-ventricular valves, apart from cusp vegetations and perforations, the subvalvular apparatus (chordae tendinae and papillary muscles) may also be affected.

Healed endocarditis is marked by indentation of the free margin of a cusp, perforation of the body of the cusp with thick edges, cusp aneurysms, ruptured chordae tendinae, and healed fistulae.

#### Pathology of prosthetic valve endocarditis (PVE)

Intracardiac pathology differs significantly from NVE. If mechanical valves are involved, the site of infection is the perivalvular tissue and the usual complications are

periprosthetic leaks and dehiscence, ring abscesses and fistulae, disruption of the conduction system and purulent pericarditis. Vegetations may interfere with the occlusive motion causing acute prosthetic valve obstruction. In bioprostheses, the mobile elements are made from tissue, which, despite glutaraldehyde fixation, may be the site of infection and of cusp perforation and vegetations.<sup>45</sup> Ring abscess and leaks may also occur.

#### Cardiac conditions/patients at risk

Although it is known that some cardiac conditions are associated with a certain risk for IE, it is impossible to measure the relative risk of a special cardiac condition to develop IE.<sup>46</sup> By tradition, these conditions are grouped into three categories, namely, cardiac disorders with high, moderate, and low/negligible risk.<sup>36,47</sup> These categories are not based on firm scientific evidence. On the other hand, changes in the epidemiology of heart valve diseases and patient profiles in Europe during the last decades should be considered. These changes are due to the decline of rheumatic heart disease, increased numbers of patients who undergo cardiac surgery, the increase in the aged population with degenerative valve lesions, and, finally, the more frequent diagnosis of mitral valve prolapse due to the widespread use of echocardiography.

#### Patient conditions in which prophylaxis for IE is not indicated

IE may develop in any individual with a more or less normal cardiac morphology and physiology. For some cardiac diseases, the risk of IE is very low and usually does not exceed that of normal population.

There is no evidence that ischaemic heart disease without concomitant valvular lesions carries an increased risk for IE and requires prophylaxis.<sup>47</sup> Patients with previous coronary artery bypass surgery or with coronary catheter-based interventions should also be considered in this category.

In different series the presence of an atrial septal defect was not associated with a special risk for IE.<sup>48,49</sup> In the grown-up congenital heart (GUCH) population, IE was not seen in secundum atrial septal defects before and after closure, in closed ventricular septal defects and ducts without left sided valvular abnormalities, in isolated pulmonary stenosis, in unrepaired Ebstein's anomalies, or after Fontan type or Mustard operations.<sup>50</sup> It is, however, recommended to perform antibiotic prophylaxis for 12 months after ASD/PFO catheter-based closure procedures.

Individuals with a murmur but no structural heart disease by echocardiography do not need antimicrobial prophylaxis. With the widespread use of echocardiography, mitral valve prolapse has become a frequently encountered disease. There is general agreement that patients with mitral valve prolapse and unthickened leaflets without regurgitation or calcification do not have an increased risk for IE.<sup>46,51–53</sup>

**Table 2** Cardiac conditions in which antimicrobial prophylaxis is indicated

|  |
|--|
| Prosthetic heart valves <sup>a</sup>   |
| Complex congenital cyanotic heart diseases <sup>a</sup>                      |
| Previous infective endocarditis <sup>a</sup>                                 |
| Surgically constructed systemic or pulmonary conduits <sup>a</sup>           |
| Acquired valvular heart diseases   |
| Mitral valve prolapse with valvular regurgitation or severe valve thickening |
| Non-cyanotic congenital heart diseases (except for secundum type ASD)        |
| Hypertrophic cardiomyopathy  |

<sup>a</sup>High-risk group (see text).

Cardiac pacemakers and defibrillator devices do not require antimicrobial prophylaxis apart from the perioperative situation.<sup>36</sup>

#### Patient conditions in which prophylaxis is indicated

Several cardiac conditions are associated with an endocarditis risk higher than expected in the normal population (Table 2). In this situation there is a general consensus to advise antimicrobial prophylaxis. It is suggested that a single dose antibiotic regimen be scheduled for all cardiac patients at risk, with a flexible formulation allowing for an optimal regimen to be recommended for each individual patient.<sup>54</sup>

Valvular heart diseases remain the most frequent underlying pathology for IE.<sup>47</sup> Although the incidence of rheumatic valvular heart diseases has been clearly reduced in the Western world, rheumatic fever is still prevalent in many parts of the world including some of the member countries of the European Society of Cardiology.<sup>55</sup> The frequency of rheumatic valvular disease as an underlying condition in recent series has been reported to range from 6% to 23%.<sup>56,57</sup> The decrease of rheumatic valvular lesions parallels an increase in degenerative valvular lesions,<sup>56,57</sup> especially aortic valve disease and mitral regurgitation.<sup>47</sup>

Many studies have shown that a subgroup of patients with mitral valve prolapse and regurgitation are at risk for IE. The presence of valvular thickening and calcification as well as holosystolic murmurs seem to determine the increased risk in mitral valve prolapse,<sup>51,57,58</sup> especially if the valve shows myxomatous degenerations. Myxomatous valves predispose to IE even if there is no associated regurgitation.<sup>52</sup>

IE is also a well-known complication of certain congenital cardiac abnormalities. Due to the increasing number of patients with complex congenital heart diseases surviving to adulthood, endocarditis is now also observed with greater frequency in the GUCH population.<sup>50</sup> In large series of paediatric patients, ventricular septal defects, tetralogy of Fallot (TOF), and aortic stenosis are the most frequently encountered congenital abnormalities predisposing to endocarditis.<sup>48,49,59</sup> Complex congenital cyanotic heart diseases other than

TOF carry a high risk of IE particularly if palliative anastomoses have been created.

A bicuspid aortic valve is also an important risk factor for the development of IE.<sup>47,54</sup> Patients with patent ductus arteriosus and aortic coarctation are supposed to be at risk of developing IE but data are scarce to support this risk.<sup>49,50</sup> The risk for IE is abolished after corrective surgery. However, antimicrobial prophylaxis should be offered to those patients before correction as well as for patients with primum atrial septal defects.

There is general agreement that prosthetic heart valves including bioprosthetic and homograft valves and surgically constructed systemic or pulmonary conduits create a definite risk for the development of endocarditis. The risk for patients with prosthetic heart valves seems approximately 5–10 times higher than in patients with native valve disease.<sup>8,60</sup> Antimicrobial prophylaxis is, therefore, recommended for patients with prosthetic valves and artificial conduits.

Hypertrophic obstructive cardiomyopathy has also been reported to be associated with IE after bacteraemia-producing procedures. Associations with valvular lesions (e.g., mitral regurgitation) should be expected to further increase the risk.<sup>46,47</sup>

A previous history of IE is an important and well-defined risk factor for the development of a second infection.<sup>47,54</sup>

#### Patients carrying a high risk for IE

Since this group of patients carries a high risk for the development of IE as well as a worse prognosis when endocarditis develops, the Task Force identifies these conditions separately (see Section 3.4). Previous history of IE, prosthetic heart valves, surgically created conduits, and complex cyanotic congenital abnormalities create high-risk situations.

#### Patient-related non-cardiac conditions

Beside older age, non-cardiac patient-related factors predisposing to IE may be separated into conditions (a), promoting non-bacterial thrombotic vegetation (NBTV); (b), compromising host defence; (c), compromising local non-immune defence mechanisms; and (d), increasing the risk for, frequency of, or amount of bacteraemia.

a NBTV is considered a major prerequisite for the adhesion of microorganism to endocardial surfaces.<sup>61</sup> Microorganisms may adhere more easily in the presence of fresh, platelet-rich thrombi often associated with leukaemia,<sup>62</sup> cirrhosis of the liver, carcinomas which may cause hypercoagulability (marantic endocarditis),<sup>63</sup> inflammatory bowel disease,<sup>64</sup> systemic lupus erythematosus,<sup>61</sup> and steroid medication.<sup>65</sup>

b Systemic immune defence may be compromised by humoral defects, cellular defects, or both. Humoral immune defence is known to be compromised in patients with steroid medication.<sup>65</sup> It is unknown from clinical data whether there is a correlation between suppression of cellular immune defence and IE. In experimental endocarditis, a higher incidence of

bacteraemias and a more severe course of IE have been demonstrated in granulocytopenic animals.<sup>66</sup>

The IE risk for intravenous drug abusers (IVDAs) has been calculated to be twelve-fold higher than in non-IVDAs.<sup>67</sup> In non-IVDAs with HIV and AIDS the risk for IE has not been reported to be increased.<sup>68</sup>

Chronic alcoholism is associated with increased infection rates.<sup>69</sup> No data for IE are available. Nevertheless, a low incidence of predisposing cardiac lesions has been reported in patients with chronic alcoholism.<sup>70</sup>

- c Compromised local non-immune defence mechanisms as found in mucous membrane lesions with a subsequent increase of transmucosal permeability (e.g., in patients with chronic inflammatory bowel disease) are associated with an increased risk for IE.<sup>64,71</sup>

Reduced capillary clearance as found in arteriovenous fistulas has been reported to be associated with an increased risk for IE in both animal models<sup>72,78</sup> and in patients on chronic haemodialysis<sup>73,74</sup>

- d Increased risk or an increased frequency for bacteraemias exist in patients with broken skin (e.g., in diabetes mellitus or burns), on intensive care (lines, respirators, etc) and with polytrauma, with poor dental status,<sup>74</sup> on haemodialysis (prevalence 2.7–6.6%),<sup>72,73,75</sup> and in IVDAs.<sup>76,77</sup>
- e The incidence and the amount of colon colonization by *Streptococcus bovis* biotype I may be the reason for the close correlation between IE due to *S. bovis* and colo-rectal tumours/chronic inflammatory bowel disease.<sup>64,77</sup>

### Predisposing diagnostic interventions

The general belief is that iatrogenic bacteraemia occurs after traumatic procedures involving the gingiva and mucosal tissue of the upper respiratory gastrointestinal or genitourinary tracts. In this regard, therapeutic interventions are much more traumatic than diagnostic procedures and regularly result in bleeding of the gums or of the mucosal system.<sup>54</sup> The probability of bacteraemia and subsequent IE is highest for dental and other oral procedures, intermediate for procedures involving the genitourinary system, and low for gastrointestinal procedures.<sup>26</sup> The shorter the time interval from the procedure to the manifestation of IE, the more likely the causal link. The duration between procedure and clinical event is at the level of a few weeks.<sup>79,80</sup>

In various series the diagnostic procedures which may cause bacteraemia and for which antimicrobial prophylaxis is recommended include bronchoscopy with a rigid bronchoscope, cystoscopy (diagnostic urethral catheterisation) if urinary tract infection is present, and biopsy of the urinary tract and prostate.<sup>26,54</sup> On the other hand, fiberoptic endoscopy, endotracheal tube insertion, gastroscopy with or without biopsy, and transoesophageal echocardiography are thought to be low-risk procedures for IE and antimicrobial prophylaxis is not warranted.<sup>81–83</sup>

Although bacteraemia may occur after prolonged heart catheterization (e.g., for mitral balloon valvulotomy) there are no sufficient data to recommend prophylaxis in these circumstances.

### Predisposing therapeutic interventions

Various therapeutic interventions have been proven to cause bacteraemia and may cause IE in predisposed patients. However, a clear relationship between such procedures and the development of IE has not been proven.

It is widely accepted that dental procedures are associated with a risk of developing IE in patients with a variety of structural cardiac diseases. The only exception could be procedures without any risk of gingival or mucosal trauma and subsequent bleeding. Dental hygiene is of major importance in the prevention of IE.<sup>74</sup> Antiseptic agents may reduce the risk for bacteraemia and/or the amount of microorganisms inoculated but cannot replace antibiotic prophylaxis.<sup>84</sup> Patients at risk for IE should be advised to have daily personal and professional dental care at least once a year. In patients with a poor oral hygiene even routine tooth brushing or chewing may cause significant bacteraemia.<sup>80</sup> Tooth extraction, periodontal surgery, scaling, root canal therapy, removal of tartar and tooth implantation are interventions for which antimicrobial prophylaxis is advised in patients at risk.<sup>85,86</sup>

Tonsillectomy and adenoidectomy frequently cause bacteraemia, and antibiotic prophylaxis is recommended.<sup>54</sup>

The frequency of bacteraemia is not significantly increased with therapeutic attempts during gastrointestinal endoscopy such as polypectomy.<sup>26,83</sup> However, certain gastrointestinal procedures carry a higher risk for bacteraemia and are to be accompanied by antimicrobial prophylaxis. Due to a high probability of bacterial colonization, this group of therapeutic interventions includes oesophageal dilatation, sclerotherapy of oesophageal varices, and instrumentation of an obstructed biliary tract.<sup>87,88</sup>

Bacteraemia is frequently encountered during instrumentations and surgical procedures of the urinary tract. The risk is definitely higher in the presence of urinary tract infection. Transurethral resection of prostate, lithotripsy, ureteral instrumentation, urethral dilatation, and cystoscopy are well-defined invasive urological procedures for which antimicrobial prophylaxis is indicated.<sup>26,54,89</sup>

Procedures performed under strict skin disinfection (including cardiac catheterization with or without interventional procedures) are not generally in need of prophylaxis. Pacemaker or ICD implantation do not require additional antimicrobial prophylaxis, as antibiotics are generally given perioperatively.

Unless infection or infected material is present, normal vaginal delivery or other gynaecologic procedures (vaginal hysterectomy, IUD placement, etc) do not require prophylaxis.



## Prophylactic antibiotic regimens

Only patients in the high or moderate-risk categories should receive prophylaxis. This is a class I recommendation based on level C evidence.

Prophylaxis aims primarily at viridans streptococci and HACEK organisms before dental, oral, respiratory, and oesophageal procedures, and at enterococci, *Streptococcus bovis* and enterobacteriaceae before gastrointestinal and genitourinary procedures.<sup>54,36</sup>

Special circumstances prevail in patients who are already receiving antibiotics for other reasons and in those who undergo cardiac surgery or procedures involving infected tissues.

Dental, oral, respiratory, and oesophageal procedures:

- Not allergic to penicillin, oral prophylaxis: Amoxicillin 2.0 g (children 50 mg/kg) 1 h before procedure.
- Not allergic to penicillin, unable to take oral medication: Amoxicillin or ampicillin 2.0 g (children 50 mg/kg) i.v. within 1/2-1 h before procedure. A second amoxicillin dose is not necessary.<sup>90</sup>
- Allergic to penicillin, oral prophylaxis: Clindamycin 600 mg (children 20 mg/kg) or azithromycin or clarithromycin 500 mg (children 15 mg/kg)<sup>91</sup> 1 h before procedure.

Genitourinary or gastrointestinal procedures:

- Not allergic to penicillin, high-risk group: Ampicillin or amoxicillin 2.0 g i.v. plus gentamicin 1.5 mg/kg within 1/2–1 h i.m. or i.v. before procedure; 6 h later, ampicillin or amoxicillin 1 g p.o.
- Not allergic to penicillin, moderate-risk group: Ampicillin or amoxicillin 2.0 g i.v. (children 50 mg/kg) within 1/2–1 h before procedure, or amoxicillin 2.0 g (children 50 mg/kg) p.o. 1 h before procedure.
- Allergic to penicillin, high-risk group: Vancomycin 1.0 g (children 20 mg/kg) over 1–2 h plus gentamicin 1.5 mg/kg i.v. or i.m.
- Allergic to penicillin, moderate-risk group: Vancomycin (see above) without gentamicin.

Patients receiving antibiotics for other reasons:

- Main danger is resistant organisms. Clindamycin, azithromycin or clarithromycin are alternatives to amoxicillin/ampicillin.

Patients undergoing cardiac surgery or procedures involving infected tissues:

- Main organisms to be covered would be staphylococci (MSSA, MRSA, MSSE, MRSE) in infections of soft tissue, bones and joints, and in cardiac surgery; and enterobacteriaceae in urinary tract infections. For the first group, a first-generation cephalosporin,<sup>92</sup> clindamycin, or vancomycin (for MRSE and MRSA) would be the drugs of choice, while the latter would call for addition of an aminoglycoside.

Despite a lack of convincing evidence, analysis of all material presently available results in a class I recommendation for antibiotic prophylaxis, which are based on level C evidences.

## Patient education, information and acceptance

Compliance with IE prophylaxis is more or less low in the medical community. Adequate patient information is thus the most critical issue to ensure proper prophylaxis. Therefore, patients who are at risk should be informed in such a way that they are really aware of the potential threats and risk which might occur in particular with dental procedures. This is best done by written information and a certificate given to the patient.

Patients often fear events that are not likely to induce IE or they do not really know their individual risk. One of the most common misinterpretations is occurrence of fever, which is most often due to a viral respiratory infection. Unfortunately, antibiotic prophylaxis is often requested and prescribed in this situation. Patients and parents of predisposed children should be informed that the course of any fever should be investigated before antibiotics are given.

Another issue to be emphasized is not to continue a prophylactic antibiotic regimen longer than for the recommended period, even if fever occurs or persists. In this situation proper diagnostic tests must be performed to rule out IE.

## Diagnosis

### History, symptoms, signs and laboratory tests

The diagnosis of IE is established (definite IE) if during a sepsis or a systemic infection involvement of the endocardium is demonstrated. If, in addition, bacteraemia (positive blood cultures) or bacterial DNA are found, IE is definite and culture/microbiologically positive, otherwise IE is definite but culture/microbiologically negative.

As the clinical history of patients with IE is highly variable depending on the causative microorganism and the presence or absence of predisposing cardiac conditions and other diseases, early suspicion of IE is decisive for an early diagnosis (Table 3).

IE may present as an acute, rapidly progressive infection, but also as a subacute or chronic disease with low-grade fever and non-specific symptoms only. In the latter type, the lack of specific complaints and clinical findings often delays the diagnosis for weeks or months, especially if there are no predisposing cardiac lesions. One of the main problems is that the majority of these patients are initially not seen by a cardiologist or an infectious disease specialist but by a general physician who has to consider a broad range of conditions such as chronic infections, rheumatoid, immunological, or malignant diseases. Even the most elaborate algorithm on the diagnosis and treatment of IE has little impact if the diagnosis is not suspected early enough. Furthermore, under real-life conditions, physicians often prescribe

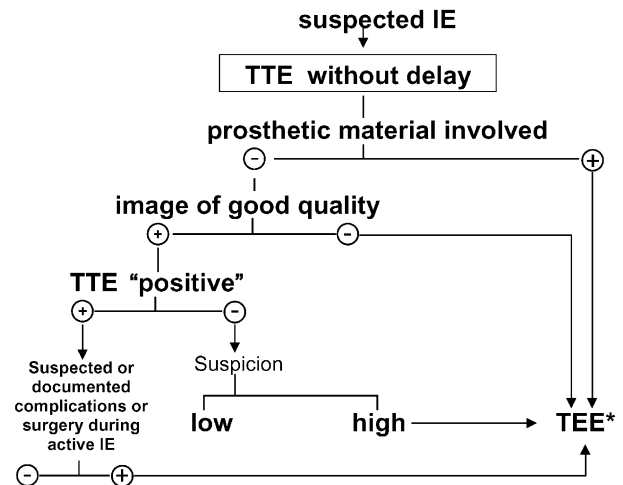
**Table 3** Criteria that should raise suspicion of IE

- High clinical suspicion (urgent indication for echocardiographic screening and eventually hospital admission)
  - New valve lesion/(regurgitant) murmur
  - Embolic event(s) of unknown origin
  - Sepsis of unknown origin
  - Haematuria, glomerulonephritis, and suspected renal infarction
  - 'Fever' plus
    - Prosthetic material inside the heart
    - Other high predisposition for IE (see 3.3)
    - Newly developed ventricular arrhythmias or conduction disturbances
    - First manifestation of CHF
    - Positive BCs ( if the organism identified is typical for NVE/PVE)
    - Cutaneous (Osler, Janeway) or ophthalmic (Roth) manifestations
    - Multifocal/rapid changing pulmonic infiltrations (right heart IE)
    - Peripheral abscesses (renal, splenic, spine) of unknown origin
    - Predisposition and recent diagnostic/therapeutic interventions known to result in significant bacteraemia
- Low clinical suspicion
  - Fever plus none of the above

antibiotics to febrile patients before a definite diagnosis is made and especially before blood cultures are obtained. Real improvement in the management of IE thus depends on a higher index of suspicion for this potentially life-threatening condition.

Among the presenting symptoms fever is a non-specific but the most frequent one. It varies from high temperatures with shivers and prostration in acute staphylococcal IE to prolonged febrile states associated with general malaise, weakness, arthralgias and loss of weight in subacute streptococcal infections. Initially, respiratory or abdominal infections are often suspected. Further symptoms often arise as a consequence of complications. Valve destruction leads to increasing shortness of breath, nocturnal dyspnoea, orthopnoea, or even acute pulmonary oedema. In patients with right-sided endocarditis clinical signs of pneumonia and/or right heart failure predominate. Emboli from cardiac vegetations results in CNS symptoms, vascular obstruction in the extremities, pleuritic or abdominal pain. Depending on the localization of embolic vascular lesions the differential diagnosis may be difficult.

Among the clinical findings cardiac murmurs in a febrile patient belong to the key ones to alert the physician to IE. Newly occurring regurgitant murmurs or growing intensity of preexisting regurgitant murmurs are of particular importance. However, murmurs are not obligatory and may not occur before perforation or valve disruption. Embolic or immunological complications from vascular occlusion in the systemic circulation present as cerebral ischaemia or haemorrhage, ischaemia of the



**Fig. 1** Algorithm for the use of transthoracic (TTE) and transoesophageal echocardiography (TEE) in suspected IE. N.B. TTE "positive" indicates finding typical of IE (e.g. fresh vegetation or abscess formation).

limbs, intestinal infarctions, or small cutaneous lesions mostly located on fingers, toes, or in the eyes. Septic pulmonary infarcts with pleuritic chest pain in drug addicts are the typical manifestations of right-sided endocarditis. It is important to realise that none of the above-mentioned clinical signs is specific enough to allow the diagnosis of IE without additional investigations. In febrile patients with cardiac murmurs the initial diagnostic suspicion can also be strengthened by laboratory signs of infection, such as elevated C-reactive protein or sedimentation rate, leukocytosis, anaemia and microscopic haematuria. The detection of endocarditis will, however, depend on the performance of the decisive diagnostic tests such as repeated blood cultures and transthoracic or transoesophageal echocardiography.

The special clinical presentation of right heart IE includes chills, fever, night sweat, malaise and symptoms attributed to pulmonary emboli. Patients having community-acquired right-sided IE often seek medical attention for suspected pneumonia. In contrast to left-sided IE, peripheral stigmata and cardiac signs and symptoms are usually absent. Cough and pleuritic chest pain occur in 40–60%.<sup>93</sup> Haemoptysis and dyspnoea are noted occasionally. Chest X-ray reveals nodular infiltrates with or without cavitation, multifocal pneumonia, effusions or pyopneumothorax in 70–85% of patients.<sup>94,95</sup> Occasionally lung injury is so extensive that respiratory insufficiency supervenes.

A murmur of tricuspid or pulmonary regurgitation is often absent or appears late in the course of the disease.

## Echocardiography

Any patient suspected of having NVE by clinical criteria (e.g., fever of unknown origin) should be screened by transthoracic echocardiography (TTE). When the images are of good quality, TTE is negative and there is only a low clinical suspicion of IE (see Fig. 1), endocarditis is unlikely and differential diagnoses are to be considered.

When the images are of poor quality the technique of choice is omniplane TEE. The semiinvasive nature of transoesophageal echocardiography (TEE) and the need for operator expertise argue against its routine use in all patients with suspected IE.<sup>96</sup> If suspicion of IE is high (e.g., in staphylococcal bacteraemia), TEE should be performed in all TTE-negative cases, in suspected PVE, and in cases of aortic location as well as before cardiac surgery during active IE.<sup>97</sup> If TEE also remains negative and there is still suspicion, TEE should be repeated after 48 h to one week to allow potential vegetations to become more apparent. A repeated negative study should virtually exclude the diagnosis unless TEE images are of poor quality (Fig. 1).<sup>98</sup>

These class I recommendations are based on level B evidence.

Three echocardiographic findings are considered to be major criteria in the diagnosis of IE: (a), a mobile, echodense mass attached to the valvular or the mural endocardium, especially if present on the preferred locations, or attached to implanted prosthetic material with no alternative anatomical explanation; (b), demonstration of abscesses or fistulas; (c), a new dehiscence of a valvular prosthesis, especially when occurring late after implantation.

#### Detection of vegetations

The detection rate by TTE in patients in whom IE is clinically suspected averages 50%.<sup>99–102</sup> Factors associated with detection rates are image quality, echogenicity and vegetation size, location of the vegetation, presence of pre-existing rheumatic/degenerative valve lesions, prosthetic material implanted, and first of all, the skill/experience of the examiner.

On native valves approximately 20% of TTEs are of suboptimal quality.<sup>99,101</sup> While only 25% of vegetations less than 5 mm in size are identified, the percentage increases to 70% in vegetations larger than 6 mm.<sup>99,102</sup> On prosthetic valves TTE as a rule is nondiagnostic. Owing to its better resolution, these limitations have been overcome by TEE, especially omniplane TEE. Sensitivity of TEE has been reported to be 88–100% and specificity, 91–100%.<sup>99,101–104</sup>

A negative TEE has an important clinical impact on the diagnosis,<sup>98,103,104</sup> with a 68–97% negative predictive value.

Echocardiography does not allow to reliably differentiate between vegetations of active and healed IE. When echocardiograms are repeated between 3 weeks and 3 months after antibiotic treatment has been started, 30% of vegetations disappear, 18% are reduced, 41% do not change, and 11% increase in size.<sup>105</sup>

Frequent causes of false-positive echocardiographic findings are non-infected intracardiac thrombi or filiform tumors (papillary fibroelastomas or fibro-elastic ('papillary') endocardial tumors, e.g., Lambl's excrescences) and non-infected valve-attached vegetations (e.g., in Libman-Sacks endocarditis, Behçets disease, carcinoid heart disease, acute rheumatic fever).

Intracardiac thrombi are rarely attached to valve leaflets or cusps. False-negative echocardiographic findings

are most frequently due to low examiner expertise, small and/or non-mobile vegetations, or inappropriate image techniques (e.g. no TEE examination).

#### Valve destruction

Insufficiency of an infected valve may result from different mechanisms: vegetations preventing proper leaflet or cusp coaptation, valvular destruction (from small perforation to flail leaflet),<sup>106</sup> or rupture of chordae tendineae. TEE is significantly more accurate in the diagnosis of valvular destruction in both aortic and mitral valve IE.<sup>99,100,107,108</sup>

Doppler imaging has greatly improved the assessment of valvular perforations and the differentiation of mitral cusp perforation from central mitral regurgitation. TEE is recommended if valvular perforation is strongly suspected on a clinical basis, especially in the presence of aortic valve involvement.<sup>106</sup> An aneurysm of the mitral valve is defined as a saccular cavity bulging toward the left atrium in systole and collapsing in diastole.<sup>106</sup>

Colour flow mapping has proved to be useful for the recognition and serial monitoring of haemodynamic complications of IE. TEE colour-flow mapping is of particular value in patients with a mitral prosthesis and periprosthetic regurgitation.

#### Perivalvular complications

The extension of the infection into the perivalvular tissue is associated with a worsened prognosis and may result in perivalvular abscesses, aneurysms and fistulae.

Perivalvular cavities are formed when annular infections spread into the adjacent tissue. Periannular extension and abscess formation are common (10–40%) in NVE, especially aortic valve IE,<sup>109–111</sup> and frequent (56–100%) in PVE.

In native aortic valve IE spreading of the infection occurs mostly through the weakest portion of the annulus, which is the mitral-aortic intervalvular fibrous tissue.

Perivalvular abscesses are diagnosed by demonstration of either echolucent or echodense regions, or echolucent cavities within the valvular annulus or adjacent myocardial structures.<sup>110</sup> Periannular abscesses of the aortic valve may be accompanied by a thickening of the aortic wall. TEE is significantly more sensitive to demonstrate periannular extension than TTE.<sup>99,109,111–113</sup> Pseudoaneurysms exhibit a distinct dynamic feature, expanding during isovoluminal contraction and early systole, and collapsing in diastole.<sup>114,115</sup> Both aortic root abscesses and pseudoaneurysms may rupture into adjacent chambers and may thereby create single or multiple intracardiac fistulas.<sup>116</sup>

Secondary involvement of the anterior mitral leaflet with or without fenestration occurs as a result of direct extension of the infection from the aortic valve ('mitral kissing vegetation'<sup>117</sup>) or, less frequently, as a result of an infected aortic regurgitation jet. The extension can form a mitral aneurysm with subsequent perforation resulting in a communication between left ventricle and left atrium. Usually, the site of communication is best defined by colour-coded Doppler. In isolated native

mitral valve IE perivalvular abscess formation is less frequent than in aortic valve IE and often difficult to diagnose even by TEE.<sup>113</sup>

#### Echocardiographic findings in PVE

Vegetations on prosthetic valves cannot be reliably detected by TTE. The sewing ring and support structures of prostheses are strongly echogenic and may prevent detection of vegetations. Infection involving mechanical prostheses usually begins in the perivalvular/annular area. Growth of vegetations appears as thickening and irregularity of the normally smooth contour of the sewing ring. Thrombus and pannus have similar characteristics and cannot be distinguished reliably from vegetations.<sup>118</sup> Bioprosthetic leaflets may become infected with subsequent destruction. Echocardiographic distinction between tissue degeneration and small vegetations may not be possible even with TEE, which is the preferred technique. The atrial aspect of mitral prostheses can be optimally assessed by TEE only.<sup>119</sup> In suspected aortic PVE, TTE usually permits correct assessment of periprosthetic regurgitation<sup>119</sup> and medium to large-size vegetations.<sup>101</sup> Differentiation of vegetations from strands frequently observed by TEE at prosthetic heart valves<sup>120</sup> requires assistance from an experienced examiner.

#### Echocardiographic findings in right-sided endocarditis, pacemaker and ICD lead infections

TTE usually permits correct diagnosis of tricuspid vegetations, probably because they are larger than those on the left side of the heart,<sup>121</sup> while TEE appears to be more sensitive in the diagnosis of pulmonary valve IE.<sup>122,123</sup>

Pacemaker lead infections are uncommon, but require rapid diagnosis. Due to reverberations and artifacts, TTE is limited to detect a vegetation close to these structures and to differentiate between tricuspid valve IE, lead infection, or both. TEE, therefore, is the imaging technique of choice, as it permits exploration of the entire intracardiac route of the leads.<sup>124,125</sup>

#### Standard blood culture techniques

In IE involving the mitral or aortic valve, cultures drawn from arterial blood have occasionally been advocated as being more effective than venous blood cultures.<sup>126</sup> On the other hand, contamination and complications at puncture sites have to be expected more frequently when arterial blood cultures are drawn. In a prospective series of patients with proven IE, from whom arterial and venous blood cultures were collected in parallel, the percentage of positive cultures was significantly higher with venous blood irrespective of the causative organisms.<sup>127</sup> Arterial blood cultures, therefore, are of no diagnostic importance in culture-negative endocarditis.

Blood cultures are often drawn when the body temperature is rising. Some recommend drawing blood culture at the height of fever. In one study, a negative correlation between body temperature and the percentage of positive blood cultures has been documented.<sup>127</sup>

Constant bacteraemia typical for IE allows the drawing of blood cultures at any time.

Modern blood culture (BC) systems are machine-monitored, agitated continuously, and do not depend on visual examination. The older systems are disappearing fast from diagnostic laboratories. A variety of modern systems are in use<sup>128,129</sup> but will not be discussed here.

At least three BCs should be taken at least 1 h apart, and not through intravenous lines, which may be contaminated. If initiation of antimicrobial therapy is urgent (e.g., in septic patients), empiric antibiotic treatment can be started thereafter. In all other cases it is recommended to postpone antimicrobial therapy until blood cultures become positive. If the patient has been on short-term antibiotics, one should wait, if possible, for at least 3 days after discontinuing antibiotic treatment before taking new BCs. Blood cultures after long-term antibiotic treatment may not become positive until treatment has been discontinued for 6–7 days. The usual multiple positivity of BC in IE may not be observed if the patient has been treated with antibiotics.<sup>128–130</sup>

One BC consists of one aerobic and one anaerobic bottle, each containing approx. 50 ml of medium (less in pediatric BC bottles). Minimally 5 ml, better 10 ml in adults and 1–5 ml in children of venous blood should be added to each bottle. 10 ml should suffice to detect even low numbers of organisms.<sup>128,129</sup> In the laboratory, venting and shaking of aerobic bottles and incubation of the BC at 37 °C for 5–6 days is routine.<sup>128,129</sup> Bottles that give a growth signal are Gram-stained and subcultured to media that support growth of fastidious organisms (e.g., *Abiotrophia* spp.), which are incubated at 37 °C for 2–3 days.

A suspicion of IE should always be noted on the requisition form. BCs should not be stored in a refrigerator. A delay in transport is not detrimental to recovery but may delay the diagnosis. If BCs become positive, the clinician has to be informed without delay by the microbiologist.

Identification should be to species level. The presence of *Abiotrophia* spp., *Streptococcus mutans*, *S. sanguis*, *S. bovis* biotype I, *Rothia dentocariosa*, organisms of the HACEK group, lactobacilli, and *Erysipelothrix rhusiopathiae* is often associated with IE. All organisms should be stored for at least one year for comparison if IE should be recurring or relapsing.

Susceptibility testing by disk diffusion helps only to rule out drugs for therapy that are ineffective in vitro. Minimum inhibitory concentrations (checkerboard testing if necessary) should be determined for the drugs of choice. Routine determination of minimum bactericidal concentrations or serum bactericidal levels are not recommended any more.<sup>131</sup> The interpretation of positive blood cultures follows rules established for bacteraemia.<sup>129,131</sup>

#### Diagnostic approach in suspected but unproven IE

There may be a constellation where IE is suspected clinically (suspected or possible IE), but involvement of the endocardium has not been demonstrated so far. For

this situation, score systems had been introduced in the era before efficient echocardiographic techniques were available to provide better entry criteria for epidemiological and clinical studies.<sup>132</sup> These criteria have been updated to increase both sensitivity and specificity by including well-defined echocardiographic findings as well as intravenous drug abuse as a predisposing risk factor.<sup>133,134</sup> They are helpful for epidemiology and standardization of diagnosis but may not be sufficient to make management decisions or to confirm or reject the diagnosis in unclear cases.<sup>135–144</sup> Even the most refined modifications of the Duke criteria do not alter this basic concept. Suggested modifications to increase the sensitivity of the Duke criteria without a loss of specificity are: the use of multiplane TEE and serological/molecular biological findings in culture-negative cases, inclusion of further minor criteria such as newly developed clubbing, splenomegaly, high CRP (above 100 mg/l) and the change of *S. aureus* bacteraemia or positive Q-fever serology from minor to major criteria.<sup>141,145–148</sup>

### Culture-negative endocarditis (CNE)

The frequency of CNE at present is around 5%.<sup>97</sup> The most frequent cause of CNE is previous antimicrobial treatment.<sup>149</sup> If traditional BC systems are used, longer incubation periods (>6 days) are required when certain organisms (the HACEK group, *Propionibacterium* spp., *Neisseria* spp., *Nocardia* spp., *Abiotrophia* spp., *Campylobacter* spp., *Brucella* spp.) are suspected. It seems as if automated BC systems do not require prolonged incubation periods although figures to support this are small.<sup>150–152</sup>

Especially in culture-negative endocarditis, all material excised during cardiac surgery in patients with active IE should also be cultured and examined (see Section Examination of valves). Whether more than three BC per day should be drawn in CNE is controversial.

### Organisms requiring special culture conditions

**Bartonella** endocarditis has been reported relatively frequently. The best BC system seems to be the Isolator<sup>153</sup> but acridine orange staining of BCs and subsequent subculturing to chocolate agar (keep for a minimum of 14 days!) has also been undertaken.<sup>154</sup> Many cases have been diagnosed serologically (e.g., by immunofluorescence).<sup>155</sup> On resected valves, Gram stain and PCR have been used.<sup>155</sup>

**Brucella** endocarditis occurs in approx. 2% of all cases of brucellosis. Most isolates are recovered within 5 days in modern BC systems.<sup>156</sup> Serology (agglutination test) is helpful.

**Fungi.** While endocarditis due to yeasts can frequently be diagnosed (>80%) in BCs designed for bacteria, BCs in endocarditis due to molds (e.g., *Aspergillus*) are rarely positive.<sup>157</sup> For those and for *Histoplasma* the Isolator seems to be the best system, with its culture on solid media to be incubated for 4 weeks. Serology is helpful only for *H. capsulatum* and perhaps for *C. neoformans*.

**Legionella** endocarditis has rarely been reported. The Isolator or periodic blind subculturing of BC bottles to *Legionella* media are preferred in suspected cases.<sup>158</sup> Serology may also be undertaken.

**Mycobacterial** endocarditis is also rare. Mycobacteria other than rapid growers have generally been diagnosed only on resected valves or at autopsy.<sup>159</sup> Rapid growers, e.g., *M. fortuitum*, are more frequent and grow within one week in modern BC systems.<sup>160</sup>

**Nocardiaspp.** have also rarely been reported as agents of endocarditis. In traditional BC systems, they have grown between 2 and 14 days after inoculation,<sup>161</sup> but such systems may remain negative;<sup>162</sup> and no data exist for new systems. *Nocardia* may also be recovered on fungal media.

### Organisms requiring serology

Some of these have been mentioned above. The value of serology for the HACEK group<sup>163</sup> and for streptococcal/enterococcal endocarditis (immunoblotting or immunoelectrophoresis)<sup>164,165</sup> has not been proven conclusively but has been proven for IE due to *Bartonella* or *Legionella* (see above).

**Chlamydial** endocarditis is rare. It has been diagnosed by serology (immunofluorescence) or microimmunofluorescence staining of valves.<sup>166</sup>

**Coxiella burnetii** endocarditis occurs in approx. 10% of all cases of *C. burnetii* infections. While the organism may be found by Giemsa staining of valves<sup>167</sup> endocarditis is best diagnosed by rising IgG and IgA titers to phase I antigen (CF) or by broad-spectrum PCR.<sup>168</sup>

### Examination of valves

Valves may be cultured in broth; prior grinding helps in the recovery of microorganisms.<sup>169</sup> Staining with immunofluorescent stains has been mentioned above. Gram stains may reveal organisms, which may have been rendered non-viable following antibiotic treatment. The only proven case of *Mycoplasma hominis* endocarditis was detected by valve culture.<sup>170</sup> Broad-spectrum PCR should be performed on all resected valves (see Section Demonstration of bacterial DNA by PCR).

### Culture of septic emboli

In rare cases with negative blood cultures, e.g., in *Aspergillus* or *Nocardia* endocarditis, culture of septic emboli may recover the causative organism.<sup>162,171</sup>

### Demonstration of bacterial DNA by PCR

The use of broad-spectrum polymerase chain reaction (PCR) provides a significant improvement in the diagnostic armamentarium for CNE if no particular single organism is suspected. This method is based on the amplification of bacterial 16S rRNA genes which are mosaic molecules consisting of conserved regions (that are almost identical in all bacterial species) and variable ones (which provide unique signature sequences) that can be used for identification. The sequence determined is then compared to the corresponding sequences of

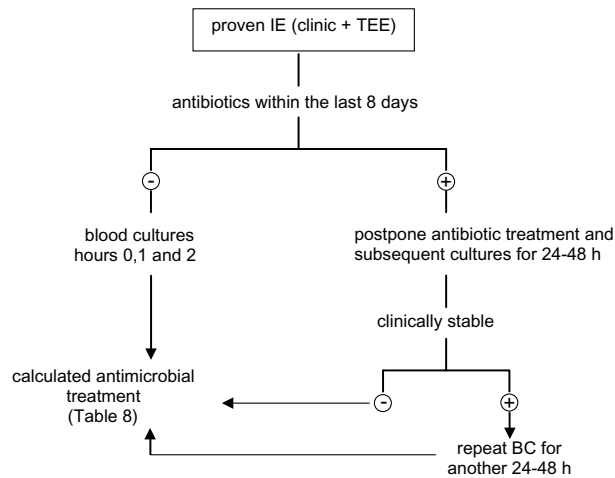


Fig. 2 Empiric antibiotic treatment before identification of causative microorganism(s).

several thousand bacterial species that are accessible in public databases. Advantages of this procedure (e.g. endocarditis due to Whipple disease) include the capability to detect difficult-to-culture organisms<sup>172,173</sup> and even dead bacteria.

Despite the very successful use of this approach it is important to realize its main shortcomings: (a) it is limited to specimens from usually sterile body sites and to monobacterial infections; (b) it is prone to contamination by DNA present in reagents;<sup>174</sup> (c), its sensitivity is lower than that of species-specific PCR.<sup>175</sup>

The chances for a reliable result increase with the number of organisms present in a particular specimen. Broad-spectrum PCR is significantly more sensitive than culture from excised heart valves so it should be applied at least in all patients with IE and negative blood cultures who undergo surgery.<sup>173</sup>

## Treatment and management

Initial treatment should be directed by clinical findings and microbiology. In uncomplicated cases, postponement for up to 48 h, e.g., until the results of initial BCs are obtained, may be advisable and should generally be pursued if the patient has been treated with antibiotics within the last 8 days (Fig. 2).

In cases complicated by sepsis, severe valvular dysfunction, conduction disturbances or embolic events, empiric antimicrobial therapy should be started after three blood cultures have been taken (see Section Standard blood culture techniques).

Conditions for optimal diagnostic procedures and safe treatment are:

- Seven-day microbiological service including identification and susceptibility testing of microorganisms, and possibility of direct contact throughout the day,
- Continuous cardiological and surgical service and expertise with continuous availability of imaging techniques, especially transoesophageal echocardiography and cardiac surgery throughout the day

If these requirements are not fulfilled, immediate transfer of the patient to a centre with cardiological, microbiological and cardio-surgical expertise is required.

In severely ill patients antimicrobial treatment is usually started before identification and susceptibility testing of the infecting organism. Thus, treatment will initially be empirical and later adjusted to the microbiological test results. With multi-resistant organisms clinical response to standard treatment is often slower and relapses are more frequent. Rapid, clinically relevant (species or at least genus) identification and susceptibility testing are necessary for adjustment of the initial empirical antibiotic regimen.

Staphylococci with reduced susceptibility to vancomycin (MIC 4–8 mg/l)<sup>176</sup> are emerging as problem organisms similar to already existing multiresistant enterococci.<sup>177,178</sup> Vancomycin resistance has been described almost exclusively in *E. faecium*, which is rarely found in IE. For enterococci in general, low-level resistance to vancomycin (MIC 8–32 mg/l) represents a considerable therapeutic challenge.<sup>178</sup> For resistant staphylococci and enterococci, treatment with oxazolidinone may be an option but should be initiated only after advice has been obtained from a reference centre.

## Antibiotic treatment of streptococcal endocarditis

Antibiotic treatment for streptococcal IE is dependent on the species as there are significant differences in antibiotic resistance, tolerance and synergistic activity among different groups of streptococci. The majority of IE cases due to the viridans group of streptococci, *Streptococcus pneumoniae*, *S. pyogenes*, Lancefield group B, C, and G streptococci, *S. bovis*, and *Abiotrophia spp.* can be treated successfully with antibiotics alone. Mortality should be less than 10%.

### Choice and dosage of antibiotics

*Penicillin, ceftriaxone, vancomycin, and teicoplanin*

The optimal interval between subsequent antibiotic administrations is not well established for patients with IE. The therapeutic goal is to produce bactericidal levels of drugs at the infected site for a maximum period of time. The *in vitro* susceptibility to antibiotics of 'planc-tonic' bacteria isolated from blood cultures may significantly differ from *in vivo* susceptibility at the site of the infection.<sup>40,41</sup>

Patients with IE caused by streptococci susceptible to penicillin G should be treated with 12–20 million units of penicillin G per 24 h IV divided into 4–6 doses.<sup>179–182</sup> Frequent dosing is necessary as the initial high peak concentration rapidly decreases due to glomerular filtration, tubular excretion in the kidneys, and inactivation of penicillin (half life 20–30 min) in the circulating blood. Single doses higher than 5 million units are not recommended in order to avoid side effects. Continuous IV administration should be reserved for special circumstances and 'difficult-to-treat' microorganisms.

Ceftriaxone has an excellent pharmacokinetic profile to treat streptococcal IE.<sup>183,184</sup> It is generally accepted

**Table 4** Principles of decision making for antibiotic treatment of native (NVE) and prosthetic valve endocarditis (PVE) due to streptococci (including *Abiotrophia* spp)<sup>a</sup>

| Regimen A NVE; full susceptibility to penicillin (MIC ≤0.1 mg/l)                             |  |
|--|--|
| • Patients ≤65 years, normal serum creatinine levels   | Penicillin G 12–20 million units/24 h IV, divided into 4–6 doses for 4 weeks plus gentamicin 3 mg/kg/24 h IV (maximum 240 mg/d), divided into 2–3 doses for 2 weeks  |
| • Same conditions as above with uncomplicated courses and rapid clinical response to therapy | Penicillin G 12–20 million units/24 h IV, divided into 4–6 doses for 2 or 4 weeks with ambulatory treatment after 7 days treatment in hospital (see Table 5)   |
| • Patients ≥65 years and/or serum creatinine levels elevated or allergy to penicillin        | Penicillin G adapted to renal function for 4 weeks or ceftriaxone 2 g/24 h IV <sup>b</sup> as single dose for 4 weeks  |
| • Patients allergic to penicillin and cephalosporins   | Vancomycin 30 mg/kg/24 h IV divided into 2 doses for 4 weeks   |
| Regimen B susceptibility to penicillin (MIC 0.1 mg/l–0.5 mg/l) or PVE                        |  |
|  | penicillin G 20–24 million units/24 h IV divided into 4–6 doses or <sup>b</sup> ceftriaxone 2 g/24 h IV or IM <sup>c</sup> as single dose both for 4 weeks plus gentamicin 3 mg/kg/24 h IV, divided into 2–3 doses for 2 weeks <sup>d</sup> , followed by ceftriaxone 2 g/24 h IV for additional 2 weeks<br>Vancomycin as single drug treatment for 4 weeks (dosage see above) |
| Regimen C resistance to penicillin; MIC >0.5 mg/l <sup>e</sup>                               |  |
|  | Treatment like IE due to enterococci   |

<sup>a</sup>Earlier classified as 'nutritionally variant streptococci' (NVS).

<sup>b</sup>Especially for patients allergic to penicillin.

<sup>c</sup>Intramuscular injections should be avoided during active IE; if unavoidable in selected patients with access problems divide into 2 doses and inject into a large muscle.

<sup>d</sup>2–3 mg/kg netilmicin once daily may be an alternative (peak serum level <16 mg/l).

<sup>e</sup>High level resistance (HLR) to penicillin or ceftriaxone (MIC >8 mg/l) and HLR to gentamicin (MIC >500 mg/l) or resistance to vancomycin or teicoplanin (MIC ≥4 mg/l) are rare among strains of streptococci. In such situations, extended susceptibility testing and a close cooperation with the clinical microbiologist are mandatory.

to use a single daily dose of 2 g ceftriaxone IV.<sup>182,184</sup> The 2 g dose can be administered as a rapid intravenous infusion. Intramuscular injection should be avoided if possible in IE patients. If intramuscular infections are unavoidable, it is recommended that no more than 1 g should be injected at one site<sup>185</sup> (see Table 4).

For the treatment of IE, it is also accepted that 30 mg/kg/day vancomycin can be administered IV divided into two doses, with the serum trough level maintained between 10–15 mg/l to ensure optimal efficacy<sup>131,180</sup> (see Table 4). The infusion time should not be less than 45 min in order to avoid side effects.

Teicoplanin is an alternative drug that might be used once daily to treat streptococcal IE. However, treatment has been associated with significant failure rates when the dosage was inadequate, as the steady state serum concentration may be achieved only after one week of teicoplanin administration.<sup>186</sup> To overcome these shortcomings, it is recommended to give 10 mg/kg IV twice daily for the first nine doses followed by 10 mg/kg/day IV as a single daily dose.<sup>185</sup>

#### Aminoglycosides

Infected vegetations represent a very particular environment; i.e., a high density of bacteria with reduced metabolic activity. Autoradiographic studies have demonstrated homogeneous distribution of aminoglyco-

sides into the vegetation.<sup>187</sup> However, investigations using an integrative computerized model in rabbits showed that supra-MBC concentrations of amikacin were achieved in the vegetations only with doses two to four times higher than those ordinarily recommended.<sup>188</sup> This finding supports a single high-dose administration of aminoglycosides. On the other hand, investigations in rabbits using simulated human serum values of amikacin administration once vs thrice daily found both regimens equally effective.<sup>189</sup> According to the design of these studies, the results are only valid for single drug therapy with an aminoglycoside, an uncommon treatment for IE. There are only two prospective comparative clinical investigations<sup>190,191</sup> for a once-daily dosing of aminoglycosides. Comparative investigations of divided doses thrice a day vs the same total dose given once daily in a rabbit model of enterococcal endocarditis demonstrate the superiority of thrice daily dosing regimens.<sup>192</sup> No differences were found between once versus thrice dosing in models of experimental *Abiotrophia adiacens*<sup>192</sup> and *Streptococcus sanguis* endocarditis.<sup>193</sup> An experimental model simulating human serum levels of ceftriaxone plus netilmicin<sup>194</sup> recommends a single dose regimen of the aminoglycoside. Generally, the experimental models in rabbits or rats make comparisons of different dosing regimens difficult because of the very short half-life of

**Table 5** A two-week treatment regimen or 1-2-week in-hospital treatment followed by an ambulatory treatment may be considered if all of the following conditions are met

- Streptococcal (non-enterococcal) isolates fully sensitive to penicillin (MIC  $\leq 0.1$  mg/l<sup>a</sup>) with infection of native valves, rapid (<7 days) response to antibiotic treatment
- Vegetations <10 mm on TEE
- No cardiovascular complications such as more than trivial valve regurgitation, heart failure, conduction abnormalities, sepsis or embolic events
- The patient's home situation is suitable for ambulatory therapy

<sup>a</sup>Patients who meet the above criteria but presenting with streptococcal isolates with reduced sensitivity (0.1 mg/l-0.5 mg/l) for penicillin G or ceftriaxone may also be considered candidates for home therapy. In this situation, following the 2-week penicillin plus gentamicin treatment regimen in hospital, an additional 2-week treatment with ceftriaxone 2 g/day IV (see Table 4) can be administered as home therapy.

these compounds in small animals.<sup>195</sup> The Task Force, therefore, can provide no clinical or experimental evidence to recommend a single or a divided dose regimen.<sup>182</sup> The recommendation of the British Society of Antimicrobial Chemotherapy of twice daily dosing of aminoglycosides is entirely speculative.<sup>180</sup> It seems, however, reasonable that the particular properties of the microbial environment in the vegetation with absence of phagocytic cells (focal agranulocytosis) and a high density of bacteria with reduced metabolic activity can explain the absence of a post-antibiotic effect (PAE) described in vivo<sup>196,197</sup> This observation supports a divided dose regimen of aminoglycosides.

#### Antibiotic treatment regimens

Penicillin, ceftriaxone, vancomycin or teicoplanin may be used for monotherapy of streptococcal IE<sup>190,198</sup> but these drugs have been used traditionally in combination with aminoglycoside antibiotics. Synergism of penicillin and aminoglycosides is well documented in vitro and vivo,<sup>199</sup> with gentamicin having shown the largest synergistic potential.<sup>200</sup> This synergistic high and rapid killing effect allows for a two-week treatment with penicillin or ceftriaxone in combination with gentamicin (see Table 5). Efficacy and safety of this treatment have been documented in clinical studies.<sup>190,199,201</sup> Tolerance, a phenomenon in which the MBC of the drug exceeds its minimal inhibitory concentration (MIC) 5-fold or more has never been shown to have any clinical relevance<sup>180</sup> so that routine determination of MBC is not recommended any longer.<sup>131</sup>

Table 4 lists different treatment regimens for streptococcal IE. It is important to recognize that a recent multicentre study has reported 56% of streptococcal isolates to be relatively penicillin-resistant (MIC >0.12 mg/l) and even in the 'low resistance area' of Europe, 44% of *S. mitis* are relatively resistant to penicillin.<sup>202</sup> The majority of these strains, however, present MICs between 0.1 and 0.5 mg/l<sup>182</sup> and can be treated successfully with a regimen similar to that used to treat IE due to strains

highly susceptible to penicillin.<sup>203</sup> Thus, treatment with penicillin for 4 weeks combined with gentamicin for the first two weeks can be considered safe.<sup>198</sup>

Treatment recommendations for streptococcal IE are based on consistent results of a large number of studies. Therefore, these are class I recommendations based on level B evidence.

#### Home and outpatient treatment

'Ambulatory treatment' refers to a healthcare setting in which the patient attends an institution where antibiotics are injected (outpatient treatment) and then returns home. The term 'non-inpatient' refers to a patient who receives his injection at home, e.g., by a visiting nurse, at the general practitioner's office, or by self-administration.<sup>204</sup> The term 'outpatient and home parenteral antibiotic therapy' (OHPAT) has been suggested to cover all these aforementioned settings.<sup>205</sup> The use of parenteral antibiotics outside the hospital has been established in the U.S. for more than 20 years, but is a relatively new practice in Europe.<sup>206</sup> There is no prospective study comparing inpatient treatment to partial or total OHPAT for IE, but several studies have shown that selected patients may be safely treated at home.<sup>206</sup>

The Task Force recommends that all patients with IE should be admitted to hospital for evaluation by a multidisciplinary expert team, and should be treated for at least 1–2 weeks in hospital and observed for cardiac and non-cardiac complications, especially embolic events. The incidence of embolic complications falls rapidly during the first week of antimicrobial treatment. Manifestation of the first emboli is unusual after two weeks of optimal treatment.<sup>44,207</sup>

A significant proportion of patients with IE could be candidates for OHPAT, but this approach needs to be carefully assessed by proper clinical studies. Conditions for the OHPAT should be outlined for each healthcare system.<sup>205</sup>

#### Antibiotic treatment of staphylococcal endocarditis

Staphylococcal IE is a particularly severe, life-threatening infection, responsible for about one-third of all IE cases.<sup>208</sup> Early start of adequate antibiotic treatment is the key to improve the overall prognosis. 90% of cases are due to *S. aureus*, the remaining 10% to coagulase-negative staphylococcal species (CONS), of which *S. lugdunensis* causes particularly severe clinical courses.<sup>209–213</sup> IE due to *S. aureus* in non-addicts involves predominantly left-sided cardiac valves. More than 75% of early PVE cases are due to CONS species, particularly methicillin-resistant *S. epidermidis* strains.<sup>214</sup> PVE identified later than 12 months after valve replacement (late PVE) is caused by *S. aureus* and CONS in about 25% each. Most of these organisms are community-acquired and usually susceptible to methicillin.



**Table 6** Decision-making for antibiotic treatment of IE due to staphylococci

|   |   |
|---|---|
| Regimen A Native valve endocarditis   |   |
| MSSA <sup>a</sup> no allergy to penicillin                                    | Oxacillin <sup>b</sup> 8–12 g/24 h IV, divided into 4 doses for at least 4 weeks <sup>c</sup> plus gentamicin 3 mg/kg/24 h IV (maximum 240 mg/d), divided into 3 doses for the first 3–5 days of treatment                                      |
| MSSA <sup>a</sup> ‘allergy’ to penicillin <sup>d</sup>                        | Vancomycin 30 mg/kg/24 h IV divided into 2 doses <sup>e</sup> for 4–6 weeks <sup>f</sup> , plus gentamicin 3 mg/kg/24 h IV (maximum 240 mg/d) divided into 3 doses for the first 3–5 days of treatment  |
| MRSA <sup>g</sup>   | Vancomycin 30 mg/kg/24 h IV divided into 2 doses <sup>e</sup> for 6 weeks   |
| Regimen B Endocarditis involving prosthetic material/cardiac valve prostheses |   |
| MSSA <sup>a</sup>   | Oxacillin <sup>b</sup> 8–12 g/24 h IV, divided into 4 doses plus rifampicin 900 mg/24 h IV divided into 3 doses, both for 6–8 weeks, plus gentamicin 3 mg/kg/24 h IV (maximum 240 mg/d) divided into 3 doses for the first 2 weeks of treatment |
| MRSA <sup>g</sup> , CONS <sup>h</sup>   | Vancomycin 30 mg/kg/24 h IV divided into 2 doses <sup>e</sup> for 6 weeks, plus rifampicin 300 mg/24 h IV divided into 3 doses, plus gentamicin <sup>i</sup> 3 mg/kg/24 h IV (maximum 240 mg/d) divided into 3 doses, all for 6–8 weeks         |

<sup>a</sup>Methicillin-susceptible *Staphylococcus aureus*.

<sup>b</sup>Or its congeners.

<sup>c</sup>Except for drug addicts for whom a two-week regimen may be sufficient (see Section Treatment and management of infective endocarditis (IE) in intravenous drug abusers (IVDA)).

<sup>d</sup>For both, immediate (IgE) type and hypersensitivity reaction during treatment.

<sup>e</sup>Infusion over at least 60 min.

<sup>f</sup>Total treatment duration for patients initially treated with oxacillin should be at least 4 weeks. These patients should not have a second course of gentamicin treatment.

<sup>g</sup>Methicillin-resistant *S. aureus*.

<sup>h</sup>Coagulase-negative staphylococci. In oxacillin-susceptible CONS vancomycin should be replaced by oxacillin.

<sup>i</sup>If gentamicin susceptibility has been shown in vitro, gentamicin is added in MRSA for the full course but for CONS only for the first two weeks of treatment. If the organism is resistant to all aminoglycosides, gentamicin may be substituted by a fluoroquinolone.

### Staphylococcal endocarditis not associated with prosthetic material

At the present time, less than 10% of *S. aureus* strains that cause IE are susceptible to penicillin. *S. aureus* strains causing community-acquired IE are usually penicillin-resistant but susceptible to methicillin (MSSA). Treatment of choice is a penicillinase-resistant penicillin (oxacillin or its congeners) at a dosage of 2 g IV as a bolus every 6 h for at least 4 weeks<sup>215,216</sup> (Table 6).

In patients with the antecedent of immediate type (IgE-type) hypersensitivity to penicillin, any beta-lactam antibiotic should be avoided. In these cases, the antibiotic of choice is vancomycin (see Table 6). In vitro and clinical studies have shown that the bactericidal activity of vancomycin against *S. aureus* is less than that of penicillinase-resistant penicillins. Therefore, the use of vancomycin should be restricted to MSSA-IE with IgE-type allergy.<sup>180,217–219</sup> In obese patients, vancomycin dosage should be adjusted to ideal body weight. The use of vancomycin requires monitoring of plasma levels to adjust the dosage (see Section Drug level monitoring).

In clinical studies it has been shown that combinations with gentamicin are associated with faster clearing of bacteraemia, which may reduce valve damage and prevent abscess formation.<sup>220</sup> There is thus consensus to combine oxacillin (or vancomycin if appropriate) with gentamicin for the first 3–5 days of treatment.<sup>180,219</sup> Gentamicin at a dosage of 3 mg/kg every 8 h (maximum 240 mg/day) should be administered as intravenous bolus injection after oxacillin (or vancomycin) has been given.

IE caused by methicillin-resistant *S. aureus* (MRSA) is a therapeutic challenge as the number of effective anti-

biotics is small. As most MRSA strains are also resistant to most aminoglycosides, the addition of gentamicin is not likely to change the course or the prognosis of the infection. Rifampicin is not indicated in uncomplicated NVE.<sup>221</sup> If the clinical course is complicated (e.g., by intracardiac abscesses or uncontrolled local infection) treatment should be as for PVE (see Section Staphylococcal endocarditis in patients with intracardiac prosthetic material).

The treatment of NVE caused by coagulase-negative staphylococcal species (CONS) is based on the susceptibility of the infecting organisms to  $\beta$ -lactam antibiotics. In community-acquired infections, most strains are susceptible to methicillin, while hospital-acquired strains are often resistant to methicillin and to all beta-lactam antibiotics in more than 50% of cases.<sup>222,223</sup> In any case, it is extremely important to detect heteroresistance of CONS strains to beta-lactam antibiotics. NVE caused by CONS can be treated following the same therapeutic algorithm given for *S. aureus* infections (see Table 6).

Despite the lack of randomized studies and thus level A evidence, the scientific material available is convincing and allows for a class I recommendation regarding antibiotic treatment of staphylococcal IE.

### Staphylococcal endocarditis in patients with intracardiac prosthetic material

Prosthetic valve endocarditis (PVE) and infections involving other prosthetic material that are caused by *S. aureus* have a high mortality.<sup>214</sup> Although there are no convincing in vitro or clinical studies, a penicillinase-resistant penicillin is used for 6–8 weeks, combined with rifampicin throughout the treatment period and with

**Table 7** Decision-making for antibiotic treatment of IE due to enterococci and penicillin-resistant streptococci

|   |  |
|---|--|
| Penicillin MIC $\leq$ 8 mg/l and gentamicin MIC $<$ 500 mg/l  | Penicillin G, 16–20 million units in 4–6 divided doses plus gentamicin 3 mg/kg, IV, divided in 2 doses for 4 weeks                     |
| Penicillin-allergic patients and penicillin/gentamicin susceptible enterococcal isolate               | Vancomycin 30 mg/kg/day IV in two divided doses plus gentamicin (dosage as above) for 6 weeks  |
| Penicillin-resistant strains (MIC $>$ 8 mg/l) <sup>a</sup>  | Vancomycin plus gentamicin (dosage as above) for 6 weeks   |
| Strains resistant or less susceptible (MIC 4–16 mg/l) to vancomycin or highly resistant to gentamicin | Assistance of an experienced microbiologist is mandatory. If antimicrobial therapy fails, valve replacement should be considered early |

<sup>a</sup>For resistant enterococci treatment with oxazolidinone may be an option but should be initiated only after advice from a reference centre has been taken.

gentamicin during the first 2 weeks<sup>180,224</sup> to treat these infections. Due to the poor prognosis even with combined antimicrobial therapy, surgery should be considered early (see Section Surgery for active PVE). Patients with PVE caused by MRSA should be treated for 6–8 weeks with a combination of vancomycin, rifampicin and gentamicin, as long as susceptibility has been demonstrated in vitro (see Table 6). This is a class IIa recommendation based on level B evidence.

CONS species causing PVE within the first year after valve replacement are usually methicillin-resistant. Up to 30% of such strains may also be resistant to aminoglycosides while all strains so far have been susceptible to vancomycin.<sup>225</sup> The optimal therapy for PVE based on the results of experimental models and clinical studies is a combination of vancomycin and rifampicin for at least 6 weeks with the addition of gentamicin for the initial 2 weeks.<sup>225</sup> If the causative organism is resistant to all aminoglycosides, they can be replaced by a fluoroquinolone.<sup>226</sup> Early PVE caused by CONS is usually associated with perivalvular and myocardial abscesses and often with valve ring dehiscence so that valve re-operation is usually mandatory during the first weeks.<sup>225,227,228</sup> In cases where the infection is due to CONS strains susceptible to methicillin, it is recommended to use oxacillin or one of its congeners instead of vancomycin.

### Antibiotic treatment for IE due to enterococci and penicillin-resistant streptococci

Currently there are at least 20 species within the genus *Enterococcus*. *E. faecalis* is the most frequent species causing IE (approx. 90%) followed by *E. faecium*. Unlike streptococci, enterococci are generally resistant to a wide range of antimicrobial agents including most cephalosporins, antistaphylococcal penicillins, clindamycin, and macrolides. The clinical efficacy of trimethoprim-sulfamethoxazol and the newer quinolones is controversial.

Enterococci are also relatively resistant to aminoglycosides (MIC for gentamicin 4–64 mg/l), however, when combined with  $\beta$ -lactam antibiotics, there is a synergistic killing effect.<sup>229</sup> The classical combinations of penicillin and streptomycin, later penicillin and gentamicin have therefore been successfully used for the treatment of enterococcal IE caused by strains susceptible to these

antibiotics. However, strains that are resistant to penicillin or ampicillin or highly resistant to aminoglycosides (gentamicin MIC  $\geq$ 500 mg/l, streptomycin MIC  $\geq$ 2000 mg/l) are no longer susceptible to synergistic killing by these combinations.<sup>229</sup>

Although the bactericidal activity of ampicillin is twofold greater than that of penicillin against *E. faecalis*, penicillin is recommended to be part of the treatment because higher serum concentrations of penicillin will compensate for this difference and because it is important to avoid ampicillin rash during long-term treatment.

Enterococci with a high-level resistance to gentamicin (MIC for gentamicin  $>$ 500 mg/l) are also resistant to all other aminoglycosides, except perhaps streptomycin, for which independent testing has to be done. On the other hand, gentamicin susceptibility does not imply susceptibility to other aminoglycosides.

Glycopeptide antibiotics are usually not bactericidal against enterococci, therefore, a combination therapy with aminoglycosides is mandatory. Resistance to vancomycin has been recognized with increasing frequency.

Strains highly resistant to vancomycin (*van A* type resistance) are also resistant to teicoplanin. Both are then useless for treatment. In these cases, assistance of an expert in clinical microbiology is necessary (see Table 7).

Duration of treatment should be at least 4 weeks for the combination and at least 6 weeks in complicated cases, in patients having symptoms for more than 3 months, and in PVE.<sup>182</sup>

These are class IIa recommendations based on level B evidence.

### Antibiotic treatment of IE due to other microorganisms

#### IE caused by gram-negative organisms

About 10% of NVE and up to 15% of PVE cases, especially those occurring within one year after valve surgery, are caused by gram-negative bacteria. Among these species, enterobacteriaceae, *Pseudomonas* species and organisms of the HACEK group (species of *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella*) are more commonly associated with IE.<sup>230</sup>

Enterobacteriaceae species most often associated with IE are *Escherichia coli*, *Klebsiella spp.*, *Enterobacter*

*spp.* and *Serratia spp.* As susceptibility of these microorganisms is unpredictable, treatment must be based on susceptibility testing. Initial treatment is usually with a  $\beta$ -lactam antibiotic at high doses plus gentamicin, 3 mg/kg/day divided into 2–3 doses for 4–6 weeks.

Treatment of IE due to *P. aeruginosa* is based on the results of in vitro susceptibility studies. The combination of high doses of a  $\beta$ -lactam antibiotic with antipseudomonas activity and tobramycin (3 mg/kg/day divided into 2–3 doses) for 6 weeks is considered the most adequate initial antibiotic treatment. It has been shown that the best therapeutic effect is obtained with peak tobramycin serum concentrations of 12 mg/l or higher.<sup>231,232</sup>

For empiric treatment decisions, HACEK group organisms causing IE should be considered ampicillin-resistant and the treatment of choice should be a third-generation cephalosporin, such as ceftriaxone 2 g/day IV in a single dose given for 3–4 weeks in NVE and for 6 weeks in PVE. Ceftriaxone has an excellent pharmacokinetic profile with a long half-life, thus a single daily dose is justified. If susceptibility to ampicillin has been demonstrated, ampicillin can be given (up to 12 g/day divided into 3–4 doses) in combination with gentamicin (3 mg/kg/day divided into 2–3 doses).<sup>224,233</sup> Aminopenicillins and semi-synthetic penicillins generally have a longer half-life in blood than penicillin and can thus be administered safely three to four times daily.

Other gram-negative bacteria identified as causative organisms of IE (for microbiological diagnosis, see Section Culture-negative endocarditis) should always be treated in close cooperation with an experienced microbiologist.

For IE due to *Coxiella burnetii*, the causative agent of Q fever, the drug of choice is doxycycline, 100 mg i.v. every 12 h in combination with rifampin. The combination of tetracyclines and fluoroquinolones has proven effective in clinical studies.<sup>234</sup> In most patients, valve replacement is required to prevent relapses. As coxiellae are intracellular organisms, antimicrobial therapy should be maintained postoperatively for a period of at least one year, or even life-long.

These class IIa recommendations are based on level B evidence.

### Fungal IE

The number of fungal IE, of which 75% are due to *Candida species*, has increased in recent years in association with a greater number of immunologically compromised patients, the high prevalence of parenteral narcotic addiction, the increased rate of cardiac surgery, and the frequent use of wide-spectrum antibiotics and parenteral nutrition in hospitalised patients.<sup>235</sup> Due to the high mortality on treatment with antimycotic agents alone and the decreasing perioperative mortality in surgery for active IE, surgery is the primary option.

Amphotericin B or the less toxic ambisome preparation are the drugs of choice for the treatment of fungal IE, with a daily dose of 1 mg/kg. A continuous infusion may help to prevent side effects, e.g., therapy-associated fever. Combination with 5-fluorocytosine has a

synergistic effect in vitro, although it has not been demonstrated that the combination is more effective in vivo than amphotericin alone.<sup>236</sup> To control the infection, surgery is necessary in almost all cases.<sup>236,237</sup>

These class IIa recommendations are based on level B evidence.

### Drug level monitoring

The initial choice of antibiotics is usually empirical, while the definite treatment should be based on minimal inhibitory concentration (MIC) testing.

Routine monitoring of the serum level of  $\beta$ -lactam antibiotics is not necessary, because it will be possible to achieve high peak concentrations of these drugs with standard dosing regimens. Generally, their bactericidal effect will not increase with increasing peak concentrations but is directly correlated with the time period above the MIC. Penicillin G should be given in at least four doses, as the initial high peak concentration will rapidly decrease (half life of penicillin is 20–30 min). In patients with severe renal failure, the half-life of penicillin may be considerably prolonged. Therefore, adjustment of doses according to creatinine clearance is required. A higher dose of penicillin G should be given in younger patients with higher glomerular filtration rates and in IE due to enterococci (see Table 7), because these bacteria are tolerant to the killing effect of penicillin and the MIC is 1–50 times higher than for the viridans group of streptococci.

Drug level monitoring during aminoglycoside therapy is recommended. Gentamicin trough levels should be less than 0.1 mg/l to avoid renal or ototoxic effects.

Optimum vancomycin effects are achieved if serum concentrations are continuously kept at least 2–4 times above the MIC of the causative organism. Trough levels should be at least 10–15 mg/l. In patients with normal renal function, the drug level should be controlled once, but 2–3 times weekly if a combination with aminoglycosides is used. In patients with impaired renal function, monitoring may be necessary 2–3 times a week or even daily.

Teicoplanin is an alternative glycopeptide that can be administered once daily. However, to achieve an optimum killing effect, it has been shown that loading doses twice daily for 4–5 days (9 doses) are necessary (see Section Penicillin, ceftriaxone, vancomycin and teicoplanin).<sup>182</sup>

For rifampicin, drug level monitoring is not necessary if standard dosage regimens are used, as this drug is excreted mainly by the hepatic route. Dose reduction or termination of treatment should be considered if hepatic function deteriorates.

### Treatment under special circumstances

#### Culture-negative endocarditis (CNE)

Before treatment is started in CNE cases, the diagnostic strategy as outlined (see Section Diagnostic approach in suspected but unproven IE) should have been employed and the history of the patient (e.g., intravenous drug

**Table 8** Empirical antimicrobial therapy in CNE of native (NVE) or prosthetic cardiac valves (PVE)

| NVE         |   |  |           |
|-------------|---|--|-----------|
| Vancomycin  | 15.0 mg/kg i.v. every 12 h <sup>a,b</sup> |  | 4–6 weeks |
| +Gentamicin | 1.0 mg/kg i.v. every 8 h                  |  | 2 weeks   |
| PVE         |   |  |           |
| Vancomycin  | 15.0 mg/kg i.v. every 12 h                |  | 4–6 weeks |
| +Rifampicin | 300–450 p.o. every 8 h                    |  | 4–6 weeks |
| +Gentamicin | 1.0 mg/kg i.v. every 8 h                  |  | 2 weeks   |

<sup>a</sup>Maximum 2 g/d; for drug level monitoring.

<sup>b</sup>Aminopenicillin may be added.

abuse, previous valve implantation, area with a high prevalence of MRSA) reviewed in order to focus on more likely organisms responsible for a particular type of IE (see Sections Treatment and management of IE in IVDA and Pregnancy). Finally, it should be noted whether the patient has been on prior antimicrobial treatment.

Unless IE due to *Bartonella spp.*, *Chlamydia spp.*, *Coxiella spp.*, *Legionella spp.*, *Nocardia spp.*, or fungi is suspected, the scheme based on clinical experience and listed in Table 8 appears most useful (class IIa recommendation) at the present time.

#### Endocarditis after intracardiac implantation of foreign material

Infections of intracardiac foreign material may occur early or late after implantation, which is a key issue defining aetiology, clinical presentation, treatment, and prognosis.

##### Prosthetic valve endocarditis (PVE)

Coagulase-negative staphylococci (CONS) are the most frequent infecting organisms in early PVE, followed by *S. aureus* and enterococci.<sup>238</sup> The microbiology of late PVE does not differ much from that of native valve endocarditis.<sup>5,239</sup> Routine antimicrobial perioperative prophylaxis has significantly contributed to the declining frequency of early PVE in recent years<sup>5,214,240</sup> while recent efforts to further reduce the incidence of PVE by silver impregnation of the sewing ring of mechanical heart valves have failed.<sup>241</sup>

Early recognition of PVE is essential as the appropriate medical and surgical therapy improves clinical outcome significantly.<sup>242</sup> The principles of antimicrobial therapy for PVE are basically the same as those for NVE. However, therapy should be prolonged for up to six weeks. Special considerations to treat PVE have been outlined in Sections Antibiotic treatment of streptococcal endocarditis and Antibiotic treatment of IE due to other Microorganisms.

After two-week in-hospital initiation of therapy, home treatment may be considered for special cases only (see Section Home and outpatient treatment). Treatment of PVE may be particularly difficult as the special environment may prevent microorganisms from being cleared by antibiotics.<sup>40,41,243</sup> CONS strains may

produce extracellular slime, which inhibits host-defence mechanisms and protects bacteria from being killed.<sup>40</sup>

##### Infection of other intracardiac foreign material

The hallmarks of permanent pacemaker or cardioverter-defibrillators infections (PPMI) are fever and continuous bacteraemia. These infections may be located either in the subcutaneous or intravascular portion or in both.<sup>244</sup> An endovascularitis with bacterial vegetations can be found on the mural endocardium, at the electrode tip, in the right heart, on the tricuspid valve, or anywhere from the subclavian vein to the superior vena cava. TEE is often helpful in identifying lead-associated vegetations. *S. aureus* is the prevailing microorganism (50%), with CONS accounting for another 25%.<sup>245,246</sup> Other organisms include gram-negative bacteria, fungi, and enterococci.<sup>245,247</sup> *S. aureus* is predominant in PPMI occurring in the first 12 months after implantation. In large series of PPMI, usually less than 10% of *S. epidermidis* isolates have been resistant to methicillin. This finding suggests that PPMI is likely to originate during the implantation procedure itself, with a long latent period before overt clinical manifestation.<sup>245,248</sup>

Antimicrobial therapy for PPMI should be individualized and based on culture and susceptibility results if possible. Duration of therapy should be 4–6 weeks in most cases. Management of patients with PPMI remains controversial because of a lack of prospective studies comparing the use of antibiotics alone with a combination of intensive antibiotic therapy and removal of leads and aggregates.<sup>249</sup> Removal of the entire system is generally recommended although it has been suggested that the need for removal of electrode leads may be related to the organism involved, with conservative therapy more likely to be successful in CONS cases.<sup>249,250</sup>

These class IIb recommendations are based on level C evidence.

In this respect, removal of the infected system may be followed by a period of temporary pacing before a new pacemaker is implanted (two-stage), or re-implantation may be performed during the same setting (one-stage).<sup>250,251</sup> If a one-stage procedure is used, a new transvenous system is usually implanted on the contralateral side. In severe infections and in patients who urgently need a pacemaker, a switch to epicardial pacing may be considered.

Little definite information has been available regarding optimal management of infections of ventricular assist devices (VAD).<sup>252–254</sup> Both ultrasound and CT imaging have been used to delineate the area around the device, but the specificity and sensitivity of the findings are not well established. Subsequent cardiac transplantation has been successful in single cases.<sup>242,255</sup>

VAD-related bacteraemias represent the most challenging infection because VAD removal is usually not a viable alternative in the absence of concurrent transplantation. As with PVE, a minimum of 6 weeks of bactericidal doses of antimicrobial therapy has been suggested. Heart transplantation prior to the completion of treatment may be performed if blood cultures become sterile and a donor heart is available.<sup>256</sup>

### Treatment and management of infective endocarditis (IE) in intravenous drug abusers (IVDA)

Parenteral drug addiction including intravenous heroin abuse involves about 750 000 people in Europe. IE is one of the most severe complications in IVDA and i.v. drug addiction one of the most important causes for (often recurrent) IE in some urban medical centres.<sup>257,258</sup>

Methicillin-susceptible *S. aureus* (MSSA) is the causative organism in about 60–70% of cases.<sup>259</sup> Other organisms are streptococci and enterococci (15–20%), *P. aeruginosa*, *S. marcescens*, other gram-negative rods (<10%), and *Candida* spp. (<2%). Polymicrobial IE (about 5%) and CNE are reported in about 5–10% of cases.<sup>257–259</sup> The tricuspid valve is most frequently affected (more than 70%) followed by left-sided valves, while infection of the pulmonary valve is extremely rare (<1%).<sup>257,258</sup> Left and right-sided valves may be simultaneously affected in 5–10% of cases. Most of these patients have no predisposing cardiac disease.

The characteristic lesion in IVDA is tricuspid valve IE due to *S. aureus*. In this setting two important features have to be recognized: (a), the amount of bacteria in tricuspid valve vegetations is much smaller than in those attached to the mitral or the aortic valves,<sup>260,27</sup> and (b), the prognosis of right-sided IE is favourable (surgery necessary in less than 2%, mortality lower than 5%).<sup>257,258</sup>

#### Empiric antimicrobial therapy

On admission, the decision for empiric therapy depends on the suspected microorganisms, the type of drug and solvent used by the addict, and the side of the heart involved.<sup>257,258</sup> The most common organism (*S. aureus*) must always be covered. Treatment will include either penicillinase-resistant penicillins or vancomycin, depending on the local prevalence of MRSA.<sup>261,262</sup> If the patient is a pentazocine addict, an antipseudomonas agent should be added.<sup>263</sup> If IVDA use brown heroin dissolved in lemon juice, *Candida* spp. (not *C. albicans*) should be considered and antifungal treatment added.<sup>264</sup> On the other hand, in IVDA with underlying valve lesions and/or left-sided involvement, antibiotic treatment against streptococci and enterococci must be added.<sup>257,258</sup> Once the causative organisms have been isolated, therapy has to be adjusted.

#### Specific antimicrobial treatment

The standard therapy for IE due to MSSA is also used in drug addicts, but there are data indicating that a two-week treatment may be sufficient.<sup>265</sup> The standard 4–6-week regimen, however, must be used in the following situations: (a), slow clinical or microbiological response (>96 h) to antibiotic therapy,<sup>266,267</sup> (b), right-sided IE complicated by right heart failure, vegetations larger than 20 mm, acute respiratory failure, septic metastatic foci outside the lungs (including empyema), or extracardiac complications like acute renal failure,<sup>266–268</sup> (c), therapy with antibiotics other than penicillinase-resistant penicillins,<sup>218,265,267,269</sup> (d), IVDA with severe immunosuppression (<200 CD4 cells/ $\mu$ l) with or without AIDS.<sup>270,271</sup>

Right-sided *S. aureus* IE in IVDA may be successfully treated with ciprofloxacin plus rifampicin given by the

oral route<sup>272</sup> provided that the compliance of the patient is monitored carefully. For organisms other than MSSA, therapy in IVDA does not differ from that in non-addicts.<sup>180,266,182</sup>

#### Surgical therapy

The indication for surgery and the perioperative approach are the same as in non-addicts but should be more conservative because IVDA have a much higher incidence of recurrence,<sup>2,259</sup> most likely due to continued i.v. drug abuse. For this reason, the surgical indication and the type of surgery should follow special considerations in order to avoid the development of PVE if drug abuse is continued.

There are two main indications for surgery (class IIa recommendations):

- a IE caused by microorganisms difficult to eradicate (e.g., persistence of fungi), or bacteraemia for at least seven days (e.g. *S. aureus*, *P. aeruginosa*) despite adequate antimicrobial therapy;<sup>2</sup>
- b tricuspid valve vegetations larger than 20 mm persistent after recurrent pulmonary emboli with or without concomitant right heart failure.<sup>268</sup>

#### Influence of HIV-1 infection on the therapy of IE in IVDA

Currently, the prevalence of HIV-1 infection among IVDA with IE ranges from 40 to 90%.<sup>270–274</sup> Although the full consequences of HIV infection in the medical and surgical therapy of IE in IVDA are not yet fully known, conclusions from published data are: (a), a two-week course of antimicrobial therapy is not suitable; (b), cardiac surgery in HIV-infected IVDA with IE worsens neither the prognosis of IE nor of HIV.<sup>275,276</sup>

#### Pregnancy

During pregnancy cardiac output increases and left ventricular afterload and colloid osmotic pressure decrease.<sup>277</sup> The hyperdynamic circulation frequently results in innocent systolic murmurs and/or a wide-split second heart sound.<sup>278</sup> Corrected congenital heart disease or undiscovered lesions may become symptomatic again or for the first time.

Due to the physiologic afterload reduction and/or the increased heart rate, acute left-sided valve regurgitation is usually better tolerated during pregnancy, while the decrease in serum colloid-osmotic pressure may aggravate pulmonary congestion and predispose to pulmonary oedema.<sup>278</sup> Right-sided valve regurgitation, on the other hand, is aggravated by the increased blood volume. Diuretics may be used to reduce blood volume and venous hypertension. If required (see Section Prevention of embolic complications), treatment with non-fractionated or low molecular weight heparins is possible during pregnancy,<sup>219,279</sup> but not recommended if prosthetic valves have been implanted.

Antimicrobial treatment decisions for pregnant women have to consider the altered pharmacokinetics. Because of the hyperdynamic state, effective renal plasma flow, glomerular filtration rates, creatinine clearance and the corresponding renal drug clearance are increased by approx. 50%,<sup>280</sup> while hepatic drug metabolism may increase, decrease, or remain unchanged.<sup>281</sup>

Most of the first choice antibiotics to treat IE are safe and effective in pregnant women. Penicillin, ampicillin, amoxicillin, and flucloxacillin have been widely used without maternal or fetal complications.<sup>282</sup> Although there are no large prospective studies using cephalosporins during pregnancy, embryotoxic effects have not been reported so far.<sup>283</sup> Macrolides have been prescribed during pregnancy without reported teratogenicity or fetal side effects. Aminoglycosides should be used in special indications only because of the potential risk of eighth cranial nerve toxicity in the fetus.<sup>284</sup> No teratogenic effects have been observed during treatment with imipenem or rifampicin.<sup>284</sup> For vancomycin, the potential for fetal ototoxicity and nephrotoxicity is discussed controversially. With standard doses and drug monitoring, the fetal risk seems not to be increased.<sup>285</sup> Quinolones are contraindicated during pregnancy.<sup>284</sup>

Major experience with antifungal drugs has been gathered for amphotericin B. Teratogenic effects have not been attributed to this agent,<sup>286</sup> while for fluconazole, a dose-dependent teratogenic effect (grossly dysmorphic infants) has been described; less than 150 mg/d seem to be safe.<sup>286,287</sup> For IE during pregnancy, consultation of an expert or a reference centre is strongly advised before antimicrobial treatment is started.

Cardiac surgery during pregnancy is possible, but remains a difficult and complex undertaking. Despite cardiopulmonary bypass techniques that provide warm perfusion temperatures and high flow rates, there is a residual risk of fetal distress, growth retardation, and fetal death. In borderline indications, surgical intervention should be postponed until the fetus is viable and heart surgery and Caesarean section can eventually be performed as concomitant procedures.<sup>219</sup> In cases with clear-cut indications for surgery, the intervention should be performed in the most experienced centre to which the woman can safely be transferred.

There is no absolute indication for termination of pregnancy in active IE. In cases with heart failure due to acute valve insufficiency, haemodynamic improvement cannot be expected by termination of pregnancy alone. With the exception of ACE-inhibitor treatment,<sup>288</sup> none of the pharmacological or surgical options available to treat heart failure need to be withheld from a pregnant woman, even though some carry an increased risk for the fetus. In critical cases, the decision will have to be evaluated and discussed individually with each patient.

### Clinical disease monitoring and assessment of therapeutic efficacy

Following the diagnosis of IE and the identification of the causative microorganism appropriate antibiotic treatment is initiated. In this phase of the disease careful observation of the patient with clinical and laboratory controls is essential to follow the evolution and to assess the efficacy of the antibiotic regimen. Follow-up consists of daily bedside examination, measurements of body temperature, and periodic blood tests to monitor signs of infection and to survey the renal function. In case of

**Table 9** Possible causes of persisting fever<sup>a</sup> in patients with IE

- Cardiac complications  
Inadequate antimicrobial therapy, paravalvular and/or myocardial abscess, large vegetations, pericarditis/myocarditis (often due to coronary emboli)
- Renal complications  
Glomerulonephritis, bacteruria
- Neurological complications  
Cerebral emboli, mycotic aneurysms, meningitis
- Pulmonary complications  
Pulmonary emboli, exudative pleuritis
- Other embolic complications  
of spleen, joints, vertebrae
- Infected lines

<sup>a</sup>Differentiation to 'drug fever', which is a recurrent fever, may be difficult.

suspected infectious complications new blood cultures, (Holter) ECG and echocardiography are also essential.

Repeated clinical examinations are performed to look for changes in cardiac murmurs, blood pressure, signs of cardiac failure, and embolic phenomena in the CNS, lungs, spleen and skin. Secondary metastatic infections in joints and spine may also occur. It is important to remember that cardiac and systemic complications often arise during the first days after the beginning of a microbiologically adequate antibiotic treatment. In patients with pleural rub or effusion and flank pain, splenic abscesses should be suspected. Patients at special risk should have regular abdominal ultrasound examinations and eventually CT/MRT scans. Ophthalmic follow-up examinations to detect Roth spots should especially be considered in IE due to staphylococci and fungi.

Fever is a very useful and important criterion to follow the evolution of IE. In patients with an uncomplicated clinical course the temperature should normalize within 5 to 10 days.<sup>250,289</sup> In general, infections due to viridans streptococci respond faster to antibiotics than those caused by *S. aureus* or enterococci. Persistent fever beyond the first week often indicates the development of complications such as progressive valve destruction, extension of infection to the valve annulus, or the occurrence of a paravalvular abscess (Table 9). Septic emboli with localized infection can also be the reason for persisting fever.<sup>290</sup> Recurrent fever in patients with stable clinical and haemodynamic conditions following an afebrile period is most frequently observed during the third and fourth weeks of treatment. Recurrent fever is often due to adverse reactions to  $\beta$ -lactam antibiotics with or without accompanying skin rash.<sup>289</sup> However, cardiac complications, arthritis and septic systemic emboli may sometimes occur at a later stage.

Among the laboratory measures C-reactive protein (CRP) is the best criterion to judge therapeutic response. CRP values usually decrease rapidly during the first or second week, but may remain slightly elevated up to 4 to 6 weeks or longer.<sup>97,289,291</sup> A persistently high CRP should be interpreted as a sign of an inadequately controlled

infection with cardiac or other septic complications. In contrast to CRP the erythrocyte sedimentation rate (ESR) is not suitable for disease evaluation since high values may persist over several weeks despite a good therapeutic response.

The normalization of elevated white blood cell counts (WBC) can also be expected during the first 1 to 2 weeks. Persistently high WBC counts also indicate active infection. It is important to recognise that prolonged high dose treatment with  $\beta$ -lactam antibiotics may inhibit granulopoiesis and result in neutropaenia.<sup>292</sup> Platelet and erythrocyte count should also be monitored regularly.

Monitoring of renal function by repeated serum creatinine measurements is essential for early detection of renal dysfunction, which is a frequent complication of IE<sup>293</sup> or an adverse effect of the antibiotic therapy, especially with aminoglycosides and vancomycin.

Echocardiography is the most relevant examination if cardiac complications are suspected (see Section Echocardiology). Despite the use of potent antibiotics the incidence of valve destruction and/or paravalvular abscesses remains high.

Echocardiography is also necessary at the end of antibiotic therapy to document the site and extent of valvular damage. The final echocardiogram is invaluable for comparison during long term follow up and facilitates the recognition of a late relapse or reinfection.

## Management of complications

### Embolic events

Embolism may follow dislodgement of fragments of vegetations, infected tissue, or sterile/infected intracardiac thrombi. Although the true incidence is unknown, embolism is the most common and prognostically relevant complication of active IE, observed in 22–43% of cases,<sup>44,100,127,294,295</sup> with a higher prevalence of cerebral than peripheral/visceral manifestations.<sup>100,294–296</sup> Studies at necropsy have demonstrated an even higher incidence of major organ involvement including kidney (60%), spleen (44%), brain (40%), and coronary arteries (30%).<sup>65,297–299</sup> Splenic abscesses following embolisation of infected material are at special risk of rupture, thus abdominal computed tomography is indicated for monitoring splenic involvement.<sup>300</sup>

### Patients at risk for embolic events

The following variables are accepted to characterize patients on level B evidence who may have an increased risk for embolic complications:

- a Causative organism. Although there is no complete consensus, most published series report a 2–3 times higher frequency of embolic complications in IE due to enterococci, staphylococci, *Abiotrophia* spp., fastidious gram-negative bacteria (HACEK) and fungi when compared to streptococci.<sup>44,127,294</sup>
- b Morphologic features. The risk for embolic events is closely correlated with the demonstration of vegetations large enough to be detected by echocardiography.<sup>301,302</sup> The exact role of morphologic features, e.g., vegetation size, as predictors for embolic compli-

cations is controversial. Beside vegetation size, such features include mobility, consistency, and rapid growth of the vegetation.<sup>105</sup> Vegetation size of  $\geq 10$  mm, particularly if the native mitral valve is involved, mobility, and low density of vegetations at the initial echocardiography have been suggested to have prognostic implications.<sup>100,303–306</sup> More recent reports have not confirmed any role of either TTE or TEE in the prediction of the occurrence of embolic events,<sup>307</sup> however, size of  $\geq 15$  mm in any location identified by TEE has a definite predictive role for embolism.<sup>299</sup> The high rate of pulmonary embolism in right-sided endocarditis may be related, however, to the larger size of vegetations on the right than on the left side of the heart. Morphologic changes during successful treatment are not predictive of late events such as embolism.<sup>105</sup>

- c Duration since onset of the infection. The hazard for embolic events peaks at the beginning of IE, often before hospital admission,<sup>207</sup> and before or within the first two weeks of antimicrobial therapy.<sup>44,207,308</sup> Fifty percent of all embolic complications occur within 20 days, and 80% within 32 days after manifestation of initial symptoms of IE.<sup>207</sup>
- d Site of infection. A higher incidence of embolic complications has been observed in native mitral as compared to aortic valve IE.<sup>207,306,309</sup>

### Prevention of embolic complications

Rapid and effective antimicrobial treatment may help to prevent embolic complications. There is growing evidence that platelets play an important role in the development of vegetations.<sup>310</sup> In experimental *S. aureus* IE, acetylsalicylic acid has been found to reduce vegetation size, to improve antimicrobial sterilization,<sup>311</sup> and to reduce the frequency of embolic events.<sup>312,313</sup> IE, however, is still no indication to initiate antithrombotic therapy with heparins as long as there is no other indication (like prolonged bed rest, intensive care, disseminated intravascular coagulation or sepsis). If the patient is on long-term oral anticoagulation (e.g., for a mechanical valve prosthesis), coumarin therapy should be discontinued and replaced by standard heparin immediately after the diagnosis of IE has been established.<sup>212</sup> After the first manifestation of an embolic complication, the risk for recurrent episodes is high, especially if vegetations are still demonstrated by echocardiography and if the infection is still active.<sup>207</sup> In more than 50% of cases, recurrences are manifest within 30 days after the index episode.<sup>314</sup>

### Surgery after cerebral embolic events

After manifestation of a cerebral embolism, cardiac surgery to prevent a recurrent episode is not contraindicated if performed early (best within 72 h)<sup>207,300,315,316</sup> and cerebral haemorrhage has been excluded by cranial computed tomography (CCT) immediately before the operation. Although surgical results are best within the first 72 h of stroke, when the blood-brain barrier is not yet altered,<sup>207</sup> surgery should not be delayed in patients with focal deficits if it is indicated for severe heart failure,

ongoing sepsis or infection resistant to antibiotic therapy as long as CCT scans exclude a haemorrhagic lesion.<sup>316</sup>

These class B recommendations are based on class IIa evidence.

#### *Mitral kissing vegetation (MKV)*

Secondary vegetation of the mitral valve apparatus in primary aortic valve endocarditis is most frequently caused by large aortic vegetations prolapsing into the left ventricular outflow tract during diastole and contacting the ventricular aspect of the anterior mitral leaflet (MKV).<sup>117</sup> Early detection of MKV by serial TEE examination is an important additional aspect to indicate cardiac surgery, as timely surgery may favourably influence the morphologic and functional integrity of the mitral valve and, thus, long-term prognosis.<sup>117</sup>

#### **Management of pulmonary complications of right-sided endocarditis**

Clinical suspicion of right-sided IE should be raised in addicts and non-addicts by the presence of recurrent pulmonary emboli or multiple pulmonary infiltrates, anaemia, and micro-haematuria of unknown origin. A high index of suspicion of right-sided IE is raised in the case of an intravenous drug user or in patients with intracardiac devices or nosocomial bacteraemia with pulmonary infiltrates. A thorough review of records for evidence of prolonged intravenous lines or indwelling devices is necessary. Serial blood cultures and echocardiography are required.<sup>317,318</sup>

The prognosis of right-sided IE with pulmonary embolism is remarkably good.<sup>319</sup> Vegetations of <10 mm size generally respond well to antibiotic treatment.<sup>320</sup> One major difference in the management of embolism in left-sided as compared to right-sided IE is that anticoagulation treatment is not necessary in the latter.<sup>95</sup> Recurrent pulmonary infiltrates are no indication for cardiac surgery.<sup>321</sup> If fever persists for more than three weeks despite adequate antimicrobial therapy re-evaluation of possible reasons (e.g., pulmonary abscess) is indicated.<sup>321</sup>

#### **Cardiac failure**

##### *Acute valve regurgitation*

Surgical intervention should be performed in severe, acute mitral regurgitation.<sup>322,323</sup> If there has been a prolonged period of acute mitral regurgitation and the cardiac index has decreased to less than 1.5 l/min/m<sup>2</sup> and the ejection fraction to less than 35%, urgent surgical intervention usually will not improve the prognosis.<sup>322,324</sup> If there is no possibility for acute surgery, medical therapy may improve symptoms of congestive heart failure. After careful introduction of 0.5 µg/kg/min sodium nitroprusside or nitrates intravenously, the dosis should be increased stepwise until the systolic blood pressure decreases to about 90–95 mmHg. In cases with critical drop of the arterial blood pressure or of the cardiac index below 1.8 l/min/m<sup>2</sup>, dobutamine combined or not combined with dopamine should be added. If the haemodynamic situation cannot be influenced by medical therapy alone and prompt surgery cannot be performed, intraor-

tic balloon pumping can significantly improve left ventricular impedance and coronary perfusion.<sup>322</sup>

For patients with severe acute aortic regurgitation, urgent surgery is indicated, as soon as a lung oedema presents which cannot be resolved rapidly by conservative measures.<sup>325</sup> In initially less severe cases, medical therapy may be started if the patient's cardiac situation is constantly reevaluated. A heart rate of up to 120 bpm is a prerequisite to minimize the transaortic regurgitant fraction. Patients who fail to increase their heart rate should be considered for temporary pacemaker treatment, especially if they present with AV block.<sup>325</sup> Unlike acute mitral or aortic regurgitation, surgery is not indicated in acute tricuspid regurgitation.<sup>326</sup>

##### *Myocarditis*

Besides haemodynamic overload due to valve dysfunction, cardiac failure may be aggravated by myocarditis, which is a frequent finding at autopsy, sometimes along with myocardial abscesses. Moreover, small areas of myocardial necrosis and frank regional infarcts can be produced by coronary artery emboli. This may be a mechanism by which rupture of a papillary muscle develops in IE. Extensive myocardial involvement during active IE should prompt surgery.

##### **Acute renal failure**

Renal involvement and the occurrence of acute renal failure indicate a poor prognosis especially in patients with non-staphylococcal IE of native and prosthetic valves. This observation is important since non-staphylococcal (e.g., viridans streptococcal) IE otherwise has a better prognosis than staphylococcal IE.

The frequency of newly occurring renal impairment (creatinine >2 mg/dl) is high.<sup>293,327</sup> Rapidly progressive glomerulonephritis may be the first manifestation of previously unrecognized IE.<sup>328</sup> Certain microorganisms responsible for IE are more often linked with the occurrence of acute renal failure.<sup>329</sup>

The different types and causes of acute renal failure are:

- a Immune complex glomerulonephritis: probably the most frequent form of renal involvement. In addition to increased serum creatinine levels proteinuria and haematuria are usually present;
- b Renal failure due to haemodynamic instability in septic syndromes occurring alone or as part of multi-organ failure;
- c Antibiotic drug toxicity, mostly due to high dose and prolonged administration of aminoglycosides. For drug level measurements refer to Section Drug level monitoring. Vancomycin and even penicillins (hypersensitivity) are other possible factors in renal failure;
- d Postoperative renal failure: usually multifactorial requiring special attention in patients with surgically treated acute IE;
- e Renal infarcts and systemic emboli: often discovered at autopsy only.
- f Application of contrast media for radiological purposes: a further possible reason for renal failure.



Treatment of patients with acute renal failure is dependent on the overall clinical situation and stage of the disease. In severely septic and/or post-operative patients haemofiltration is usually necessary to overcome the critical period.<sup>330</sup> Fortunately, renal failure is reversible in most patients surviving the acute infection.

Prevention of renal impairment should be attempted by early diagnosis and appropriate choice of antibiotic therapy. Aminoglycosides should only be used if required for control of the bacterial infections or before the results of blood cultures are known. Drug dosage has to be carefully adjusted and monitored, especially if prolonged administration is necessary. If possible, contrast media for radiological investigations should be avoided.

### Arrhythmias and conduction disturbances

Arrhythmias are usually the consequence of septic dissemination (e.g., originating from concomitant myocarditis) or of an ischaemic injury of the myocardium following coronary embolism. Conduction disturbances (CD) are the result of damage to the conduction system due to direct infiltration (e.g., of the bundle of His,<sup>331</sup> or to embolism into nodal arteries).<sup>332,333</sup> Involvement of the specific conduction system is more frequent in PVE and native aortic valve IE than in NVE and native mitral valve IE.<sup>334,335</sup>

The onset of CD may signal perivalvular extension of the infection and indicate a worse prognosis.<sup>336</sup> ECG monitoring and (repeat) TEE evaluation for detection and follow-up of perivalvular extension are indicated.<sup>337</sup> Although CD are reversible with medical therapy alone in some cases, surgical intervention should be considered in all cases where CD are progressive, and in PVE if a perivalvular extension is demonstrable.<sup>127</sup>

Ventricular arrhythmias may indicate involvement of the myocardium and have a worse prognosis.<sup>333,338</sup> Drug treatment of arrhythmias does not differ from generally accepted clinical principles except that surgery should be considered whenever myocardial involvement or abscess formation have been demonstrated.

### Relapsing endocarditis

The term 'relapse' implies that, after initial improvement, clinical deterioration occurs and the same microorganism (molecular biology eventually necessary) is found in blood cultures, normally within weeks but sometimes as late as one year (in *Brucella* and Q fever endocarditis even later). For a possible documentation of most types of relapsing of IE, storage of endocarditis isolates for at least one year is mandatory. Proof of identical isolates should be based on genotyping methods. In IE due to rare microorganisms, new positive blood cultures, PCR, serology, or other methods to demonstrate persistence of an infection would be sufficient to prove relapse. Factors associated with an increased relapse rate are listed in Table 10. Relapses are most often due to insufficient length of treatment or a suboptimal choice of the initially used antibiotics, e.g., following suboptimal characterization of the infecting strain. Relapsing IE due to insufficient length of treatment should be retreated for 4–6 weeks with the same antimicrobial agent(s) unless resistance has developed in the

**Table 10** Factors associated with an increased relapse rate

- 'Difficult-to-treat microorganisms', e.g. *Brucella* spp., *Legionella* spp., *Chlamydia* spp., *Mycoplasma* spp., *Mycobacterium* spp., *Bartonella* spp., *Coxiella burnetii*, fungi
- 'Difficult-to-treat microorganisms' plus intracardiac foreign bodies
- Polymicrobial IVDA<sup>a</sup> endocarditis
- Empirical antimicrobial therapy for microbiologically negative endocarditis<sup>b</sup>

<sup>a</sup>IVDA=intravenous drug addict.

<sup>b</sup>Relapse of typical symptoms, IE confirmed by relevant clinical criteria, microorganism remaining speculative.

meantime. If the initial antibiotic choice was suboptimal, it should be corrected according to the causative organism and its susceptibility.<sup>339–342</sup>

Surgical treatment has to be considered in cases in which 'difficult-to-treat organisms' (Table 10) have been found and in patients with intracardiac devices/foreign bodies. For patients who are not candidates for surgical intervention, lifelong antimicrobial treatment might be necessary.<sup>343</sup>

## Surgery for active infective endocarditis

### Summary of indications for surgery

Surgery is mandatory in at least 30% of cases with active IE and in another 20–40% after healing.<sup>41,102,315,344–346</sup> Prognosis is better if surgery is performed before cardiac pathology develops and the general condition of the patient severely deteriorates<sup>119,315,345–348</sup> regardless of the duration of prior antibiotic therapy.<sup>349</sup> Age per se is no contraindication for surgery.

Indications for surgery should be based on a correct, careful clinical evaluation, microbiological test results, and on the information provided by (repeated) echocardiographic examinations.<sup>102,110,119,330,350</sup>

### Surgery for active NVE

Variables that should be considered are: (a), current haemodynamic status, recent deterioration of an acute valve regurgitation and severity of subsequent congestive heart failure; (b), persistence of infection/sepsis; (c), locally or generally uncontrolled infective processes; (d), microorganisms involved; (e), morphology of vegetations and embolic events; and (f), neurological complications. See Table 11.

a Congestive heart failure (CHF) is the most common indication for surgery.<sup>9,342,351–353</sup> Mortality of CHF due to acute aortic regurgitation has been dramatically reduced by surgery. There is no true alternative treatment option (see Section Acute valve regurgitation).

For acute mitral regurgitation, the indication for surgery is more complex as potent pharmacological options to influence left ventricular impedance and thus to reduce the transmitral regurgitant volume are available (for details of treatment options refer to Section Acute valve regurgitation).

b Persistent fever and demonstration of bacteraemia for more than 7–10 days despite adequate antimicrobial therapy indicate a failure of conservative management<sup>351</sup> and are associated with increased mortality.<sup>2,9,351,354,355</sup> In relapses due to multi-resistant or 'difficult-to-treat' microorganisms, surgery is also indicated. Although preoperative duration of antibiotic therapy does not influence operative mortality, adequate antibiotic coverage during the operation and postoperatively is essential. Even adequate antibiotic therapy should not postpone surgery. Surgery during active IE is associated with an increased risk of early PVE and of sterile leaks.<sup>341</sup>

c In cases where the infection is limited to valve structures with or without destruction of one or more valves, IE is considered locally limited/controlled. If peri- or paravalvular structures<sup>354</sup> are involved and the pathology includes cellulitis, abscess, pseudoaneurysm, abnormal communications like fistulas or rupture of one or more valves, conduction disturbances, myocarditis or other findings indicating local spread, the infection is considered locally uncontrolled.

Locally uncontrolled infections require urgent surgery.<sup>347–359,352,356,357</sup> The type of repair (valve replacement vs. valve reconstruction) does not influence operative mortality.<sup>358,359</sup>

Abdominal abscesses (most often splenic) should be operated on, if possible before cardiac surgery.<sup>360</sup> To detect such complications, sonography should be performed routinely and CT scans initiated if abnormalities are found.

d Apart from the established indications, surgery should also be considered if microorganisms are involved which are frequently not cured by antimicrobial therapy, e.g., fungi, *Brucella* spp. and *Coxiella* spp., which indeed have mostly not been shown to be cleared without surgery, or those that have a potential for rapid destruction of cardiac structures, e.g. *Staphylococcus lugdunensis*.

e (Recurrent) emboli following adequate antibiotic treatment may represent an indication for surgery (see Section Embolic events). If vegetations are mobile and larger than 10–15 mm on the mitral valve, if they are increasing in size despite antibiotic therapy or if they represent mitral kissing vegetations (see Section Mitral kissing vegetation), early surgery should be considered.<sup>105,361,362</sup>

f Severe native valve obstruction is very rare but also an indication for urgent surgery.

g Neurological complications are observed in up to 40% of patients with active IE (for details refer to Section Surgery after cerebral embolic events).

Material published about the beneficial role of surgery during active IE is consistent and convincing (class I/IIa recommendations).

### Surgery for active PVE

Despite a higher perioperative mortality with surgery for PVE than NVE, the general beneficial effect of surgery versus medical treatment has been demonstrated.<sup>346</sup> In early PVE cases, surgery should generally be consid-

**Table 11** Complications where surgery should be considered during active NVE

- Acute aortic or mitral regurgitation and CHF
- Evidence of perivalvular extension (locally uncontrolled infection)
- Persistent infection after 7–10 days of adequate antibiotic therapy
- Infection due to microorganisms with a poor response to antibiotic treatment (fungi, *Brucella* spp., *Coxiella* spp., *Staphylococcus lugdunensis*, enterococcus ssp. with high-level resistance to gentamicin, gram-negative organisms)
- Mobile vegetation >10 mm size before or during the first week of antibiotic treatment
- Recurrent emboli despite appropriate antibiotic therapy
- Obstructive vegetations

**Table 12** Complications where surgery should be considered during active PVE

- Early PVE
- Haemodynamically significant prosthetic valve malfunction
- Evidence of perivalvular extension
- Persistent infection after 7–10 days of adequate antibiotic therapy
- Recurrent emboli despite appropriate antibiotic therapy
- Infections due to microorganisms with a poor response to antibiotic treatment
- Obstructive vegetations

ered.<sup>54</sup> Surgery is also indicated in late PVE complicated by prosthetic valve dysfunction including significant perivalvular leaks, persistent positive blood cultures, abscess formation, conduction abnormalities, or large vegetations,<sup>5,238,239,363</sup> particularly if left-sided valves are involved and staphylococci are the infecting agents. Mechanical obstruction of prosthetic valves is an urgent indication for surgery. See Table 12 .

These class I/IIa recommendations are based on level B and C evidence.

## Perioperative management

### Preoperative considerations

Preoperative catheterisation has historically been performed to identify the site of infection and the degree of regurgitation. This is now unnecessary because non-invasive imaging techniques, first of all multiplane TEE, are much more sensitive and specific.<sup>110,133</sup> Coronary angiography should be considered in patients with suspicion of coronary artery embolism, symptoms suggestive for ischaemic heart disease, or a significant atherosclerosis risk profile.<sup>321,364</sup> Coronary angiography in aortic valve IE may be complicated by dislodgement of vegetations. This may be avoided by prior TEE examination, which enables detection of vegetations, which are large

or located close to the coronary ostia. If available, volume CT or MRT images may also be used to exclude proximal coronary artery stenoses.

### Prevention of recurrences

If a primary focus likely responsible for IE has been identified, it should be eliminated prior to an elective cardiac surgical intervention.

### Antithrombotic therapy

Antithrombotic therapy should be with heparin. Oral anticoagulation carries an increased risk of bleeding, especially intracranial haemorrhage following cerebral embolism, and should not be administered.<sup>212,365,366</sup>

### Intraoperative echocardiography

IE may spread from one valve to another valve (e.g., mitral kissing vegetation in primary aortic valve endocarditis).<sup>117</sup> Another mechanism may be through an anterior mitral leaflet jet lesion.<sup>367</sup> Infection can also extend into the perivalvular tissues causing abscesses or fistulas. TEE performed immediately preoperatively or intraoperatively is important to determine the exact location and the extent of the infection, to allow complete extirpation of infected tissue as well as to guide planning of surgery and early perioperative management.

In less complicated cases valve repair or debridement of vegetation can be performed as alternative to valve replacement<sup>2,321</sup> but these techniques are complex and unstandardized so that TEE is most useful to guide planning and to check the results.<sup>368</sup>

### Intraoperative microbiology

Regardless of whether there is culture-negative or culture-positive IE at the time of surgery, the excised valve or valve prosthesis should be put into physiological saline (no formalin!) and sent to the microbiology laboratory.

### Postoperative management

Postoperative antibiotic treatment should aim to eradicate not only the cardiac infection but also potential metastatic and primary infectious foci.

After surgery for active NVE or any PVE and a positive valve culture, another full course of antimicrobial treatment (see Section Treatment and management) should be performed regardless of duration of treatment prior to surgery. In all cases, the normal full treatment course has to be completed, but treatment should be continued for at least 7–15 days postoperatively.

Patients under treatment for IE do not need standard perioperative antimicrobial prophylaxis usually given to patients undergoing open-heart surgery.

### Intraoperative approach

Preoperative evaluation by (repeated) TEE assessments is essential for timing surgery and planning perioperative strategy (see Section Echocardiography). A full appreciation of the cardiac pathology is, however, often impos-

sible preoperatively, and many decisions have to be taken intraoperatively, including the final choice for reconstruction procedures.

The two primary objectives of surgery are control of the infection through debridement with removal of infected and necrotic tissue, and reconstruction of cardiac morphology including repair or replacement of the affected valve(s).

### Debridement

Debridement should be radical. If the infection extends beyond the valve cusps or leaflets, extensive reconstruction is required. The presence of annular damage and tissue defects may impair secure placing of a prosthesis.<sup>369,370</sup>

### Methods for reconstruction and valve replacement

For patients with uncomplicated IE (where the pathology by definition is confined to valve cusps or leaflets) any method to repair or replace the valve may be used. Whenever possible valve repair is favoured, particularly in cases of tricuspid or mitral IE.

A perforation/defect in a valve cusp or leaflet may be repaired with a pericardial patch. A secondary ('kissing') lesion on the anterior mitral valve leaflet in primary aortic valve IE is often suitable for excision and autologous pericardial patch repair, especially when detected early.<sup>117</sup> Judgement whether a remaining valve insufficiency is acceptable or not should follow the criteria accepted to test post-repair valve competence by intraoperative TEE.

In cases of locally uncontrolled IE, excision of all infected and devitalised tissue needs to be followed by repair of all associated defects to secure valve fixation.

Sub-annular, annular or supra-annular tissue defects are preferably repaired with autologous pericardium. The use of foreign material should be kept to a minimum. Cavities should, whenever possible, be allowed to drain into the pericardium or, occasionally, into the circulation.

The use of homografts (cryopreserved or antibiotic sterilized) has been advocated irrespective of the severity of the pathology, if necessary together with pericardium for the reconstruction of the left ventricular outflow tract (LVOT),<sup>369,371,372</sup> because the risk for persistent and recurrent IE is low.<sup>342,371,373</sup> However, after implantation of mechanical prostheses the incidence of early and late reinfections compares well with the results and the life expectancy of homografts and tissue valves.<sup>374</sup>

Therefore, the Task Force does not generally favour any specific substitute for a valve removed during active IE and recommends an individual approach.

Small abscesses can be closed directly by using patch material or autologous pericardium. Closure of the abscess cavity without drainage will only be successful if the cavity is sterile. In some cases with extensive horseshoe or circumferential abscesses, it may be impossible to insert a valve prosthesis in the anatomical position without reconstruction of the annulus. The choice of technique depends on the vertical extension

of the lesion/tissue defect.<sup>369,370,375–377</sup> Filling of abnormal cavities with glue has also been recommended.<sup>376</sup>

In extreme cases, after multiple re-operations for persistent or recurrent PVEs, some authors have proposed closure of the destroyed LVOT and insertion of a valve conduit between the apex of the left ventricle and the thoraco-abdominal aorta with exclusion of the ascending aorta.

In cases of advanced mitral valve IE, repair is most often impossible. After excision of the entire infected tissue, the annulus is repaired with a patch technique using autologous or bovine pericardium,<sup>378</sup> and a prosthetic valve is secured on the reconstructed/reinforced mitral annulus.

### Right-sided endocarditis

The approach should be conservative.<sup>379,380</sup> Surgical therapy is only indicated if fever persists for more than 3 weeks of adequate antibiotic treatment.<sup>381</sup> Recurrent pulmonary infiltrates are no indications for surgery.<sup>321</sup> Current surgical options for the treatment of right-sided endocarditis include debridement of the infected area or vegetectomy with either valve preservation or valve repair, or excision of the tricuspid valve with prosthetic valve replacement, or valvectomy without prosthetic replacement.<sup>2,380,382–384</sup> The pulmonary valve is best not replaced, or, if judged necessary, replaced with a pulmonary homograft.

Valve-related morbidity after prosthetic valve replacement is high, particularly in addicts, and includes reinfection or perivalvular leak. Valve excision may be associated with postoperative severe right heart failure, particularly in those who have elevated pulmonary pressure, e.g., after multiple pulmonary embolisms. Thus, valve repair and vegetectomy are the preferred surgical techniques.<sup>374,380,384</sup> If pulmonary pressure and vascular resistance are normal, the right ventricle can usually manage with one competent valve.

### Prosthetic valve endocarditis (PVE)

Most cases of PVE represent by definition uncontrolled IE and are treated accordingly. Radical debridement in these cases means removal of all foreign material. Aortic PVE constitutes an argument for choosing homografts or autografts.<sup>371</sup> Nevertheless, the rate of recurrence is 9–20% in reported series.<sup>356,385,386</sup> The presence of a ring abscess at the first operation is an important risk factor.<sup>358</sup>

### Endocarditis in children with congenital heart disease

Children with congenital heart disease may develop IE prior to or following cardiac surgery whether corrective or palliative. The feasibility of the same treatment principles as in adult patients has been well demonstrated.<sup>13</sup>

### Endocarditis related to permanent pacemakers and defibrillators

Endocarditis involving transvenous and intracardiac leads requires the same surgical approach as right-sided IE. A

good exposure is mandatory under extra-corporeal circulation to allow complete removal of all foreign material.<sup>387</sup> Excision of all infected contact lesions are essential at the level of the tricuspid valve, the right atrium and the free wall of the right ventricle.<sup>388</sup> The infection has to be eradicated before a new permanent system is implanted.

### Endocarditis in intravenous drug abusers (IVDA)

For treatment of IVDA refer to Section Treatment and management of IE in IVDA.

## Outcome and long-term prognosis

In NVE, morbidity and mortality are influenced by the type of infecting organism and the time of diagnosis.<sup>389</sup> IE due to streptococci should easily be cured with antibiotics if diagnosed early, i.e., before haemodynamic or embolic complications occur. If the diagnosis is delayed or IE is due to microorganisms other than streptococci (especially staphylococci) the need for surgical treatment is higher and the overall prognosis is worse because these organisms are more virulent, intracardiac destruction is more severe, and embolic complications are more likely to occur.

In recent years, IE has been found increasingly more often in older people, many of them unaware of suffering from predisposing heart disease, and with an increasing frequency of enterococci and staphylococci. Also, the rate of nosocomial IE, occurring in populations with other debilitating diseases (e.g., chronic renal failure) is increasing. Overall prognosis for hospital survivors is quite good (81% at 10 years),<sup>355</sup> although a significant proportion of these patients initially cured medically will need surgery later. Patients with previous IE are at risk for a second infection, therefore, prophylactic measures should be very strict.<sup>355,344</sup>

Severe periprosthetic damage, abscess formation, prosthetic valve dysfunction, and embolic episodes are frequent with PVE. Mortality in this type of IE is high (around 50% in most series). Early recognition of the disease, diagnostic confirmation using TEE, and prompt surgical treatment may improve the prognosis significantly.<sup>12,344</sup>

In late PVE overall outcome and complications are related to the infective organism. Mortality in late PVE caused by viridans streptococci has been reported to be less than 10%. Few patients with this type of infection suffer from abscesses or prosthetic valve dysfunction if the disease is diagnosed early and cured medically. In other types of infection, those caused by enterococci and especially those produced by *S. aureus* the prognosis is very poor. In those cases, severe periprosthetic damage, abscess formation and embolic episodes are common and it is likely that an early medico-surgical approach would improve in-hospital mortality.<sup>390</sup>

Overall, long-term survival is worse for patients with PVE than for patients with NVE.<sup>344</sup> This fact probably represents the overall outcome of a population of patients who have submitted to several surgical procedures.

## Appendix 1

### List of Abbreviations

|       |   |
|-------|---|
| AIDS  | Acquired immunodeficiency syndrome  |
| ASD   | Atrial septal defect  |
| BC    | Blood culture   |
| CD    | Conduction disturbances   |
| CFU   | Colony-forming unit   |
| CHF   | Congestive heart failure  |
| CNE   | Culture-negative endocarditis   |
| CNS   | Central nervous system  |
| CONS  | Coagulase-negative staphylococci  |
| CRP   | C-reactive protein  |
| CT    | Computed tomography   |
| ESR   | Erythrocyte sedimentation rate  |
| GUCH  | Grown-up congenital heart disease   |
| HACEK | Group of bacteria consistent of <i>Haemophilus</i> spp., <i>Actinobacillus actinomycetemcomitans</i> , <i>Cardiobacterium hominis</i> , <i>Eikenella corrodens</i> , <i>Kingella kingae</i> |
| HIV   | Human immunodeficiency virus  |
| ICD   | Implantable cardioverter defibrillator  |
| IE    | Infective endocarditis  |
| IVDA  | Intravenous drug abuser   |
| LVOT  | Left ventricular outflow tract  |
| MBC   | Minimal bactericidal concentration  |
| MIC   | Minimal inhibitory concentration  |
| MRSA  | Methicillin-resistant <i>Staphylococcus aureus</i>  |
| MRSA  | Methicillin-resistant <i>Staphylococcus epidermidis</i>   |
| MSSA  | Methicillin-sensitive <i>Staphylococcus aureus</i>  |
| MSE   | Methicillin-sensitive <i>Staphylococcus epidermidis</i>   |
| MRT   | Magnetic resonance tomography   |
| NBTV  | Non-bacterial thrombotic vegetation   |
| NVE   | Native valve endocarditis   |
| OHPAT | Outpatient and home parenteral antibiotic therapy   |
| PAE   | Post-antibiotic effect  |
| PCR   | Polymerase chain reaction   |
| PFO   | Persistent foramen ovale  |
| PPMI  | Infection of permanent pacemaker leads  |
| PVE   | Prosthetic valve endocarditis   |
| spp   | Plural of 'species'   |
| TEE   | Transoesophageal echocardiography   |
| TOF   | Tetralogy of Fallot   |
| TTE   | Transthoracic echocardiography  |
| VAD   | Ventricular assist device   |
| WBC   | White blood cell count  |

### Appendix 2

The Task Force on Infective Endocarditis thanks the following corresponding members for their cooperation: Prof. Martin Altwegg, University of Zurich, Department of Medical Microbiology, Gloriastr. 32, CH-8028 Zürich, Switzerland. Prof. Michael Hennerici, University Hospital Mannheim, Department of Neurology, Theodor Kutzer-Ufer, D-68135 Mannheim, Germany.

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