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2015 ESC Guidelines for the management of infective endocarditis

The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC)

Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM)

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Abbreviations and acronyms

3D	three-dimensional
AIDS	acquired immune deficiency syndrome
b.i.d.	bis in die (twice daily)
BCNIE	blood culture-negative infective endocarditis
CDRIE	cardiac device-related infective endocarditis
CHD	congenital heart disease
CIED	cardiac implantable electronic device
CoNS	coagulase-negative staphylococci
CPG	Committee for Practice Guidelines
CRP	C-reactive protein
CT	computed tomography
E.	Enterococcus
ESC	European Society of Cardiology
ESR	erythrocyte sedimentation rate
EuroSCORE	European System for Cardiac Operative Risk Evaluation
FDG	fluorodeoxyglucose
HF	heart failure
HIV	human immunodeficiency virus
HLAR	high-level aminoglycoside resistance
i.m.	intramuscular
i.v.	intravenous
ICE	International Collaboration on Endocarditis
ICU	intensive care unit
ID	infectious disease
IE	infective endocarditis
Ig	immunoglobulin
IVDA	intravenous drug abuser
MIC	minimum inhibitory concentration
MR	magnetic resonance
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
MSCT	multislice computed tomography
MSSA	methicillin-susceptible *Staphylococcus aureus*
NBTE	non-bacterial thrombotic endocarditis
NICE	National Institute for Health and Care Excellence
NVE	native valve endocarditis
OPAT	outpatient parenteral antibiotic therapy
PBP	penicillin binding protein
PCR	polymerase chain reaction
PET	positron emission tomography
PVE	prosthetic valve endocarditis
SOFA	Sequential Organ Failure Assessment
SPECT	single-photon emission computed tomography
TOE	transoesophageal echocardiography
TTE	transthoracic echocardiography
WBC	white blood cell

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1. Preamble

Guidelines summarize and evaluate all available evidence on a particular issue at the time of the writing process, with the aim of assisting health professionals in selecting the best management strategies for an individual patient with a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines and recommendations should help health professionals to make decisions in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

A great number of Guidelines have been issued in recent years by the European Society of Cardiology (ESC) as well as by other societies and organisations. Because of the impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (http://www.escardio.org/Guidelines-&-Education/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines). ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

Members of this Task Force were selected by the ESC to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management (including diagnosis, treatment, prevention and rehabilitation) of a given condition according to ESC Committee for Practice Guidelines (CPG) policy. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. Estimates of expected health outcomes for larger populations were included, where data exist. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined in *Tables 1* and *2*.

The experts of the writing and reviewing panels provided declarations of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC website (http://www.escardio.org/guidelines). Any changes in declarations of interest that arise during the writing period must be notified to the ESC and updated. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.

The ESC CPG supervises and coordinates the preparation of new Guidelines produced by task forces, expert groups or consensus panels. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts. After appropriate revisions the Guidelines are approved by all the experts involved in the Task Force. The finalized document is approved by the CPG for publication in the European Heart Journal. The Guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

The task of developing ESC Guidelines covers not only integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. To implement the guidelines, condensed pocket guidelines versions, summary slides, booklets with essential messages, summary cards for non-specialists, and an electronic version for digital applications (smartphones, etc.) are produced. These versions are abridged and thus, if needed, one should always refer to the full text version, which is freely available on the ESC website. The National Societies of the ESC are encouraged to endorse, translate and implement all ESC Guidelines. Implementation programmes are needed because it

Table 1 Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

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has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Surveys and registries are needed to verify that real-life daily practice is in keeping with what is recommended in the guidelines, thus completing the loop between clinical research, writing of guidelines, disseminating them and implementing them into clinical practice.

Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies. However, the ESC Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

Table 2 Levels of evidence

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

2. Justification/scope of the problem

Infective endocarditis (IE) is a deadly disease.[1,2] Despite improvements in its management, IE remains associated with high mortality and severe complications. Until recently, guidelines on IE were mostly based on expert opinion because of the low incidence of the disease, the absence of randomized trials and the limited number of meta-analyses.[3–7]

The 2009 ESC Guidelines on the prevention, diagnosis and treatment of IE[8] introduced several innovative concepts, including limitation of antibiotic prophylaxis to the highest-risk patients, a focus on healthcare-associated IE and identification of the optimal timing for surgery. However, several reasons justify the decision of the ESC to update the previous guidelines: the publication of new large series of IE, including the first randomized study regarding surgical therapy;[9] important improvements in imaging procedures,[10] particularly in the field of nuclear imaging; and discrepancies between previous guidelines.[5–8] In addition, the need for a collaborative approach involving primary care physicians, cardiologists, surgeons, microbiologists, infectious disease (ID) specialists and frequently other specialists—namely the 'Endocarditis Team'—has been underlined recently[11,12] and will be developed in these new guidelines.

The main objective of the current Task Force was to provide clear and simple recommendations, assisting healthcare providers in their clinical decision making. These recommendations were obtained by expert consensus after thorough review of the available literature. An evidence-based scoring system was used, based on a classification of the strength of recommendations and the levels of evidence.

3. Prevention

3.1 Rationale

The principle of antibiotic prophylaxis for IE was developed on the basis of observational studies and animal models and aimed at preventing the attachment of bacteria onto the endocardium after transient bacteraemia following invasive procedures. This concept led to the recommendation for antibiotic prophylaxis in a large number of patients with predisposing cardiac conditions undergoing a wide range of procedures.[13]

The restriction of indications for antibiotic prophylaxis was initiated in 2002 because of changes in pathophysiological conceptions and risk–benefit analyses as follows:[14]

- Low-grade but repeated bacteraemia occurs more frequently during daily routine activities such as toothbrushing, flossing or chewing, and even more frequently in patients with poor dental health.[15] The accountability of low-grade bacteraemia was demonstrated in an animal model.[16] The risk of IE may therefore be related more to cumulative low-grade bacteraemia during daily life rather than sporadic high-grade bacteraemia after dental procedures.
- Most case–control studies did not report an association between invasive dental procedures and the occurrence of IE.[17–19]
- The estimated risk of IE following dental procedures is very low. Antibiotic prophylaxis may therefore avoid only a small number of IE cases, as shown by estimations of 1 case of IE per 150 000 dental procedures with antibiotics and 1 per 46 000 for procedures unprotected by antibiotics.[20]
- Antibiotic administration carries a small risk of anaphylaxis, which may become significant in the event of widespread use. However, the lethal risk of anaphylaxis seems very low when using oral amoxicillin.[21]
- Widespread use of antibiotics may result in the emergence of resistant microorganisms.[13]
- The efficacy of antibiotic prophylaxis on bacteraemia and the occurrence of IE has only been proven in animal models. The effect on bacteraemia in humans is controversial.[15]
- No prospective randomized controlled trial has investigated the efficacy of antibiotic prophylaxis on the occurrence of IE and it is unlikely that such a trial will be conducted given the number of subjects needed.[22]

These points have been progressively taken into account in most guidelines, including the 2009 ESC guidelines,[5,8,23–26] and led to the restriction of antibiotic prophylaxis to the highest-risk patients (patients with the highest incidence of IE and/or highest risk of adverse outcome from IE).

In 2008 the National Institute for Health and Care Excellence (NICE) guidelines went a step further and advised against any antibiotic prophylaxis for dental and non-dental procedures whatever

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the patient's risk.[27] The authors concluded there was an absence of benefit of antibiotic prophylaxis, which was also highly cost-ineffective. These conclusions have been challenged since estimations of the risks of IE are based on low levels of evidence due to multiple extrapolations.[28,29]

Four epidemiological studies have analysed the incidence of IE following restricted indications for antibiotic prophylaxis. The analysis of 2000–2010 national hospital discharge codes in the UK did not show an increase in the incidence of streptococcal IE after the release of NICE guidelines in 2008.[30] The restriction of antibiotic prophylaxis was seen in a 78% decrease in antibiotic prescriptions before dental care. However, residual prescriptions raised concerns regarding a persisting use of antibiotic prophylaxis. A survey performed in 2012 in the UK showed that the majority of cardiologists and cardiac surgeons felt that antibiotic prophylaxis was necessary in patients with valve prosthesis or prior IE.[31] Recently an analysis of UK data collected from 2000 to 2013 showed a significant increase in the incidence of IE in both high-risk and lower-risk patients in the UK starting in 2008.[32] However, this temporal relationship should not be interpreted as a direct consequence of the NICE guidelines. These findings may be influenced by confounding factors, in particular changes in the number of patients at risk of hospitalizations and healthcare-associated IE. Moreover, microbiological data were not available. Thus we cannot know whether that increase is due to the microbiological species covered by antibiotic prophylaxis.

A repeated prospective 1-year population-based French survey did not show an increase in the incidence of IE, in particular streptococcal IE, between 1999 and 2008, whereas antibiotic prophylaxis had been restricted for native valve disease since 2002.[33]

Two studies from the USA did not find a negative impact of the abandonment of antibiotic prophylaxis in native valve disease in the 2007 American Heart Association guidelines.[34,35] A more recent analysis on an administrative database found an increase in the incidence of IE hospitalizations between 2000 and 2011, with no significant change after the change of American guidelines in 2007.[36] The increase in IE incidence was observed for all types of microorganisms, but was significant for streptococci after 2007.[36] It was not stated whether this was due to oral streptococci and if intermediate- or high-risk patients were involved.

The present guidelines maintain the principle of antibiotic prophylaxis in high-risk patients for the following reasons:

- The remaining uncertainties regarding estimations of the risk of IE, which play an important role in the rationale of NICE guidelines.
- The worse prognosis of IE in high-risk patients, in particular those with prosthetic IE.
- The fact that high-risk patients account for a much smaller number than patients at intermediate risk, thereby reducing potential harm due to adverse events of antibiotic prophylaxis.

3.2 Population at risk

Patients with the highest risk of IE can be placed in three categories (*Table 3*):

(1) Patients with a prosthetic valve or with prosthetic material used for cardiac valve repair: these patients have a higher risk of IE, a higher mortality from IE and more often develop complications of the disease than patients with native valves and an identical pathogen.[37] This also applies to transcatheter-implanted prostheses and homografts.

(2) Patients with previous IE: they also have a greater risk of new IE, higher mortality and higher incidence of complications than patients with a first episode of IE.[38]

(3) Patients with untreated cyanotic congenital heart disease (CHD) and those with CHD who have postoperative palliative shunts, conduits or other prostheses.[39,40] After surgical repair with no residual defects, the Task Force recommends prophylaxis for the first 6 months after the procedure until endothelialisation of the prosthetic material has occurred.

Table 3 Cardiac conditions at highest risk of infective endocarditis for which prophylaxis should be considered when a high-risk procedure is performed

Recommendations	Class[a]	Level[b]
Antibiotic prophylaxis should be considered for patients at highest risk for IE: (1) Patients with any prosthetic valve, including a transcatheter valve, or those in whom any prosthetic material was used for cardiac valve repair. (2) Patients with a previous episode of IE. (3) Patients with CHD: (a) Any type of cyanotic CHD. (b) Any type of CHD repaired with a prosthetic material, whether placed surgically or by percutaneous techniques, up to 6 months after the procedure or lifelong if residual shunt or valvular regurgitation remains.	IIa	C
Antibiotic prophylaxis is not recommended in other forms of valvular or CHD.	III	C

CHD = congenital heart disease; IE = infective endocarditis.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Although American Heart Association/American College of Cardiology guidelines recommend prophylaxis in cardiac transplant recipients who develop cardiac valvulopathy, this is not supported by strong evidence[5,25,41] and is not recommended by the ESC Task Force.

Antibiotic prophylaxis is not recommended for patients at intermediate risk of IE, i.e. any other form of native valve disease (including the most commonly identified conditions: bicuspid aortic valve, mitral valve prolapse and calcific aortic stenosis). Nevertheless, both intermediate- and high-risk patients should be advised of the importance of dental and cutaneous hygiene[13] (*Table 4*). These measures of general hygiene apply to patients and healthcare workers and should ideally be applied to the general population, as IE frequently occurs without known cardiac disease.

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Table 4 Non-specific prevention measures to be followed in high-risk and intermediate-risk patients

These measures should ideally be applied to the general population and particularly reinforced in high-risk patients:
• Strict dental and cutaneous hygiene. Dental follow-up should be performed twice a year in high-risk patients and yearly in the others.
• Disinfection of wounds.
• Eradication or decrease of chronic bacterial carriage: skin, urine.
• Curative antibiotics for any focus of bacterial infection.
• No self-medication with antibiotics.
• Strict infection control measures for any at-risk procedure.
• Discourage piercing and tattooing.
• Limit the use of infusion catheters and invasive procedure when possible. Favour peripheral over central catheters, and systematic replacement of the peripheral catheter every 3–4 days. Strict adherence to care bundles for central and peripheral cannulae should be performed.

3.3 Situations and procedures at risk

3.3.1 Dental procedures

At-risk procedures involve manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa (including scaling and root canal procedures) (*Table 5*).[15,20] The use of dental implants raises concerns with regard to potential risk due to foreign material at the interface between the buccal cavity and blood. Very few data are available.[42] The opinion of the Task Force is that there is no evidence to contraindicate implants in all patients at risk. The indication should be discussed on a case-by-case basis. The patient should be informed of the uncertainties and the need for close follow-up.

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

Recommendations	Class[a]	Level[b]
A. Dental procedures		
• Antibiotic prophylaxis should only be considered for dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa	IIa	C
• Antibiotic prophylaxis is not recommended for local anaesthetic injections in non-infected tissues, treatment of superficial caries, removal of sutures, dental X-rays, placement or adjustment of removable prosthodontic or orthodontic appliances or braces or following the shedding of deciduous teeth or trauma to the lips and oral mucosa	III	C

Continued

Table 5 *Continued*

Recommendations	Class[a]	Level[b]
B. Respiratory tract procedures[c]		
• Antibiotic prophylaxis is not recommended for respiratory tract procedures, including bronchoscopy or laryngoscopy, or transnasal or endotracheal intubation	III	C
C. Gastrointestinal or urogenital procedures or TOE[c]		
• Antibiotic prophylaxis is not recommended for gastroscopy, colonoscopy, cystoscopy, vaginal or caesarean delivery or TOE	III	C
D. Skin and soft tissue procedures[c]		
• Antibiotic prophylaxis is not recommended for any procedure	III	C

TOE = transoesophageal echocardiography.
[a]Class of recommendation.
[b]Level of evidence.
[c]For management when infections are present, please refer to Section 3.5.3.

3.3.2 Other at-risk procedures

There is no compelling evidence that bacteraemia resulting from respiratory tract procedures, gastrointestinal or genitourinary procedures, including vaginal and caesarean delivery, or dermatological or musculoskeletal procedures causes IE (*Table 5*).

3.4 Prophylaxis for dental procedures

Antibiotic prophylaxis should only be considered for patients at highest risk for endocarditis, as described in *Table 3*, undergoing at-risk dental procedures listed in *Table 5*, and is not recommended in other situations. The main targets for antibiotic prophylaxis in these patients are oral streptococci. *Table 6* summarizes the main regimens of antibiotic prophylaxis recommended before dental procedures. Fluoroquinolones and glycopeptides are not recommended due to their unclear efficacy and the potential induction of resistance.

Table 6 Recommended prophylaxis for high-risk dental procedures in high-risk patients

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

[a]Alternatively, cephalexin 2 g i.v. for adults or 50 mg/kg i.v. for children, cefazolin or ceftriaxone 1 g i.v. for adults or 50 mg/kg i.v. for children.
Cephalosporins should not be used in patients with anaphylaxis, angio-oedema, or urticaria after intake of penicillin or ampicillin due to cross-sensitivity.

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

3.5 Prophylaxis for non-dental procedures

Systematic antibiotic prophylaxis is not recommended for non-dental procedures. Antibiotic therapy is only needed when invasive procedures are performed in the context of infection.

3.5.1 Respiratory tract procedures

Patients listed in *Table 3* who undergo an invasive respiratory tract procedure to treat an established infection (i.e. drainage of an abscess) should receive an antibiotic regimen that contains an anti-staphylococcal drug.

3.5.2 Gastrointestinal or genitourinary procedures

In the case of an established infection or if antibiotic therapy is indicated to prevent wound infection or sepsis associated with a gastrointestinal or genitourinary tract procedure in patients described in *Table 3*, it is reasonable that the antibiotic regimen includes an agent active against enterococci (i.e. ampicillin, amoxicillin or vancomycin; only in patients unable to tolerate beta-lactams). The use of intrauterine devices was regarded as contra-indicated, but this was based on low levels of evidence. Use of an intrauterine device is now considered acceptable, in particular when other contraceptive methods are not possible and in women at low risk of genital infections.[43]

3.5.3 Dermatological or musculoskeletal procedures

For patients described in *Table 3* undergoing surgical procedures involving infected skin (including oral abscesses), skin structure or musculoskeletal tissue, it is reasonable that the therapeutic regimen contains an agent active against staphylococci and beta-haemolytic streptococci.

3.5.4 Body piercing and tattooing

These growing societal trends are a cause for concern, particularly for individuals with CHD who are at increased susceptibility for the acquisition of IE. Case reports of IE after piercing and tattooing are increasing, particularly when piercing involves the tongue,[44] although publication bias may over- or underestimate the problem. Currently no data are available on the incidence of IE after such procedures and the efficacy of antibiotics for prevention. Education of patients at risk of IE is paramount. They should be informed about the hazards of piercing and tattooing and these procedures should be discouraged not only in high-risk patients, but also in those with native valve disease. If undertaken, procedures should be performed under strictly sterile conditions, though antibiotic prophylaxis is not recommended.

3.5.5 Cardiac or vascular interventions

In patients undergoing implantation of a prosthetic valve, any type of prosthetic graft or pacemakers, perioperative antibiotic prophylaxis should be considered due to the increased risk and adverse outcome of an infection[45–49] (*Table 7*). The most frequent microorganisms underlying early (1 year after surgery) prosthetic valve infections are coagulase-negative staphylococci (CoNS) and *Staphylococcus aureus*. Prophylaxis should be started immediately before the procedure, repeated if the procedure is prolonged and terminated 48 h afterwards. A randomized trial has shown the efficacy of 1 g intravenous (i.v.) cefazolin on the prevention of local and systemic infections before pacemaker implantation.[45] Preoperative screening of nasal carriage of *S. aureus* is recommended before elective cardiac surgery in order to treat carriers using local mupirocin and chlorhexidine.[46,47] Rapid identification techniques using gene amplification are useful to avoid delaying urgent surgery. Systematic local treatment without screening is not recommended. It is strongly recommended that potential sources of dental sepsis should be eliminated at least 2 weeks before implantation of a prosthetic valve or other intracardiac or intravascular foreign material, unless the latter procedure is urgent.[48]

Table 7 Recommendations for antibiotic prophylaxis for the prevention of local and systemic infections before cardiac or vascular interventions

Recommendations	Class[a]	Level[b]	Ref.[c]
Preoperative screening of nasal carriage of *Staphylococcus aureus* is recommended before elective cardiac surgery in order to treat carriers	I	A	46,47
Perioperative prophylaxis is recommended before placement of a pacemaker or implantable cardioverter defibrillator	I	B	45
Potential sources of sepsis should be eliminated ≥2 weeks before implantation of a prosthetic valve or other intracardiac or intravascular foreign material, except in urgent procedures	IIa	C	
Perioperative antibiotic prophylaxis should be considered in patients undergoing surgical or transcatheter implantation of a prosthetic valve, intravascular prosthetic or other foreign material	IIa	C	
Systematic local treatment without screening of *S. aureus* is not recommended	III	C	

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

3.5.6 Healthcare-associated infective endocarditis

Healthcare-associated IE represents up to 30% of all cases of IE and is characterized by an increasing incidence and a severe prognosis, thus presenting an important health problem.[50,51] Although routine antimicrobial prophylaxis administered before most invasive

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procedures is not recommended, aseptic measures during the insertion and manipulation of venous catheters and during any invasive procedures, including in outpatients, are mandatory to reduce the rate of this healthcare-associated IE.[52]

In summary, these guidelines propose continuing to limit antibiotic prophylaxis to patients at high risk of IE undergoing the highest-risk dental procedures. They highlight the importance of hygiene measures, in particular oral and cutaneous hygiene. Epidemiological changes are marked by an increase in IE due to staphylococcus and of healthcare-associated IE, thereby highlighting the importance of non-specific infection control measures.[51,53] This should concern not only high-risk patients, but should also be part of routine care in all patients since IE occurring in patients without previously known heart disease now accounts for a substantial and increasing incidence. This means that although antibiotic prophylaxis should be restricted to the highest-risk patients, preventive measures should be maintained or extended to all patients with cardiac disease.

Although this section of the guidelines on IE prophylaxis is based on weak evidence, they have been strengthened recently by epidemiological surveys, most of which did not show an increased incidence of IE due to oral streptococci.[33–35] Their application by patients should follow a shared decision-making process. Future challenges are to gain a better understanding of the mechanisms associated with valve infection, the adaptation of prophylaxis to the ongoing epidemiological changes and the performance of specific prospective surveys on the incidence and characteristics of IE.

4. The 'Endocarditis Team'

IE is a disease that needs a collaborative approach for the following reasons:

- First, IE is not a single disease, but rather may present with very different aspects depending on the first organ involved, the underlying cardiac disease (if any), the microorganism involved, the presence or absence of complications and the patient's characteristics.[8] No single practitioner will be able to manage and treat a patient in whom the main clinical symptoms might be cardiac, rheumatological, infectious, neurological or other.
- Second, a very high level of expertise is needed from practitioners from several specialties, including cardiologists, cardiac surgeons, ID specialists, microbiologists, neurologists, neurosurgeons, experts in CHD and others. Echocardiography is known to have a major importance in the diagnosis and management of IE. However, other imaging techniques, including magnetic resonance imaging (MRI), multislice computed tomography (MSCT), and nuclear imaging, have also been shown to be useful for diagnosis, follow-up and decision making in patients with IE.[10] Including all of these specialists in the team is becoming increasingly important.
- Finally, about half of the patients with IE undergo surgery during the hospital course.[54] Early discussion with the surgical team is important and is considered mandatory in all cases of complicated IE [i.e. endocarditis with heart failure (HF), abscess or embolic or neurological complications].

Therefore the presence of an Endocarditis Team is crucial. This multidisciplinary approach has already been shown to be useful in the management of valve disease[11] (the 'Heart Valve Clinic'), particularly in the selection of patients for transcatheter aortic valve implantation procedures ('Heart Team' approach).[55] In the field of IE, the team approach adopted in France, including standardized medical therapy, surgical indications following guideline recommendations and 1 year of close follow-up, has been shown to significantly reduce the 1-year mortality, from 18.5% to 8.2%.[12] Other authors have recently reported similar results.[56] Taking these reports together, such a team approach has been recommended recently as class IB in the 2014 American Heart Association/American College of Cardiology guideline for the management of patients with valvular heart disease.[25]

The present Task Force on the management of IE of the ESC strongly supports the management of patients with IE in reference centres by a specialized team (the 'Endocarditis Team'). The main characteristics of the Endocarditis Team and the referring indications are summarized in Tables 8 and 9.

Table 8 Characteristics of the 'Endocarditis Team'

When to refer a patient with IE to an 'Endocarditis Team' in a reference centre
1. Patients with complicated IE (i.e. endocarditis with HF, abscess, or embolic or neurological complication or CHD), should be referred early and managed in a reference centre with immediate surgical facilities.
2. Patients with non-complicated IE can be initially managed in a non-reference centre, but with regular communication with the reference centre, consultations with the multidisciplinary 'Endocarditis Team', and, when needed, with external visit to the reference centre.
Characteristics of the reference centre
1. Immediate access to diagnostic procedures should be possible, including TTE, TOE, multislice CT, MRI, and nuclear imaging.
2. Immediate access to cardiac surgery should be possible during the early stage of the disease, particularly in case of complicated IE (HF, abscess, large vegetation, neurological, and embolic complications).
3. Several specialists should be present on site (the 'Endocarditis Team'), including at least cardiac surgeons, cardiologists, anaesthesiologists, ID specialists, microbiologists and, when available, specialists in valve diseases, CHD, pacemaker extraction, echocardiography and other cardiac imaging techniques, neurologists, and facilities for neurosurgery and interventional neuroradiology .
Role of the 'Endocarditis Team'
1. The 'Endocarditis Team' should have meetings on a regular basis in order to discuss cases, take surgical decisions, and define the type of follow-up.
2. The 'Endocarditis Team' chooses the type, duration, and mode of follow up of antibiotic therapy, according to a standardized protocol, following the current guidelines.
3. The 'Endocarditis Team' should participate in national or international registries, publicly report the mortality and morbidity of their centre, and be involved in a quality improvement programme, as well as in a patient education programme.
4. The follow-up should be organized on an outpatient visit basis at a frequency depending on the patient's clinical status (ideally at 1, 3, 6, and 12 months after hospital discharge, since the majority of events occur during this period[57]).

CHD = Congenital heart disease; CT = computed tomography; HF = heart failure; ID = Infectious disease; IE = infective endocarditis; MRI = magnetic resonance imaging; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.

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Table 9 Recommendations for referring patients to the reference centre

Recommendations	Class[a]	Level[b]	Ref.[c]
Patients with complicated IE should be evaluated and managed at an early stage in a reference centre, with immediate surgical facilities and the presence of a multidisciplinary 'Endocarditis Team', including an ID specialist, a microbiologist, a cardiologist, imaging specialists, a cardiac surgeon and, if needed, a specialist in CHD	IIa	B	12,56
For patients with uncomplicated IE managed in a non-reference centre, early and regular communication with the reference centre and, when needed, visits to the reference centre should be made	IIa	B	12,56

CHD = congenital heart disease; ID = infectious disease; IE = infective endocarditis.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

5. Diagnosis

5.1 Clinical features

The diverse nature and evolving epidemiological profile of IE ensure that it remains a diagnostic challenge. The clinical history of IE is highly variable according to the causative microorganism, the presence or absence of pre-existing cardiac disease, the presence or absence of prosthetic valves or cardiac devices and the mode of presentation. Thus IE should be suspected in a variety of very different clinical situations. It may present as an acute, rapidly progressive infection, but also as a subacute or chronic disease with low-grade fever and non-specific symptoms that may mislead or confuse initial assessment. Patients may therefore present to a variety of specialists who may consider a range of alternative diagnoses, including chronic infection; rheumatological, neurological and autoimmune diseases; or malignancy. The early involvement of a cardiologist and an ID specialist to guide management is highly recommended.

Up to 90% of patients present with fever, often associated with systemic symptoms of chills, poor appetite and weight loss. Heart murmurs are found in up to 85% of patients. Up to 25% of patients have embolic complications at the time of diagnosis. Therefore IE has to be suspected in any patient presenting with fever and embolic phenomena. Classic signs may still be seen in the developing world in subacute forms of IE, although peripheral stigmata of IE are increasingly uncommon elsewhere, as patients generally present at an early stage of the disease. However, vascular and immunological phenomena such as splinter haemorrhages, Roth spots and glomerulonephritis remain common. Emboli to the brain, lung or spleen occur in 30% of patients and are often the presenting feature.[58] In a febrile patient, diagnostic suspicion may be strengthened by laboratory signs of infection, such as elevated C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), leucocytosis, anaemia and microscopic haematuria. However, these signs lack specificity and have not been integrated into current diagnostic criteria. Atypical presentation is common in elderly or immunocompromised patients,[59] in whom fever is less common than in younger individuals. A high index of suspicion and low threshold for investigation are therefore essential in these and other high-risk groups, such as those with CHD or prosthetic valves, to exclude IE or avoid delays in diagnosis.

5.2 Laboratory findings

In addition to specialized microbiological and imaging investigations, a number of laboratory investigations and biomarkers have been evaluated in sepsis/sepsis syndromes and endocarditis. The large number of proposed potential biomarkers reflects the complex pathophysiology of the disease process, involving pro- and anti-inflammatory processes, humoral and cellular reactions and both circulatory and end-organ abnormalities.[60] However, owing to their poor positive predictive value for the diagnosis of sepsis and lack of specificity for endocarditis, these biomarkers have been excluded from being major diagnostic criteria and are only used to facilitate risk stratification.

Sepsis severity may be indicated by the demonstration of a number of laboratory investigations, including the degree of leucocytosis/leucopoenia, the number of immature white cell forms, concentrations of CRP and procalcitonin, ESR and markers of end-organ dysfunction (lactataemia, elevated bilirubin, thrombocytopaenia and changes in serum creatinine concentration); however, none are diagnostic for IE.[61] Further, certain laboratory investigations are used in surgical scoring systems relevant to risk stratification in patients with IE, including bilirubin, creatinine and platelet count [Sequential Organ Failure Assessment (SOFA) score] and creatinine clearance [European System for Cardiac Operative Risk Evaluation (EuroSCORE) II]. Finally, the pattern of increase in inflammatory mediators or immune complexes may support, but not prove, the diagnosis of IE, including the finding of hypocomplementaemia in the presence of elevated antineutrophil cytoplasmic antibody in endocarditis-associated vasculitis or, where lead infection is suspected clinically, the laboratory finding of a normal procalcitonin and white cell count in the presence of significantly elevated CRP and/or ESR.[62]

5.3 Imaging techniques

Imaging, particularly echocardiography, plays a key role in both the diagnosis and management of IE. Echocardiography is also useful for the prognostic assessment of patients with IE, for its follow-up under therapy and during and after surgery.[63] Echocardiography is particularly useful for initial assessment of the embolic risk and in decision making in IE. Transoesophageal echocardiography (TOE) plays a major role both before and during surgery (intraoperative echocardiography). However, the evaluation of patients with IE is no longer limited to conventional echocardiography, but should include several other imaging techniques such as MSCT, MRI, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) or other functional imaging modalities.[10]

5.3.1 Echocardiography

Echocardiography, either transthoracic echocardiography (TTE) or TOE, is the technique of choice for the diagnosis of IE, and plays a

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key role in the management and monitoring of these patients.[64,65] Echocardiography must be performed as soon as IE is suspected. TOE must be performed in case of negative TTE when there is a high index of suspicion for IE, particularly when TTE is of suboptimal quality. TOE should also be performed in patients with positive TTE to rule out local complications. The indications of echocardiographic examination for diagnosis and follow-up of patients with suspected IE are summarized in *Table 10* and *Figure 1*. In patients with *S. aureus* bacteraemia, echocardiography is justified in view of the frequency of IE in this setting, the virulence of this organism and its devastating effects once intracardiac infection is established.[66,67] In these patients, TTE or TOE should be considered according to individual patient risk factors and the mode of acquisition of *S. aureus* bacteraemia.[66,67]

Table 10 Role of echocardiography in infective endocarditis

Recommendations	Class[a]	Level[b]	Ref.[c]
A. Diagnosis			
• TTE is recommended as the first-line imaging modality in suspected IE.	I	B	64,65
• TOE is recommended in all patients with clinical suspicion of IE and a negative or non-diagnostic TTE.	I	B	64, 68–71
• TOE is recommended in patients with clinical suspicion of IE, when a prosthetic heart valve or an intracardiac device is present.	I	B	64,71
• Repeat TTE and /or TOE within 5–7 days is recommended in case of initially negative examination when clinical suspicion of IE remains high.	I	C	
• Echocardiography should be considered in *Staphylococcus aureus* bacteraemia.	IIa	B	66,67
• TOE should be considered in patients with suspected IE, even in cases with positive TTE, except in isolated right-sided native valve IE with good quality TTE examination and unequivocal echocardiographic findings.	IIa	C	
B. Follow-up under medical therapy			
• Repeat TTE and/or TOE are recommended as soon as a new complication of IE is suspected (new murmur, embolism, persisting fever, HF, abscess, atrioventricular block).	I	B	64,72
• Repeat TTE and/or TOE should be considered during follow-up of uncomplicated IE, in order to detect new silent complications and monitor vegetation size. The timing and mode (TTE or TOE) of repeat examination depend on the initial findings, type of microorganism, and initial response to therapy.	IIa	B	64,72
C. Intraoperative echocardiography			
• Intraoperative echocardiography is recommended in all cases of IE requiring surgery.	I	B	64,73
D. Following completion of therapy			
• TTE is recommended at completion of antibiotic therapy for evaluation of cardiac and valve morphology and function.	I	C	

HF = heart failure; IE = infective endocarditis; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

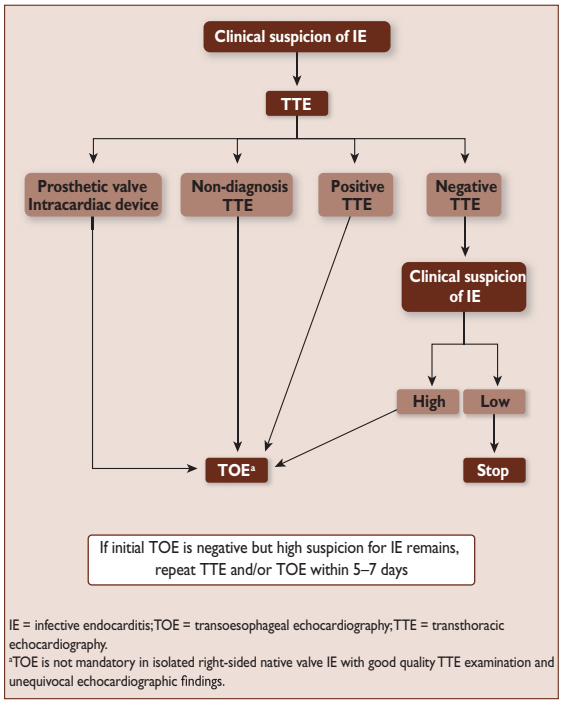

Figure 1 Indications for echocardiography in suspected infective endocarditis.

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Three echocardiographic findings are major criteria in the diagnosis of IE: vegetation, abscess or pseudoaneurysm and new dehiscence of a prosthetic valve[8,64,65] (see *Table 11* for anatomical and echocardiographic definitions). Nowadays, the sensitivity for the diagnosis of vegetations in native and prosthetic valves is 70% and 50%, respectively, for TTE and 96% and 92%, respectively, for TOE.[64,65] Specificity has been reported to be around 90% for both TTE and TOE. Identification of vegetations may be difficult in the presence of pre-existing valvular lesions (mitral valve prolapse, degenerative calcified lesions), prosthetic valves, small vegetations ($< 2-3$ mm), recent embolization and in non-vegetant IE. Diagnosis may be particularly challenging in IE affecting intracardiac devices, even with the use of TOE.

False diagnosis of IE may occur, and in some instances it may be difficult to differentiate vegetations from thrombi, Lambl's excrescences, cusp prolapse, chordal rupture, valve fibroelastoma, degenerative or myxomatous valve disease, strands, systemic lupus (Libman–Sacks) lesions, primary antiphospholipid syndrome, rheumatoid lesions or marantic vegetations.[74] Therefore the results of the echocardiographic study must be interpreted with caution, taking into account the patient's clinical presentation and the likelihood of IE.

Table 11 Anatomical and echocardiographic definitions

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

TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.

The sensitivity of TTE for the diagnosis of abscesses is about 50%, compared with 90% for TOE. Specificity higher than 90% has been reported for both TTE and TOE.[64,65] Small abscesses may be difficult to identify, particularly in the earliest stage of the disease, in the postoperative period and in the presence of a prosthetic valve. IE must always be suspected in patients with new periprosthetic regurgitation, even in the absence of other echocardiographic findings of IE.[64]

In cases with an initially negative examination, repeat TTE/TOE must be performed 5–7 days later if the clinical level of suspicion is still high, or even earlier in the case of *S. aureus* infection.[75] Other imaging techniques should also be used in this situation (see section 5.5). Finally, follow-up echocardiography to monitor complications and response to treatment is mandatory (*Figure 1*).

Real-time three-dimensional (3D) TOE allows the analysis of 3D volumes of cardiac structures in any possible plane. A recent study has shown that conventional TOE underestimates vegetation size and that 3D TOE is a feasible technique for the analysis of vegetation morphology and size that may overcome the shortcomings of conventional TOE, leading to a better prediction of the embolic risk in IE.[76] 3D TOE is particularly useful in the assessment of perivalvular extension of the infection, prosthetic valve dehiscence and valve perforation.[77] Although in clinical practice 3D TOE is increasingly performed along with conventional TOE in many centres, at present 3D TOE should still be regarded as a supplement to standard echocardiography in most cases.

5.3.2 Multislice computed tomography

The potential risks of vegetation embolization and/or haemodynamic decompensation during coronary angiography (when indicated) have led to proposals to consider MSCT coronary angiography as an alternative technique for some patients with endocarditis.[78]

MSCT can be used to detect abscesses/pseudoaneurysms with a diagnostic accuracy similar to TOE, and is possibly superior in the provision of information regarding the extent and consequences of any perivalvular extension, including the anatomy of pseudoaneurysms, abscesses and fistulae.[79] In aortic IE, CT may additionally be useful to define the size, anatomy and calcification of the aortic valve, root and ascending aorta, which may be used to inform surgical planning. In pulmonary/right-sided endocarditis, CT may reveal concomitant pulmonary disease, including abscesses and infarcts.

In the evaluation of prosthetic valve dysfunction, one recent study has suggested that MSCT may be equivalent or superior to echocardiography for the demonstration of prostheses-related vegetations, abscesses, pseudoaneurysms and dehiscence.[80] However, large comparative studies between the two techniques are missing, and echocardiography should always be performed first.

The higher sensitivity of MRI compared with CT for the detection of cerebral lesions is well known and has been confirmed in the context of endocarditis. However, in the critically ill patient, CT may be more feasible and practical and is an acceptable alternative when MRI is not available. MSCT angiography allows complete

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visualization of the intracranial vascular tree and carries a lower contrast burden and risk of permanent neurological damage than conventional digital subtraction angiography, with a sensitivity of 90% and specificity of 86%.[81] Where subarachnoid and/or intraparenchymal haemorrhage is detected, other vascular imaging (i.e. angiography) is required to diagnose or exclude a mycotic aneurysm if not detected on CT.

Contrast-enhanced MSCT has a high sensitivity and specificity for the diagnosis of splenic and other abscesses; however, the differentiation with infarction can be challenging. MSCT angiography provides a rapid and comprehensive exploration of the systemic arterial bed. Detailed multiplanar and 3D contrast-enhanced angiographic reconstructions allow vascular mapping with identification and characterization of peripheral vascular complications of IE and their follow-up.[82]

5.3.3 Magnetic resonance imaging

Given its higher sensitivity than CT, MRI increases the likelihood of detecting cerebral consequences of IE. Different studies including systematic cerebral MRI during acute IE have consistently reported frequent lesions, in 60–80% of patients.[83] Regardless of neurological symptoms, most abnormalities are ischaemic lesions (in 50–80% of patients), with more frequent small ischaemic lesions than larger territorial infarcts.[84] Other lesions are found in <10% of patients and are parenchymal or subarachnoidal haemorrhages, abscesses or mycotic aneurysms.[83–86]

Systematic cerebral MRI has an impact on the diagnosis of IE since it adds one minor Duke criterion[87] in patients who have cerebral lesions and no neurological symptoms. In one study, findings of cerebral MRI upgraded the diagnosis of IE in 25% of patients presenting initially with non-definite IE, thereby leading to earlier diagnosis.[85]

Cerebral microbleeds are detected only when using gradient echo T2* sequences and are found in 50–60% of patients.[85] Microbleeds represent small areas of haemosiderin deposits and are considered as an indicator of small vessel disease. The lack of concordance between ischaemic lesions and microbleeds and the differences in their predictive factors suggest that microbleeds are not of embolic origin.[86,88] Therefore, although IE and the presence of microbleeds are strongly linked, microbleeds should not be considered as a minor criterion in the Duke classification.[87]

Cerebral MRI is, in the majority of cases, abnormal in IE patients with neurological symptoms.[89] It has a higher sensitivity than CT in the diagnosis of the culprit lesion, in particular with regards to stroke, transient ischaemic attack and encephalopathy. MRI may also detect additional cerebral lesions that are not related to clinical symptoms. Cerebral MRI has no impact on the diagnosis of IE in patients with neurological symptoms, as they already have one minor Duke criterion, but MRI may impact the therapeutic strategy, particularly the timing of surgery.[89] In patients without neurological symptoms, MRI shows cerebral lesions in at least half of the patients, most often ischaemic lesions.[90] Systematic abdominal MRI detects lesions in one of three patients evaluated, most often affecting the spleen.[91] Ischaemic lesions are most common, followed by abscesses and haemorrhagic lesions. Abdominal MRI findings have no incremental impact on the diagnosis of IE when taking into account the findings of cerebral MRI.

To summarize, cerebral MRI allows for a better lesion characterization in patients with IE and neurological symptoms, whereas its impact on IE diagnosis is marked in patients with non-definite IE and without neurological symptoms.

5.3.4 Nuclear imaging

With the introduction of hybrid equipment for both conventional nuclear medicine [e.g. single-photon emission CT (SPECT)/CT] and PET (i.e. PET/CT), nuclear molecular techniques are evolving as an important supplementary method for patients with suspected IE and diagnostic difficulties. SPECT/CT imaging relies on the use of autologous radiolabelled leucocytes (^{111}In-oxine or ^{99m}Tc-hexamethylpropyleneamine oxime) that accumulate in a time-dependent fashion in late images versus earlier images,[92] whereas PET/CT is generally performed using a single acquisition time point (generally at 1 h) after administration of ^{18}F-FDG, which is actively incorporated *in vivo* by activated leucocytes, monocyte-macrophages and $CD4^+$ T-lymphocytes accumulating at the sites of infection.

Several reports have shown promising results for radiolabelled white blood cell (WBC) SPECT/CT and ^{18}F-FDG PET/CT imaging in IE. The main added value of using these techniques is the reduction in the rate of misdiagnosed IE, classified in the 'Possible IE' category using the Duke criteria, and the detection of peripheral embolic and metastatic infectious events.[93] Limitations to the use of ^{18}F-FDG PET/CT are represented by localization of septic emboli in the brain, due to the high physiological uptake of this tracer in the brain cortex, and to the fact that at this site, metastatic infections are generally <5 mm, the spatial resolution threshold of current PET/CT scanners.

Caution must be exercised when interpreting ^{18}F-FDG PET/CT results in patients who have recently undergone cardiac surgery, as a postoperative inflammatory response may result in non-specific ^{18}F-FDG uptake in the immediate postoperative period. Furthermore, a number of pathological conditions can mimic the pattern of focally increased ^{18}F-FDG uptake that is typically observed in IE, such as active thrombi, soft atherosclerotic plaques, vasculitis, primary cardiac tumours, cardiac metastasis from a non-cardiac tumour, post-surgical inflammation and foreign body reactions.[94]

Radiolabelled WBC SPECT/CT is more specific for the detection of IE and infectious foci than ^{18}F-FDG PET/CT and should be preferred in all situations that require enhanced specificity.[95] Disadvantages of scintigraphy with radiolabelled WBC are the requirement of blood handling for radiopharmaceutical preparation, the duration of the procedure, which is more time consuming than PET/CT, and a slightly lower spatial resolution and photon detection efficiency compared with PET/CT.

An additional promising role of ^{18}F-FDG PET/CT may be seen in patients with established IE, in whom it could be employed to monitor response to antimicrobial treatment. However, sufficient data are not available at this time to make a general recommendation.

5.4 Microbiological diagnosis

5.4.1 Blood culture–positive infective endocarditis

Positive blood cultures remain the cornerstone of diagnosis and provide live bacteria for both identification and susceptibility testing. At

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least three sets are taken at 30-min intervals, each containing 10 mL of blood, and should be incubated in both aerobic and anaerobic atmospheres. Sampling should be obtained from a peripheral vein rather than from a central venous catheter (because of the risk of contamination and misleading interpretation), using a meticulous sterile technique. This is virtually always sufficient to identify the usual causative microorganisms. The need for culture before antibiotic administration is self-evident. In IE, bacteraemia is almost constant and has two implications: (i) there is no rationale for delaying blood sampling with peaks of fever and (ii) virtually all blood cultures are positive. As a result, a single positive blood culture should be regarded cautiously for establishing the diagnosis of IE. The microbiology laboratory should be aware of the clinical suspicion of IE at the time of blood culture sampling. When a microorganism has been identified, blood cultures should be repeated after 48–72 h to check the effectiveness of treatment. Automated machines perform continuous monitoring of bacterial growth, which ensures quick provision of reports to physicians. When a positive blood culture bottle is identified, presumptive identification is based on Gram staining. This information is immediately given to clinicians in order to adapt presumptive antibiotic therapy. Complete identification is routinely achieved within 2 days, but may require longer for fastidious or atypical organisms. Since the delay between blood culture sampling and definitive identification of the organism responsible for the bacteraemia and antibiotic susceptibility testing is long, many improvements have been proposed to speed up the process of detection and identification. One of the most recent procedures for rapid bacterial identification is based on peptide spectra obtained by matrix-assisted laser desorption ionization time-of-flight mass spectrometry. This technique has recently demonstrated its usefulness in clinical microbiology; it also has the potential for direct identification of bacterial colonies in the blood culture bottle supernatant.[96]

5.4.2 Blood culture–negative infective endocarditis

Blood culture–negative IE (BCNIE) refers to IE in which no causative microorganism can be grown using the usual blood culture methods. BCNIE can occur in up to 31% of all cases of IE and often poses considerable diagnostic and therapeutic dilemmas. BCNIE most commonly arises as a consequence of previous antibiotic administration, underlying the need for withdrawing antibiotics and repeating blood cultures in this situation. BCNIE can be caused by fungi or fastidious bacteria, notably obligatory intracellular bacteria. Isolation of these microorganisms requires culturing them on specialized media, and their growth is relatively slow. According to local epidemiology, systematic serological testing for *Coxiella burnetii*, *Bartonella* spp., *Aspergillus* spp., *Mycoplasma pneumonia*, *Brucella* spp. and *Legionella pneumophila* should be proposed, followed by specific polymerase chain reaction (PCR) assays for *Tropheryma whipplei*, *Bartonella* spp. and fungi (*Candida* spp., *Aspergillus* spp.) from the blood[97] (*Table 12*). Most studies using blood PCR for the diagnosis of BCNIE have highlighted the importance of *Streptococcus gallolyticus* and *Streptococcus mitis*, enterococci, *S. aureus*, *Escherichia coli* and fastidious bacteria, the respective prevalence of which varies according to the status and condition of the patient.[98]

Table 12 Investigation of rare causes of blood culture negative infective endocarditis

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

Ig = immunoglobulin; PCR = polymerase chain reaction.

When all microbiological assays are negative, the diagnosis of non-infectious endocarditis should systematically be considered and assays for antinuclear antibodies as well as antiphospholipid syndrome {anticardiolipin antibodies [immunoglobulin (Ig)G] and anti-β_2-glycoprotein 1 antibodies [IgG and IgM]} should be performed. When all other tests are negative and the patient has a porcine bioprosthesis together with markers of allergic response, anti-pork antibodies should be sought.[99]

5.4.3 Histological diagnosis of infective endocarditis

Pathological examination of resected valvular tissue or embolic fragments remains the gold standard for the diagnosis of IE. All tissue samples that are excised during the course of the surgical removal of cardiac valves must be collected in a sterile container without fixative or culture medium. The entire sample should be taken to the diagnostic microbiology laboratory for optimal recovery and identification of microorganisms.

5.4.4 Proposed strategy for a microbiological diagnostic algorithm in suspected IE

A proposed diagnostic scheme is provided in *Figure 2*. When there is clinical suspicion of IE and blood cultures remain negative at 48 h, liaison with the microbiologist is necessary. A suggested strategy is the use of a diagnostic kit including blood cultures and systematic serological testing for *C. burnetii*, *Bartonella* spp., *Aspergillus* spp., *L. pneumophila*, *Brucella* spp., *M. pneumonia*, as well as rheumatoid factor, the serological tests for antiphospholipid syndrome [anticardiolipin (IgG) and anti-β_2-glycoprotein 1 (IgG and IgM)], antinuclear antibodies and anti-pork antibodies. In addition, cardiac valvular materials obtained at surgery have to be subjected to systematic culture, histological examination and PCR aimed at documenting the presence of fastidious organisms.

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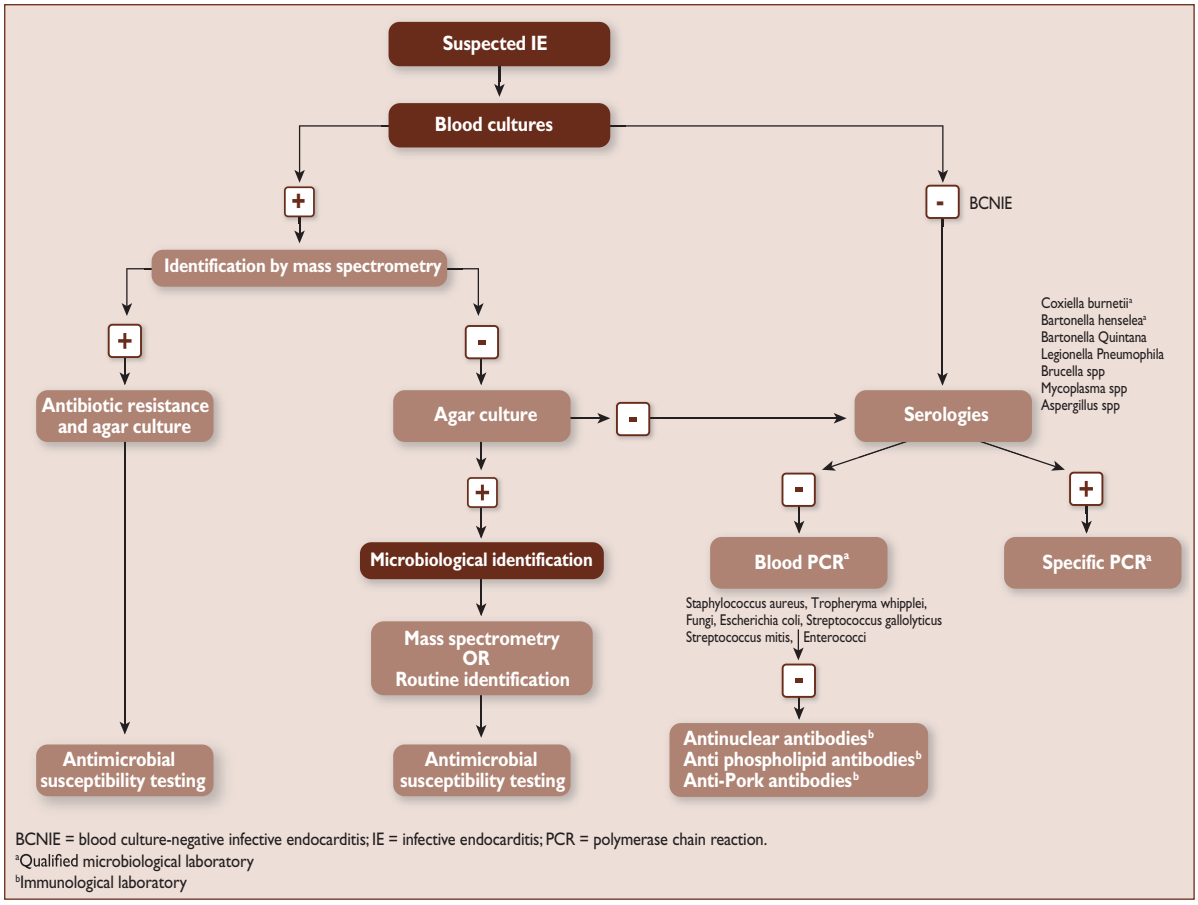

Figure 2 Microbiological diagnostic algorithm in culture-positive and culture-negative IE.

5.5 Diagnostic criteria

Besides the pathological aspect obtained after valve surgery, in clinical practice the diagnosis of IE usually relies on the association between an infective syndrome and recent endocardial involvement. This is the cornerstone of the various criteria proposed to facilitate the difficult diagnosis of this disease. Thus, in 2000, the modified Duke criteria were recommended for diagnostic classification (*Table 13*). These criteria are based on clinical, echocardiographic and biological findings, as well as the results of blood cultures and serologies.[87] This classification has a sensitivity of approximately 80% overall when the criteria are evaluated at the end of patient follow-up in epidemiological studies.[100] However, the modified Duke criteria show a lower diagnostic accuracy for early diagnosis in clinical practice, especially in the case of prosthetic valve endocarditis (PVE) and pacemaker or defibrillator lead IE, for which echocardiography is normal or inconclusive in up to 30% of cases.[101,102] Recent advances in imaging techniques have resulted in an improvement in identification of endocardial involvements and extracardiac complications of IE.[10,103] Thus recent works have demonstrated that cardiac/whole-body CT scan, cerebral MRI, ^{18}F-FDG PET/CT and radiolabelled leucocyte SPECT/CT might improve the detection of silent vascular phenomena (embolic events or infectious aneurysms) as well as endocardial lesions.[79,80,83–85,93,94,104–108] The addition of the results of these imaging modalities may improve the sensitivity of the modified Duke criteria in difficult cases.

Table 13 Definition of infective endocarditis according to the modified Duke criteria (adapted from Li *et al.*[87])

Definite IE
Pathological criteria • Microorganisms demonstrated by culture or on histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or • Pathological lesions; vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis **Clinical criteria** • 2 major criteria; or • 1 major criterion and 3 minor criteria; or • 5 minor criteria
Possible IE
• 1 major criterion and 1 minor criterion; or • 3 minor criteria
Rejected IE
• Firm alternate diagnosis; or • Resolution of symptoms suggesting IE with antibiotic therapy for ≤4 days; or • No pathological evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 days; or • Does not meet criteria for possible IE, as above

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Given the recent published data, the Task Force proposes the addition of three further points in the diagnostic criteria (*Table 14*):

(1) The identification of paravalvular lesions by cardiac CT should be considered a major criterion.
(2) In the setting of the suspicion of endocarditis on a prosthetic valve, abnormal activity around the site of implantation detected by ^{18}F-FDG PET/CT (only if the prosthesis was implanted for >3 months) or radiolabelled leucocyte SPECT/CT should be considered a major criterion.
(3) The identification of recent embolic events or infectious aneurysms by imaging only (silent events) should be considered a minor criterion.

Table 14 Definitions of the terms used in the European Society of Cardiology 2015 modified criteria for the diagnosis of infective endocarditis

Major criteria
1. Blood cultures positive for IE
a. Typical microorganisms consistent with IE from 2 separate blood cultures: • *Viridans streptococci, Streptococcus gallolyticus (Streptococcus bovis), HACEK group, Staphylococcus aureus;* or • Community-acquired enterococci, in the absence of a primary focus; or
b. Microorganisms consistent with IE from persistently positive blood cultures: • ≥2 positive blood cultures of blood samples drawn >12 h apart; or • All of 3 or a majority of ≥4 separate cultures of blood (with first and last samples drawn ≥1 h apart); or
c. Single positive blood culture for Coxiella burnetii or phase I IgG antibody titre >1:800
2. Imaging positive for IE
a. Echocardiogram positive for IE: • Vegetation; • Abscess, pseudoaneurysm, intracardiac fistula; • Valvular perforation or aneurysm; • New partial dehiscence of prosthetic valve.
b. Abnormal activity around the site of prosthetic valve implantation detected by ^{18}F-FDG PET/CT (only if the prosthesis was implanted for >3 months) or radiolabelled leukocytes SPECT/CT.
c. Definite paravalvular lesions by cardiac CT.
Minor criteria
1. Predisposition such as predisposing heart condition, or injection drug use.
2. Fever defined as temperature >38°C.
3. Vascular phenomena (including those detected by imaging only): major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway's lesions.
4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor.
5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE.

CT = computed tomography; FDG = fluorodeoxyglucose; HACEK = Haemophilus parainfluenzae, H. aphrophilus, H. paraphrophilus, H. influenzae, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae, and K. denitrificans; IE = infective endocarditis; Ig = immunoglobulin; PET = positron emission tomography; SPECT = single photon emission computerized tomography. Adapted from Li *et al.*[87]

Figure 3 presents the proposed ESC diagnostic algorithm including the ESC 2015 modified diagnostic criteria. The diagnosis of IE is still based on the Duke criteria, with a major role of echocardiography and blood cultures. When the diagnosis remains only 'possible' or even 'rejected' but with a persisting high level of clinical suspicion, echocardiography and blood culture should be repeated and other imaging techniques should be used, either for diagnosis of cardiac involvement (cardiac CT, ^{18}F-FDG PET/CT or radiolabelled leucocyte SPECT/CT) or for imaging embolic events (cerebral MRI, whole-body CT and/or PET/CT). The results of these new investigations should then be integrated in the ESC 2015 modified diagnostic criteria.

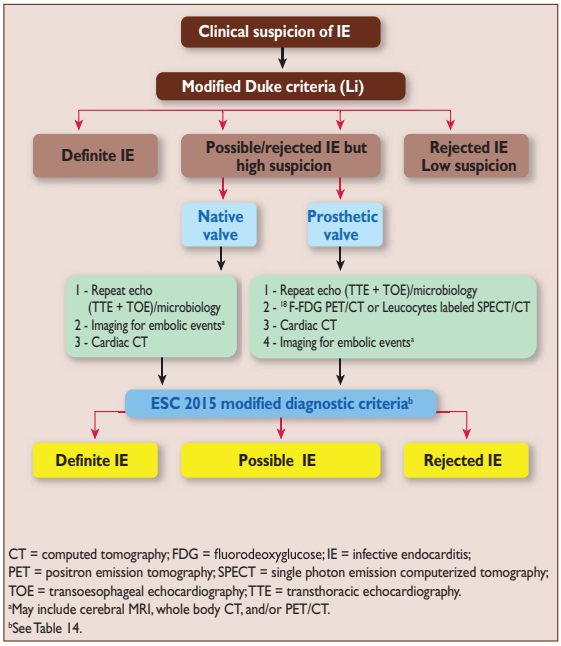

Figure 3 European Society of Cardiology 2015 algorithm for diagnosis of infective endocarditis.

Finally, ^{18}F-FDG PET/CT and radiolabelled leucocyte SPECT/CT have proven their role in the diagnosis of cardiovascular electronic implanted devices,[108] but the data are not sufficient for them to be included in the diagnostic criteria of the specific topic of IE on pacemaker or defibrillator leads.

In summary, echocardiography (TTE and TOE), positive blood cultures and clinical features remain the cornerstone of IE diagnosis. When blood cultures are negative, further microbiological studies are needed. The sensitivity of the Duke criteria can be improved by new imaging modalities (MRI, CT, PET/CT) that allow the diagnosis of embolic events and cardiac involvement when TTE/TOE findings are negative or doubtful. These criteria are useful, but they do not replace the clinical judgement of the Endocarditis Team.

6. Prognostic assessment at admission

The in-hospital mortality rate of patients with IE varies from 15% to 30%.[109–114] Rapid identification of patients at highest risk of death

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may offer the opportunity to change the course of the disease (i.e. emergency or urgent surgery) and improve prognosis.[115] Prognosis in IE is influenced by four main factors: patient characteristics, the presence or absence of cardiac and non-cardiac complications, the infecting organism and the echocardiographic findings (*Table 15*). The risk of patients with left-sided IE has been formally assessed according to these variables.[116,117] Patients with HF, periannular complications and/or *S. aureus* infection are at highest risk of death and need for surgery in the active phase of the disease.[117] When three of these factors are present, the risk reaches 79%.[117] Therefore these patients with complicated IE should be referred early and managed in a reference centre with surgical facilities and preferably by an Endocarditis Team.[118] A high degree of co-morbidity, diabetes, septic shock, moderate-to-severe ischaemic stroke, brain haemorrhage or the need for haemodialysis are also predictors of poor in-hospital outcome.[111–115,119–122] Persistence of positive blood cultures 48–72 h after initiation of antibiotic treatment indicates a lack of infection control and is an independent risk factor for in-hospital mortality.[123]

Table 15 Predictors of poor outcome in patients with infective endocarditis

Patient characteristics
• Older age
• Prosthetic valve IE
• Diabetes mellitus
• Comorbidity (e.g., frailty, immunosuppression, renal or pulmonary disease)
Clinical complications of IE
• Heart failure
• Renal failure
• >Moderate area of ischaemic stroke
• Brain haemorrhage
• Septic shock
Microorganism
• *Staphylococcus aureus*
• Fungi
• Non-HACEK Gram-negative bacilli
Echocardiographic findings
• Periannular complications
• Severe left-sided valve regurgitation
• Low left ventricular ejection fraction
• Pulmonary hypertension
• Large vegetations
• Severe prosthetic valve dysfunction
• Premature mitral valve closure and other signs of elevated diastolic pressures

HACEK = Haemophilus parainfluenzae, H. aphrophilus, H. paraphrophilus, H. influenzae, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae, and K. denitrificans; IE = infective endocarditis.

Nowadays, 40–50% of patients undergo cardiac surgery during hospitalization.[37,109–114] Surgical mortality in IE strongly depends on its indication. Among patients who need emergency or urgent surgery, septic shock, persistent signs of infection and renal failure are predictors of mortality.[112,120,124] Predictably, patients with an indication for surgery who cannot proceed due to prohibitive surgical risk have the worst prognosis.[125]

In summary, prognostic assessment at admission can be performed using simple clinical, microbiological and echocardiographic parameters and should be used to select the best initial approach. Patients with persistently positive blood cultures 48–72 h after starting antibiotics have a worse prognosis.

7. Antimicrobial therapy: principles and methods

7.1 General principles

Successful treatment of IE relies on microbial eradication by antimicrobial drugs. Surgery contributes by removing infected material and draining abscesses. Host defences are of little help. This explains why bactericidal regimens are more effective than bacteriostatic therapy, both in animal experiments and in humans.[126,127] Aminoglycosides synergize with cell-wall inhibitors (i.e. beta-lactams and glycopeptides) for bactericidal activity and are useful for shortening the duration of therapy (e.g. oral streptococci) and eradicating problematic organisms (e.g. *Enterococcus* spp.).

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

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

In NVE needing valve replacement by a prosthesis during antibiotic therapy, the postoperative antibiotic regimen should be that recommended for NVE, not for PVE. In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy (negative blood culture in the case of initial positive blood culture), not on the day of surgery. A new full course of treatment should only start if valve cultures are positive, with the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate.

Finally, there are six important considerations in the current recommendations:

(1) The indications and pattern of use of aminoglycosides have changed. They are no longer recommended in staphylococcal NVE because their clinical benefits have not been demonstrated, but they can increase renal toxicity;[128] when they are indicated in other conditions, aminoglycosides should be given in a single daily dose to reduce nephrotoxicity.[129]

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(2) Rifampin should be used only in foreign body infections such as PVE after 3–5 days of effective antibiotic therapy, once the bacteraemia has been cleared. The rationale supporting this recommendation is based on the likely antagonistic effect of the antibiotic combinations with rifampin against planktonic/replicating bacteria,[130] the synergy seen against dormant bacteria within the biofilms and prevention of rifampin-resistant variants.[131]

(3) Daptomycin and fosfomycin have been recommended for treating staphylococcal endocarditis and netilmicin for treating penicillin-susceptible oral and digestive streptococci, but they are considered alternative therapies in these guidelines because they are not available in all European countries. When daptomycin is indicated, it must be given at high doses (≥10 mg/kg once daily[132]) and combined with a second antibiotic to increase activity and avoid the development of resistance.[133,134]

(4) Only published antibiotic efficacy data from clinical trials and cohort studies in patients with endocarditis (or bacteraemia if there are no endocarditis data) have been considered in these guidelines. Data from experimental endocarditis models have not been taken into account in most cases.

(5) We are still using the Clinical and Laboratory Standards Institute minimum inhibitory concentration (MIC) breakpoints instead of the European Committee on Antimicrobial Susceptibility Testing ones because most endocarditis data are derived from studies using the former breakpoints.

(6) Although a consensus was obtained for the majority of antibiotic treatments, the optimal treatment of staphylococcal IE and the empirical treatment are still debated.

7.2 Penicillin-susceptible oral streptococci and *Streptococcus bovis* group

Recommended regimens against susceptible streptococci (penicillin MIC ≤0.125 mg/L) are summarized in *Table 16*.[6,8,135,136] The cure rate is expected to be >95%. In uncomplicated cases, short-term 2-week therapy can be administered by combining penicillin or ceftriaxone with gentamicin or netilmicin.[137,138] Gentamicin and netilmicin can be given once daily in patients with IE due to susceptible streptococci and normal renal function. Ceftriaxone alone or combined with gentamicin or netilmicin given once a day is particularly convenient for outpatient therapy.[137–139] If desensitization cannot be performed, patients allergic to beta-lactam should receive vancomycin. Teicoplanin has been proposed as an alternative,[8] but requires loading doses (6 mg/kg/12 h for 3 days) followed by 6–10 mg/kg/day. Loading is critical because the drug is highly bound (≥98%) to serum proteins and penetrates slowly into vegetations.[140] However, only limited retrospective studies have assessed its efficacy in streptococcal[141] and enterococcal[142] IE.

7.3 Penicillin-resistant oral streptococci and *Streptococcus bovis* group

Penicillin-resistant oral streptococci are classified as intermediate resistant (MIC 0.25–2 mg/L) and fully resistant (MIC ≥4 mg/L). However, some guidelines consider an MIC >0.5 mg/L as fully resistant.[6,8,135] Such resistant streptococci are increasing in number. Large strain collections have reported >30% of intermediate- and fully resistant *Streptococcus mitis* and *Streptococcus oralis*.[142,143] Conversely, >99% of digestive streptococci remain penicillin susceptible.

Treatment guidelines for penicillin-resistant streptococcal IE rely on retrospectives series. Compiling four of them, 47 of 60 patients (78%) were treated with penicillin or ceftriaxone, mostly combined with aminoglycosides, and some with either clindamycin or aminoglycosides alone.[144–147] Most penicillin MICs were ≥1 mg/L. Fifty patients (83%) were cured and 10 (17%) died. Death was not related to resistance, but to the patients' underlying conditions.[146] Treatment outcomes were similar in PVE and NVE.[145] Hence antibiotic therapy for penicillin-resistant and penicillin-susceptible oral streptococci is qualitatively similar (*Table 16*). However, in penicillin-resistant cases, aminoglycoside treatment must be given for at least 2 weeks and short-term therapy regimens are not recommended. Little experience exists with highly resistant isolates (MIC ≥4 mg/L), but vancomycin might be preferred in such circumstances (combined with aminoglycosides). There is very limited experience with daptomycin.

7.4 *Streptococcus pneumoniae*, beta-haemolytic streptococci (groups A, B, C, and G)

IE due to *S. pneumoniae* has become rare since the introduction of antibiotics. It is associated with meningitis in up to 30% of cases,[149] which requires special consideration in cases with penicillin resistance. Treatment of penicillin-susceptible strains (MIC ≤0.06 mg/L) is similar to that of oral streptococci (*Table 16*), except for the use of short-term 2-week therapy, which has not been formally investigated. The same holds true for penicillin intermediate (MIC 0.125–2 mg/L) or resistant strains (MIC ≥4 mg/L) without meningitis, although for resistant strains some authors recommend high doses of cephalosporins (e.g. cefotaxime or ceftriaxone) or vancomycin. In cases with meningitis, penicillin must be avoided because of its poor penetration of the cerebrospinal fluid, and should be replaced with ceftriaxone or cefotaxime alone or in association with vancomycin[150] according to the antibiotic susceptibility pattern.

IE due to group A, B, C, or G streptococci—including *Streptococcus anginosus* group (*S. constellatus*, *S. anginosus*, and *S. intermedius*)—is relatively rare.[151] Group A streptococci are uniformly susceptible to beta-lactams (MIC ≤0.12 mg/L), whereas other serogroups may display some degree of resistance. IE due to group B streptococci was once associated with the peripartum period, but it now occurs in other adults, especially the elderly. Group B, C, and G streptococci and *S. anginosus* produce abscesses and thus may require adjunctive surgery.[151] Mortality from group B PVE is very high and cardiac surgery is recommended.[152] Antibiotic treatment is similar to that of oral streptococci (*Table 16*), except that short-term therapy is not recommended. Gentamicin should be given for 2 weeks.

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Table 16 **Antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus* bovis group[a]**

Antibiotic	Dosage and route	Duration (weeks)	Class[b]	Level[c]	Ref.[d]	Comments
Strains penicillin-susceptible (MIC ≤ 0.125 mg/L) oral and digestive streptococci						
Standard treatment: 4-week duration						
Penicillin G *or* Amoxicillin[e] *or* Ceftriaxone[f]	12–18 million U/day i.v. either in 4–6 doses or continuously 100–200 mg/kg/day i.v. in 4–6 doses 2 g/day i.v. or i.m. in 1 dose	4 4 4	I I I	B B B	6,8, 135–139	Preferred in patients > 65 years or with impaired renal or VIII (vestibulocochlear) cranial nerve functions. 6-week therapy recommended for patients with PVE
	Paediatric doses:[g] Penicillin G 200,000 U/kg/day i.v. in 4–6 divided doses Amoxicillin 300 mg/kg/day i.v. in 4–6 equally divided doses Ceftriaxone 100 mg/kg/day i.v. or i.m. in 1 dose					
Standard treatment: 2-week duration						
Penicillin G *or* Amoxicillin[e] *or* Ceftriaxone[f] combined with Gentamicin[h] *or* Netilmicin	12–18 million U/day i.v. either in 4–6 doses or continuously 100–200 mg/kg/day i.v. in 4–6 doses 2 g/day i.v. or i.m. in 1 dose 3 mg/kg/day i.v. or i.m. in 1 dose 4–5 mg/kg/day i.v. in 1 dose	2 2 2 2 2	I I I I I	B B B B B	6,8, 127, 135–138	Only recommended in patients with non-complicated NVE with normal renal function. Netilmicin is not available in all European countries.
	Paediatric doses:[g] Penicillin G, amoxicillin, and ceftriaxone as above Gentamicin 3 mg/kg/day i.v. or i.m. in 1 dose or 3 equally divided doses					
In beta-lactam allergic patients[i]						
Vancomycin[j]	30 mg/kg/day i.v. in 2 doses	4	I	C		6-week therapy recommended for patients with PVE
	Paediatric doses:[g] Vancomycin 40 mg/kg/day i.v. in 2 or 3 equally divided doses					
Strains relatively resistant to penicillin (MIC 0.250–2 mg/l)[k]						
Standard treatment						
Penicillin G *or* Amoxicillin[e] *or* Ceftriaxone[f] combined with Gentamicin[h]	24 million U/day i.v. either in 4–6 doses or continuously 200 mg/kg/day i.v. in 4–6 doses 2 g/day i.v. or i.m. in 1 dose 3 mg/kg/day i.v. or i.m. in 1 dose	4 4 4 2	I I I I	B B B B	6,8, 135, 136	6-week therapy recommended for patients with PVE
In beta-lactam allergic patients[i]						
Vancomycin[j] with Gentamicin[k]	30 mg/kg/day i.v. in 2 doses 3 mg/kg/day i.v. or i.m. in 1 dose	4 2	I I	C C		6-week therapy recommended for patients with PVE
	Paediatric doses:[g] As above					

C_{min} = minimum concentration; IE = infective endocarditis; i.m. = intramuscular; i.v. = intravenous; MIC = minimum inhibitory concentration; NVE = native valve endocarditis; PVE = prosthetic valve endocarditis; U = units.

[a]Refer to text for other streptococcal species; [b]Class of recommendation; [c]Level of evidence; [d]Reference(s) supporting recommendations; [e]Or ampicillin, same dosages as amoxicillin; [f]Preferred for outpatient therapy; [g]Paediatric doses should not exceed adult doses; [h]Renal function and serum gentamicin concentrations should be monitored once a week. When given in a single daily dose, pre-dose (trough) concentrations should be < 1 mg/L and post-dose (peak; 1 hours after injection) serum concentrations should be ~10–12 mg/L.[148]; [i]Penicillin desensitization can be attempted in stable patients; [j]Serum vancomycin concentrations should achieve 10–15 mg/L at pre-dose (trough) level, although some experts recommend to increase the dose of vancomycin to 45–60 mg/kg/day i.v. in 2 or 3 divided doses to reach serum trough vancomycin levels (C_{min}) of 15–20 mg/L as in staphylococcal endocarditis. However, vancomycin dose should not exceed 2 g/d unless serum levels are monitored and can be adjusted to obtain a peak plasma concentration of 30–45 μg/mL 1 hour after completion of the i.v. infusion of the antibiotic; [k]Patients with penicillin-resistant strains (MIC > 2 mg/L) should be treated as enterococcal endocarditis (see *Table 18*).

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7.5 *Granulicatella* and *Abiotrophia* (formerly nutritionally variant streptococci)

Granulicatella and *Abiotrophia* produce IE with a protracted course, which is associated with large vegetations (>10 mm), higher rates of complications and valve replacement (around 50%),[153,154] possibly due to delayed diagnosis and treatment. Antibiotic recommendations include penicillin G, ceftriaxone or vancomycin for 6 weeks, combined with an aminoglycoside for at least the first 2 weeks.[153,154]

7.6 *Staphylococcus aureus* and coagulase-negative staphylococci

Staphylococcus aureus is usually responsible for acute and destructive IE, whereas CoNS produce more protracted valve infections (except *S. lugdunensis*[155] and some cases of *S. capitis*).[156,157] *Table 17* summarizes treatment recommendations for methicillin-susceptible and methicillin-resistant *S. aureus* and CoNS in both native and prosthetic valve IE. Of note, the addition of an aminoglycoside in staphylococcal native valve IE is no longer recommended because it increases renal toxicity.[128,158] Short-term (2-week) and oral treatments have been proposed for uncomplicated right-sided native valve methicillin-susceptible *S. aureus* (MSSA) IE (see also section 12.4.2), but these regimens cannot be applied to left-sided IE. For penicillin-allergic patients with MSSA IE, penicillin desensitization can be attempted in stable patients since vancomycin is inferior to beta-lactams[159] and should not be given. If beta-lactams cannot be given, where available, daptomycin should be chosen and given in combination with another effective antistaphylococcal drug to increase activity and avoid the development of resistance. Some experts have recommended a combination of high doses of cotrimoxazole plus clindamycin as an alternative for *S. aureus* IE.[160] *S. lugdunensis* is always methicillin susceptible and can be treated with cloxacillin.[155]

Staphylococcus aureus PVE carries a very high risk of mortality (>45%)[161] and often requires early valve replacement. Other differences in comparison with NVE include the overall duration of therapy, the use of aminoglycosides and the addition of rifampin after 3–5 days of effective antibiotic therapy once the bacteraemia has been cleared. The rationale supporting this recommendation is based on the antagonistic effect of the antibiotic combinations with rifampin against planktonic/replicating bacteria and the synergy seen against dormant bacteria within the biofilm, as it has been demonstrated in foreign body infection models and clinically in prosthetic orthopaedic and vascular infections. Although the level of evidence is poor, adding rifampin to the treatment of staphylococcal PVE is standard practice, although treatment may be associated with microbial resistance, hepatotoxicity and drug interactions.[164]

7.7 Methicillin-resistant and vancomycin-resistant staphylococci

Methicillin-resistant *S. aureus* (MRSA) produces low-affinity penicillin binding protein 2a (PBP2a), which confers cross-resistance to most beta-lactams. MRSA are usually resistant to multiple antibiotics, leaving only vancomycin and daptomycin to treat severe infections. However, vancomycin-intermediate *S. aureus* (MIC 4–8 mg/L) and hetero-vancomycin-intermediate *S. aureus* (MIC ≤2 mg/L, but with subpopulations growing at higher concentrations) have emerged worldwide and are associated with IE treatment failures.[165,166] Moreover, some highly vancomycin-resistant *S. aureus* strains have been isolated from infected patients in recent years, requiring new approaches to treatment. In addition, a systematic review and meta-analysis of studies published between 1996 and 2011 in patients with MRSA bacteraemia with vancomycin-susceptible strains (MIC ≤2 mg/L)[167] showed that a high vancomycin MIC (≥1.5 mg/L) was associated with higher mortality. Daptomycin is a lipopeptide antibiotic approved for *S. aureus* bacteraemia and right-sided IE.[168] Cohort studies of *S. aureus* and CoNS IE[132,168–170] have shown that daptomycin is at least as effective as vancomycin, and in two cohort studies of MRSA bacteraemia with high vancomycin MICs (>1 mg/L),[171,172] daptomycin was associated with better outcomes (including survival) compared with vancomycin. Importantly, daptomycin needs to be administered in appropriate doses and combined with other antibiotics to avoid further resistance in patients with IE.[168,173] For this reason, daptomycin should be given at high doses (≥10 mg/kg), and most experts recommend it be combined with beta-lactams[133] or fosfomycin[134] [beta-lactams (and probably fosfomycin) increase membrane daptomycin binding by decreasing the positive surface charge] for NVE and with gentamicin and rifampin for PVE.[168,173,174]

Other alternatives include fosfomycin plus imipenem,[175] newer beta-lactams with relatively good PBP2a affinity such as ceftaroline,[176] quinupristin–dalfopristin with or without beta-lactams,[177,178] beta-lactams plus oxazolidinones (linezolid),[179] beta-lactams plus vancomycin[180] and high doses of trimethoprim/sulfamethoxazole and clindamycin.[160] Such cases warrant collaborative management with an ID specialist.

7.8 Enterococcus spp.

Enterococcal IE is primarily caused by *Enterococcus faecalis* (90% of cases) and, more rarely, by *Enterococcus faecium* (5% of cases) or other species.[181] They pose two major problems. First, enterococci are highly resistant to antibiotic-induced killing, and eradication requires prolonged administration (up to 6 weeks) of synergistic bactericidal combinations of two cell wall inhibitors (ampicillin plus ceftriaxone, which synergize by inhibiting complementary PBPs) or one cell wall inhibitor with aminoglycosides (*Table 18*). Second, they may be resistant to multiple drugs, including aminoglycosides [high-level aminoglycoside resistance (HLAR)], beta-lactams (via PBP5 modification and sometimes beta-lactamases) and vancomycin.[182]

Fully penicillin-susceptible strains (penicillin MIC ≤8 mg/L) are treated with penicillin G or ampicillin (or amoxicillin) combined with gentamicin. Ampicillin (or amoxicillin) might be preferred since MICs are two to four times lower. Gentamicin resistance is frequent in both *E. faecalis* and *E. faecium*.[182] An aminoglycoside MIC >500 mg/L (HLAR) is associated with the loss of bactericidal synergism with cell wall inhibitors, and aminoglycosides should not be used in such conditions. Streptomycin may remain active in such cases and is a useful alternative.

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Table 17 Antibiotic treatment of infective endocarditis due to *Staphylococcus* spp.

Antibiotic	Dosage and route	Duration (weeks)	Class[i]	Level[j]	Ref.[k]	Comments
Native valves						
Methicillin-susceptible staphylococci						
(Flu)cloxacillin *or* oxacillin	12 g/day i.v. in 4–6 doses	4–6	I	B	6,8, 128, 135, 136, 158	Gentamicin addition is not recommended because clinical benefit has not been demonstrated and there is increased renal toxicity
	Paediatric doses:[g] 200–300 mg/kg/day i.v. in 4–6 equally divided doses					
Alternative therapy* Cotrimoxazole[a]	Sulfamethoxazole 4800 mg/day and Trimethoprim 960 mg/day (i.v. in 4–6 doses)	1 i.v. + 5 oral intake	IIb	C		*for *Stahylococcus aureus*
with Clindamycin	1800mg/day i.v. in 3 doses	1	IIb	C		
	Paediatric doses:[g] Sulfamethoxazole 60 mg/kg/day and Trimethoprim 12 mg/kg/day (i.v. in 2 doses) Clindamycin 40 mg/kg/day (i.v. in 3 doses)					
Penicillin-allergic patients[h] or methicillin-resistant staphylococci						
Vancomycin[b] **	30–60 mg/kg/day i.v. in 2–3 doses	4–6	I	B	6,8, 135, 136	**Cephalosporins** (cefazolin 6 g/day or cefotaxime 6 g/day i.v. in 3 doses) are recommended for penicillin-allergic patients with non-anaphylactic reactions with methicillin-susceptible endocarditis
	Paediatric doses:[g] 40 mg/kg/day i.v. in 2–3 equally divided doses					
Alternative therapy**: Daptomycin[c,d]	10 mg/kg/day i.v. once daily	4–6	IIa	C		**Daptomycin** is superior to vancomycin for MSSA and MRSA bacteraemia with vancomycin MIC > 1 mg/L
	Paediatric doses:[g] 10 mg/kg/day i.v. once daily					
Alternative therapy* Cotrimoxazole[a]	Sulfamethoxazole 4800 mg/day and Trimethoprim 960 mg/day (i.v. in 4–6 doses)	1 i.v. + 5 oral intake	IIb	C		*for *Stahylococcus aureus*
with Clindamycin	1800mg/day IV in 3 doses	1	IIb	C		
Prosthetic valves						
Methicillin-susceptible staphylococci						
(Flu)cloxacillin *or* oxacillin with Rifampin[e] and Gentamicin[f]	12 g/day i.v. in 4–6 doses	≥ 6	I	B	6,8, 135, 136	Starting rifampin 3–5 days later than vancomycin and gentamicin has been suggested by some experts. Gentamicin can be given in a single daily dose in order to reduce renal toxicity
	900–1200 mg i.v. or orally in 2 or 3 divided doses	≥ 6	I	B		
	3 mg/kg/day i.v. or i.m. in 1 or 2 doses	2	I	B		
	Paediatric doses:[g] Oxacillin and (flu)cloxacillin as above Rifampin 20 mg/kg/day i.v. or orally in 3 equally divided doses					
Penicillin-allergic patients[h] and methicillin-resistant staphylococci						
Vancomycin[b] with Rifampin[e] and Gentamicin[f]	30–60 mg/kg/day i.v. in 2–3 doses	≥ 6	I	B	6,8, 135, 136	**Cephalosporins** (cefazolin 6 g/day or cefotaxime 6 g/day i.v. in 3 doses) are recommended for penicillin-allergic patients with non-anaphylactic reactions with methicillin-susceptible endocarditis. Starting rifampin 3–5 days later than vancomycin and gentamicin has been suggested by some experts. Gentamicin can be given in a single daily dose in order to reduce renal toxicity
	900–1200 mg i.v. or orally in 2 or 3 divided doses	≥ 6	I	B		
	3 mg/kg/day i.v. or i.m. in 1 or 2 doses	2	I	B		
	Paediatric dosing:[g] As above					

AUC = area under the curve; C_{min} = minimum concentration; IE = infective endocarditis; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *S. aureus*; PVE = prosthetic valve endocarditis.
[a]Renal function, serum Cotrimoxazole concentrations should be monitored once/week (twice/week in patients with renal failure); [b]Serum trough vancomycin levels (C_{min}) should be ≥20 mg/L. A vancomycin AUC/MIC >400 is recommended for MRSA infections; [c]Monitor plasma CPK levels at least once a week. Some experts recommend adding cloxacillin (2 g/4 h i.v.) or fosfomycin (2 g/6 h i.v.) to daptomycin in order to increase activity and avoid the development of daptomycin resistance; [d]Daptomycin and fosfomycin are not available in some European countries; [e]Rifampin is believed to play a special role in prosthetic device infection because it helps eradicate bacteria attached to foreign material.[157] The sole use of rifampin is associated with a high frequency of microbial resistance and is not recommended. Rifampin increases the hepatic metabolism of warfarin and other drugs; [f]Renal function and serum gentamicin concentrations should be monitored once/week (twice/week in patients with renal failure); [g]Paediatric doses should not exceed adult doses; [h]Penicillin desensitization can be attempted in stable patients; [i]Class of recommendation; [j]Level of evidence; [k]Reference(s) supporting recommendations.
** No clinical benefit of adding rifampicin or gentamicin

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Table 18 Antibiotic treatment of infective endocarditis due to *Enterococcus* spp.

Antibiotic	Dosage and route	Duration, weeks	Class[g]	Level[h]	Ref.[i]	Comments
Beta-lactam and gentamicin-susceptible strains (for resistant isolates see [a,b,c])						
Amoxicillin* with Gentamicin[d]	200 mg/kg/day i.v. in 4–6 doses 3 mg/kg/day i.v. or i.m. in 1 dose **Paediatric doses**:[e] Ampicillin 300 mg/kg/day i.v. in 4–6 equally divided doses Gentamicin 3 mg/kg/day i.v. or i.m. in 3 equally divided doses	4–6 2–6**	I I	B B	6,8, 129, 135, 136, 186	6-week therapy recommended for patients with >3 months symptoms or PVE
Ampicillin with Ceftriaxone	200 mg/kg/day i.v. in 4–6 doses 4 g/day i.v. or i.m. in 2 doses **Paediatric doses**:[e] Amoxicillin as above Ceftriaxone 100 mg/kg/12 h i.v. or i.m.	6 6	I I	B B	183–185	This combination is active against *Enterococcus faecalis* strains with and without HLAR, being the combination of choice in patients with HLAR *E. faecalis* endocarditis. This combination is not active against *E. faecium*
Vancomycin[f] with Gentamicin[d]	30 mg/kg/day i.v. in 2 doses 3 mg/kg/day i.v. or i.m. in 1 dose **Paediatric doses**:[e] Vancomycin 40 mg/kg/day i.v. in 2–3 equally divided doses. Gentamicin as above	6 6	I I	C C		

HLAR: high-level aminoglycoside resistance; IE: infective endocarditis; MIC: minimum inhibitory concentration; PBP: penicillin binding protein; PVE: prosthetic valve endocarditis.
[a]High-level resistance to gentamicin (MIC >500 mg/L): if susceptible to streptomycin, replace gentamicin with streptomycin 15 mg/kg/day in two equally divided doses.
[b]Beta-lactam resistance: (i) if due to beta-lactamase production, replace ampicillin with ampicillin–sulbactam or amoxicillin with amoxicillin–clavulanate; (ii) if due to PBP5 alteration, use vancomycin-based regimens.
[c]Multiresistance to aminoglycosides, beta-lactams and vancomycin: suggested alternatives are (i) daptomycin 10 mg/kg/day plus ampicillin 200 mg/kg/day i.v. in four to six doses; (ii) linezolid 2 × 600 mg/day i.v. or orally for ≥8 weeks (IIa, C) (monitor haematological toxicity); (iii) quinupristin–dalfopristin 3 × 7.5 mg/kg/day for ≥8 weeks. Quinupristin–dalfopristin is not active against *E. faecalis*; (iv) for other combinations (daptomycin plus ertapenem or ceftaroline), consult infectious diseases specialists.
[d]Monitor serum levels of aminoglycosides and renal function as indicated in *Table 16*.
[e]Paediatric doses should not exceed adult doses.
[f]Monitor serum vancomycin concentrations as stated in *Table 16*.
[g]Class of recommendation.
[h]Level of evidence.
[i]Reference(s) supporting recommendations.
*Or ampicillin, same dosages as amoxicillin.
**Some experts recommend giving gentamicin for only 2 weeks (IIa, B).

There have been two important advances in recent years. First is the demonstration, in several cohort studies of *E. faecalis* IE including hundreds of cases, that ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin for non-HLAR *E. faecalis* IE. It is also safer, without any nephrotoxicity.[183–185] In addition, this is the combination of choice for treating HLAR *E. faecalis* IE. Second, the total daily dose of gentamicin can be given in a single daily dose instead of the two or three divided doses recommended up to now, and the length of the treatment for non-HLAR *E. faecalis* IE may be safely shortened from 4–6 weeks to 2 weeks, reducing the rates of nephrotoxicity to very low levels.[129,186,187]

Beta-lactam and vancomycin resistance are mainly observed in *E. faecium*. Since dual resistance is rare, beta-lactam might be used against vancomycin-resistant strains and vice versa. Varying results have been reported with quinupristin–dalfopristin (not active against *E. faecalis*), linezolid, daptomycin (combined with ampicillin, ertapenem or ceftaroline) and tigecycline. Again, these situations require the expertise of an ID specialist.

7.9 Gram-negative bacteria

7.9.1 HACEK-related species

HACEK Gram-negative bacilli are fastidious organisms and the laboratory should be made aware that infection with these agents is under consideration, as specialist investigations may be required (see also section 5). Because they grow slowly, standard MIC tests may be difficult to interpret. Some HACEK-group bacilli produce beta-lactamases, and ampicillin is therefore no longer the first-line option. Conversely, they are susceptible to ceftriaxone, other third-generation cephalosporins and quinolones; the standard treatment is ceftriaxone 2 g/day for 4 weeks in NVE and for 6

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weeks in PVE. If they do not produce beta-lactamase, ampicillin (12 g/day i.v. in four or six doses) plus gentamicin (3 mg/kg/day divided into two or three doses) for 4–6 weeks is an option. Ciprofloxacin (400 mg/8–12 h i.v. or 750 mg/12 h orally) is a less well-validated alternative.[188,189]

7.9.2 Non-HACEK species

The International Collaboration on Endocarditis (ICE) reported non-HACEK Gram-negative bacteria in 49 of 2761 (1.8%) IE cases.[190] Recommended treatment is early surgery plus long-term (at least 6 weeks) therapy with bactericidal combinations of beta-lactams and aminoglycosides, sometimes with additional quinolones or cotrimoxazole. *In vitro* bactericidal tests and monitoring of serum antibiotic concentrations may be helpful. Because of their rarity and severity, these conditions should be discussed by the Endocarditis Team or with an ID specialist.

7.10 Blood culture–negative infective endocarditis

The main causes of BCNIE are summarized in section 5.4.2.[191,192] Treatment options are summarized in *Table 19*.[192,193] Consultation with an ID specialist from the Endocarditis Team is recommended.

7.11 Fungi

Fungi are most frequently observed in PVE and in IE affecting i.v. drug abusers (IVDAs) and immunocompromised patients.[198] *Candida* and *Aspergillus* spp. predominate, the latter resulting in BCNIE.[199,200] Mortality is very high (>50%), and treatment necessitates combined antifungal administration and surgical valve replacement.[135,198–200] Antifungal therapy for *Candida* IE includes liposomal amphotericin B (or other lipid formulations) with or without flucytosine or an echinocandin at high doses; and for *Aspergillus* IE, voriconazole is the drug of choice and some experts recommend the addition of an echinocandin or amphotericin B.[135,198,200,201] Suppressive long-term treatment with oral azoles (fluconazole for *Candida* and voriconazole for *Aspergillus*) is recommended, sometimes for life.[135,198,201] Consultation with an ID specialist from the Endocarditis Team is recommended.

7.12 Empirical therapy

Treatment of IE should be started promptly. Three sets of blood cultures should be drawn at 30-min intervals before initiation of antibiotics.[202] The initial choice of empirical treatment depends on several considerations:

(1) Whether the patient has received previous antibiotic therapy.
(2) Whether the infection affects a native valve or a prosthesis [and if so, when surgery was performed (early vs. late PVE)].
(3) The place of the infection (community, nosocomial, or non-nosocomial healthcare-associated IE) and knowledge of the local epidemiology, especially for antibiotic resistance and specific genuine culture-negative pathogens (*Table 19*).
(4) Cloxacillin/cefazolin administration is associated with lower mortality rates than other beta-lactams, including

Table 19 Antibiotic treatment of blood culture-negative infective endocarditis (adapted from Brouqui *et al.*[193])

Pathogens	Proposed therapy[a]	Treatment outcome
Brucella spp.	Doxycycline (200 mg/24 h) plus cotrimoxazole (960 mg/12 h) plus rifampin (300–600/24 h) for ≥3–6 months[b] orally	Treatment success defined as an antibody titre <1:60. Some authors recommend adding gentamicin for the first 3 weeks.
C. burnetii (agent of Q fever)	Doxycycline (200 mg/24 h) plus hydroxychloroquine (200–600 mg/24 h)[c] orally (>18 months of treatment)	Treatment success defined as anti-phase I IgG titre <1:200, and IgA and IgM titres <1:50.
Bartonella spp.[d]	Doxycycline 100 mg/12 h orally for 4 weeks plus gentamicin (3 mg/24 h) i.v. for 2 weeks	Treatment success expected in ≥90%.
Legionella spp.	Levofloxacin (500 mg/12 h) i.v. or orally for ≥6 weeks or clarithromycin (500 mg/12 h) i.v. for 2 weeks, then orally for 4 weeks plus rifampin (300–1200 mg/24 h)	Optimal treatment unknown.
Mycoplasma spp.	Levofloxacin (500 mg/12 h) i.v. or orally for ≥6 months[e]	Optimal treatment unknown.
T. whipplei (agent of Whipple's disease)[f]	Doxycycline (200 mg/24 h) plus hydroxychloroquine (200–600 mg/24 h)[c] orally for ≥18 months	Long-term treatment, optimal duration unknown.

ID = infectious disease; IE = infective endocarditis; Ig = immunoglobulin; i.v. = intravenous; U = units.
[a]Owing to the lack of large series, the optimal duration of treatment of IE due to these pathogens is unknown. The presented durations are based on selected case reports. Consultation with an ID specialist is recommended.
[b]Addition of streptomycin (15 mg/kg/24 h in 2 doses) for the first few weeks is optional.
[c]Doxycycline plus hydroxychloroquine (with monitoring of serum hydroxychloroquine levels) is significantly superior to doxycycline.[194]
[d]Several therapeutic regimens have been reported, including aminopenicillins (ampicillin or amoxicillin, 12 g/24 h i.v.) or cephalosporins (ceftriaxone, 2 g/24 h i.v.) combined with aminoglycosides (gentamicin or netilmicin).[195] Dosages are as for streptococcal and enterococcal IE (*Tables 16* and *18*).[196,197]
[e]Newer fluoroquinolones (levofloxacin, moxifloxacin) are more potent than ciprofloxacin against intracellular pathogens such as *Mycoplasma spp., Legionella spp., and Chlamydia spp.*
[f]Treatment of Whipple's IE remains highly empirical. In the case of central nervous system involvement, sulfadiazine 1.5 g/6 h orally must be added to doxycycline. An alternative therapy is ceftriaxone (2 g/24 h i.v.) for 2–4 weeks or penicillin G (2 million U/4 h) and streptomycin (1 g/24 h) i.v. for 2–4 weeks followed by cotrimoxazole (800 mg/12 h) orally. Trimethoprim is not active against *T. whipplei*. Successes have been reported with long-term therapy (>1 year).

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Table 20 Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification)[a]

Antibiotic	Dosage and route	Class[b]	Level[c]	Comments
Community-acquired native valves or late prosthetic valves (≥12 months post surgery) endocarditis				
Ampicillin with (Flu)cloxacillin *or* oxacillin with Gentamicin[d]	12 g/day i.v. in 4–6 doses 12 g/day i.v. in 4–6 doses 3 mg/kg/day i.v. or i.m. in 1 dose	IIa	C	Patients with BCNIE should be treated in consultation with an ID specialist.
Vancomycin[d] with Gentamicin[d]	30–60 mg/kg/day i.v. in 2–3 doses 3 mg/kg/day i.v. or i.m. in 1 dose	IIb	C	For penicillin-allergic patients
Early PVE (<12 months post surgery) or nosocomial and non-nosocomial healthcare associated endocarditis				
Vancomycin[d] with Gentamicin[d] with Rifampin	30 mg/kg/day i.v. in 2 doses 3 mg/kg/day i.v. or i.m. in 1 dose 900–1200 mg i.v. or orally in 2 or 3 divided doses	IIb	C	Rifampin is only recommended for PVE and it should be started 3–5 days later than vancomycin and gentamicin has been suggested by some experts. In healthcare associated native valve endocarditis, some experts recommend in settings with a prevalence of MRSA infections >5% the combination of cloxacillin plus vancomycin until they have the final S. aureus identification

BCNIE = blood culture-negative infective endocarditis; ID = infectious disease; i.m. = intramuscular; i.v. = intravenous; PVE = prosthetic valve endocarditis.
[a]If initial blood cultures are negative and there is no clinical response, consider BCNIE aetiology (see Section 7.10) and maybe surgery for molecular diagnosis and treatment, and extension of the antibiotic spectrum to blood culture-negative pathogens (doxycycline, quinolones) must be considered.
[b]Class of recommendation.
[c]Level of evidence.
[d]Monitoring of gentamicin or vancomycin dosages is as described in *Tables 16* and *17*.

amoxicillin/clavulanic acid or ampicillin/sulbactam,[203] and vancomycin for empirically treating MSSA bacteraemia/endocarditis.[159]

Suggested regimens for empirical treatment in acute patients are summarized in *Table 20*. NVE and late PVE regimens should cover staphylococci, streptococci and enterococci. Early PVE or healthcare-associated IE regimens should cover methicillin-resistant staphylococci, enterococci and, ideally, non-HACEK Gram-negative pathogens. Once the pathogen is identified (usually in <48 h), the antibiotic treatment must be adapted to its antimicrobial susceptibility pattern.

7.13 Outpatient parenteral antibiotic therapy for infective endocarditis

Outpatient parenteral antibiotic therapy (OPAT) is used to consolidate antimicrobial therapy once critical infection-related complications are under control (e.g. perivalvular abscesses, acute HF, septic emboli and stroke).[204–207] Two different phases may be identified during the course of antibiotic therapy: (i) a first critical phase (the first 2 weeks of therapy), during which OPAT has a restricted indication; and (ii) a second, continuation phase (beyond 2 weeks of therapy), where OPAT may be feasible. *Table 21* summarizes the salient questions to address when considering OPAT for IE.[205]

Table 21 Criteria that determine suitability of outpatient parenteral antibiotic therapy for infective endocarditis (adapted from Andrews *et al.*[205])

Phase of treatment	Guidelines for use
Critical phase (weeks 0–2)	• Complications occur during this phase • Preferred inpatient treatment during this phase • Consider OPAT if: oral streptococci or *Streptococcus bovis*,[a] native valve,[b] patient stable, no complications
Continuation phase (beyond week 2)	• Consider OPAT if medically stable • Do not consider OPAT if: HF, concerning echocardiographic features, neurological signs, or renal impairment
Essential for OPAT	• Educate patient and staff • Regular post-discharge evaluation (nurses 1/day, physician[c] in charge 1 or 2/week)[d] • Prefer physician-directed programme, not home-infusion model

HF = heart failure; ID = infectious disease; IE = infective endocarditis; OPAT = outpatient parenteral antibiotic therapy; PVE = prosthetic valve endocarditis.
[a]For other pathogens, consultation with an ID specialist is recommended.
[b]For patients with late PVE, consultation with an ID specialist is recommended.
[c]Preferably from the Endocarditis Team.
[d]General physician can see the patient once a week, if needed.

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8. Main complications of left-sided valve infective endocarditis and their management

Surgical treatment is required in approximately half of the patients with IE because of severe complications.[54] Reasons to consider early surgery in the active phase (i.e. while the patient is still receiving antibiotic treatment) are to avoid progressive HF and irreversible structural damage caused by severe infection and to prevent systemic embolism.[6,54,115,208–210] On the other hand, surgical therapy during the active phase of the disease is associated with significant risk. Surgery is justified in patients with high-risk features that make the possibility of cure with antibiotic treatment unlikely and who do not have co-morbid conditions or complications that make the prospect of recovery remote. Age *per se* is not a contraindication to surgery.[211]

Early consultation with a cardiac surgeon is recommended in order to determine the best therapeutic approach. Identification of patients requiring early surgery is frequently difficult and is an important objective of the 'Heart Team'. Each case must be individualized and all factors associated with increased risk identified at the time of diagnosis. Frequently the need for surgery will be determined by a combination of several high-risk features.[211]

In some cases, surgery needs to be performed on an emergency (within 24 h) or urgent (within a few days, <7 days) basis, irrespective of the duration of antibiotic treatment. In other cases, surgery can be postponed to allow 1 or 2 weeks of antibiotic treatment under careful clinical and echocardiographic observation before an elective surgical procedure is performed.[63,115] The three main indications for early surgery in IE are HF, uncontrolled infection and prevention of embolic events[212–216] (*Table 22*).

8.1 Heart failure

8.1.1 Heart failure in infective endocarditis

HF is the most frequent complication of IE and represents the most common indication for surgery in IE.[54] HF is observed in 42–60% of cases of NVE and is more often present when IE affects the aortic rather than the mitral valve.[111,208,212] HF is mainly caused by new

Table 22 Indications and timing of surgery in left-sided valve infective endocarditis (native valve endocarditis and prosthetic valve endocarditis)

Indications for surgery	Timing[a]	Class[b]	Level[c]	Ref.[d]
1. Heart failure				
Aortic or mitral NVE or PVE with severe acute regurgitation, obstruction or fistula causing refractory pulmonary oedema or cardiogenic shock	Emergency	I	B	111,115, 213,216
Aortic or mitral NVE or PVE with severe regurgitation or obstruction causing symptoms of HF or echocardiographic signs of poor haemodynamic tolerance	Urgent	I	B	37,115, 209,216, 220,221
2. Uncontrolled infection				
Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	Urgent	I	B	37,209, 216
Infection caused by fungi or multiresistant organisms	Urgent/ elective	I	C	
Persisting positive blood cultures despite appropriate antibiotic therapy and adequate control of septic metastatic foci	Urgent	IIa	B	123
PVE caused by staphylococci or non-HACEK gram-negative bacteria	Urgent/ elective	IIa	C	
3. Prevention of embolism				
Aortic or mitral NVE or PVE with persistent vegetations >10 mm after one or more embolic episode despite appropriate antibiotic therapy	Urgent	I	B	9,58,72, 113,222
Aortic or mitral NVE with vegetations >10 mm, associated with severe valve stenosis or regurgitation, and low operative risk	Urgent	IIa	B	9
Aortic or mitral NVE or PVE with isolated very large vegetations (>30 mm)	Urgent	IIa	B	113
Aortic or mitral NVE or PVE with isolated large vegetations (>15 mm) and no other indication for surgery[e]	Urgent	IIb	C	

HACEK = *Haemophilus parainfluenzae*, *Haemophilus aphrophilus*, *Haemophilus paraphrophilus*, *Haemophilus influenzae*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae* and *Kingella denitrificans*; HF = heart failure; IE = infective endocarditis; NVE = native valve endocarditis; PVE = prosthetic valve endocarditis.
[a]Emergency surgery: surgery performed within 24 h; urgent surgery: within a few days; elective surgery: after at least 1–2 weeks of antibiotic therapy.
[b]Class of recommendation.
[c]Level of evidence.
[d]Reference(s) supporting recommendations.
[e]Surgery may be preferred if a procedure preserving the native valve is feasible.

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or worsening severe aortic or mitral regurgitation, although intracardiac fistulae[213] and, more rarely, valve obstruction may also lead to HF.

Valvular regurgitation in native IE may occur as a result of mitral chordal rupture, leaflet rupture (flail leaflet), leaflet perforation or interference of the vegetation mass with leaflet closure. A particular situation is infection of the anterior mitral leaflet secondary to an infected regurgitant jet of a primary aortic IE.[214] Resultant aneurysm formation on the atrial side of the mitral leaflet may later lead to mitral perforation.[215]

Clinical presentation of HF may include dyspnoea, pulmonary oedema and cardiogenic shock.[111,120] Among the large ICE Prospective Cohort Study patients with HF and IE, 66% were in New York Heart Association class III or IV.[216] In addition to clinical findings, TTE is of crucial importance for initial evaluation and follow-up.[64] Valve perforation, secondary mitral lesions and aneurysms are best assessed using TOE.[64,65,214] Echocardiography is also useful to evaluate the haemodynamic consequences of valvular dysfunction, measurement of pulmonary artery pressure, detection of pericardial effusion and assessment and monitoring of left ventricular systolic function and left and right heart filling pressures.[64] B-type natriuretic peptide has potential use in the diagnosis and monitoring of HF in IE.[217] Both elevated levels of cardiac troponins and B-type natriuretic peptide are associated with adverse outcomes in IE.[218,219] Moderate to severe HF is the most important predictor of in-hospital, 6-month and 1-year mortality.[52,109,111,117,208]

8.1.2 Indications and timing of surgery in the presence of heart failure in infective endocarditis (*Table 22*)

Identification of surgical candidates and timing of surgery decisions should preferably be made by the Endocarditis Team.[118] The presence of HF indicates surgery in the majority of patients with IE and is the principal indication for urgent surgery.[115,124] Surgery is indicated in patients with HF caused by severe aortic or mitral regurgitation, intracardiac fistulae or valve obstruction caused by vegetations. Surgery is also indicated in patients with severe acute aortic or mitral regurgitation without clinical HF but with echocardiographic signs of elevated left ventricular end-diastolic pressure (e.g. premature closure of the mitral valve), high left atrial pressure or moderate to severe pulmonary hypertension. These rules apply in both NVE and PVE.[37,220,221]

Surgery must be performed on an emergency basis, irrespective of the status of infection, when patients are in persistent pulmonary oedema or cardiogenic shock despite medical therapy.[63] Surgery must be performed on an urgent basis when HF is less severe. Urgent surgery should also be performed in patients with severe aortic or mitral insufficiency with large vegetations, even without HF.[9]

In patients with well-tolerated (New York Heart Association class I or II) severe valvular regurgitation and no other reasons for surgery, medical management with antibiotics under strict clinical and echocardiographic observation is a good option, although early surgery may be an option in selected patients at low risk for surgery. Elective surgery should be considered depending on the tolerance of the valve lesion and according to the recommendations of the ESC Guidelines on the management of valvular heart disease.[55]

In summary, HF is the most frequent and among the most severe complications of IE. Unless severe co-morbidity exists, the presence of HF is an indication for early surgery in NVE and PVE, even in patients with cardiogenic shock.

8.2 Uncontrolled infection

Uncontrolled infection is one of the most feared complications of IE and is the second most frequent cause for surgery.[54] Uncontrolled infection is considered to be present when there is persisting infection and when there are signs of locally uncontrolled infection. Infection due to resistant or very virulent organisms often results in uncontrolled infection.

8.2.1 Persisting infection

The definition of persisting infection is arbitrary and consists of fever and persisting positive cultures after 7–10 days of antibiotic treatment. Persisting fever is a frequent problem observed during treatment of IE. Usually, temperature normalizes within 7–10 days under specific antibiotic therapy. Persisting fever may be related to several factors, including inadequate antibiotic therapy, resistant organisms, infected lines, locally uncontrolled infection, embolic complications or extracardiac site of infection and adverse reaction to antibiotics.[3] Management of persisting fever includes replacement of i.v. lines, repeat laboratory measurements, blood cultures, echocardiography, and the search for an intracardiac or extracardiac focus of infection.

8.2.2 Perivalvular extension in infective endocarditis

Perivalvular extension of IE is the most frequent cause of uncontrolled infection and is associated with a poor prognosis and high likelihood of the need for surgery. Perivalvular complications include abscess formation, pseudoaneurysms and fistulae (defined in *Table 11*).[223,224]

Perivalvular abscess is more common in aortic IE (10–40% in NVE)[3,225–227] and is frequent in PVE (56–100%).[3,6] In mitral IE, perivalvular abscesses are usually located posteriorly or laterally.[228] In aortic IE, perivalvular extension occurs most frequently in the mitral-aortic intervalvular fibrosa.[229] Serial echocardiographic studies have shown that abscess formation is a dynamic process, starting with aortic root wall thickening and extending to the development of fistulae.[229] In one study, the most important risk factors for perivalvular complications were prosthetic valve, aortic location and infection with CoNS.[230]

Pseudoaneurysms and fistulae are severe complications of IE and are frequently associated with very severe valvular and perivalvular damage.[213,231–233] The frequency of fistula formation in IE has been reported to be 1.6%, with *S. aureus* being the most commonly associated organism (46%).[233]

Despite high rates of surgery in this population (87%), hospital mortality remains high (41%).[213,233,234] Other complications due to major extension of infection are less frequent and may include ventricular septal defect, third-degree atrio-ventricular block and acute coronary syndrome.[223,224,234]

Perivalvular extension should be suspected in cases with persistent unexplained fever or new atrio-ventricular block. Therefore an electrocardiogram should be performed frequently during continuing treatment, particularly in aortic IE. TOE, MSCT and PET/CT[103] are particularly useful for the diagnosis of perivalvular complications,

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while the sensitivity of TTE is <50%[225–228] (see section 5). Indeed, perivalvular extension is frequently discovered on a systematic TOE. However, small abscesses can be missed, even using TOE, particularly those in a mitral location when there is co-existent annular calcification.[101]

8.2.3 Indications and timing of surgery in the presence of uncontrolled infection in infective endocarditis (*Table 22*)

The results of surgery when the reason for the procedure is uncontrolled infection are worse than when surgery is performed for other reasons.[124,235]

8.2.3.1 Persistent infection

In some cases of IE, antibiotics alone are insufficient to eradicate the infection. Surgery has been indicated when fever and positive blood cultures persist for several days (7–10 days) despite an appropriate antibiotic regimen and when extracardiac abscesses (splenic, vertebral, cerebral or renal) and other causes of fever have been excluded. However, the best timing for surgery in this difficult situation is unclear. Recently it has been demonstrated that persistent blood cultures 48–72 h after initiation of antibiotics are an independent risk factor for hospital mortality.[123] These results suggest that surgery should be considered when blood cultures remain positive after 3 days of antibiotic therapy, after the exclusion of other causes of persistent positive blood cultures (adapted antibiotic regimen).

8.2.3.2 Signs of locally uncontrolled infection

Signs of locally uncontrolled infection include increasing vegetation size, abscess formation, false aneurysms, and the creation of fistulae.[213,236,237] Persistent fever is also usually present and surgery is recommended as soon as possible. Rarely when there are no other reasons for surgery and fever is easily controlled with antibiotics, small abscesses or false aneurysms can be treated conservatively under close clinical and echocardiographic follow-up.

8.2.3.3 Infection by microorganisms at low likelihood of being controlled by antimicrobial therapy

Surgery is indicated in fungal IE,[238,239] in cases of multiresistant organisms (e.g. MRSA or vancomycin-resistant enterococci) or in the rare infections caused by Gram-negative bacteria. Surgery should also be considered in PVE caused by staphylococci or non-HACEK Gram-negative bacteria. In NVE caused by *S. aureus*, surgery is indicated if a favourable early response to antibiotics is not achieved[161,240,241] (*Table 22*). Finally, surgery should be performed in patients with PVE and *S. aureus* infection.

In summary, uncontrolled infection is most frequently related to perivalvular extension or 'difficult-to-treat' organisms. Unless severe co-morbidity exists, the presence of locally uncontrolled infection is an indication for early surgery in patients with IE.

8.3 Prevention of systemic embolism

8.3.1 Embolic events in infective endocarditis

Embolic events are a frequent and life-threatening complication of IE related to the migration of cardiac vegetations. The brain and spleen are the most frequent sites of embolism in left-sided IE, while pulmonary embolism is frequent in native right-sided and pacemaker lead IE. Stroke is a severe complication and is associated with increased morbidity and mortality.[105] Conversely, embolic events may be totally silent in 20–50% of patients with IE, especially those affecting the splenic or cerebral circulation, and can be diagnosed by non-invasive imaging.[83,85,242] Thus systematic abdominal and cerebral CT scanning may be helpful. However, contrast media should be used with caution in patients with renal impairment or haemodynamic instability because of the risk of worsening renal impairment in combination with antibiotic nephrotoxicity.

Overall, embolic risk is very high in IE, with embolic events occurring in 20–50% of patients.[72,242–249] However, the risk of new events (occurring after initiation of antibiotic therapy) is only 6–21%.[72,115,243] A study from the ICE group[250] demonstrated that the incidence of stroke in patients receiving appropriate antimicrobial therapy was 4.8/1000 patient-days in the first week of therapy, falling to 1.7/1000 patient-days in the second week, and further thereafter.

8.3.2 Predicting the risk of embolism

Echocardiography plays a key role in predicting embolic events,[72,115,246–252] although prediction remains difficult in the individual patient. Several factors are associated with increased risk of embolism, including the size and mobility of vegetations,[72,242,246–253] the location of the vegetation on the mitral valve,[72,246–249] the increasing or decreasing size of the vegetation under antibiotic therapy,[72,253] particular microorganisms (*S. aureus*,[72] *S. bovis*,[254] *Candida* spp.), previous embolism,[72] multivalvular IE[246] and biological markers.[255] Among these, the size and mobility of the vegetations are the most potent independent predictors of a new embolic event.[253] Patients with vegetations >10 mm in length are at higher risk of embolism,[58,253] and this risk is even higher in patients with larger (>15 mm) and mobile vegetations, especially in staphylococcal IE affecting the mitral valve.[219] A recent study[113] found that the risk of neurological complications was particularly high in patients with very large (>30 mm length) vegetations.

Several factors should be taken into account when assessing embolic risk. In a recent study of 847 patients with IE, the 6-month incidence of new embolism was 8.5%.[222] Six factors (age, diabetes, atrial fibrillation, previous embolism, vegetation length and *S. aureus* infection) were associated with an increased embolic risk and were used to create an 'embolic risk calculator'.[222]

Whatever the risk factors observed in an individual patient, it must be re-emphasized that the risk of new embolism is highest during the first days following initiation of antibiotic therapy and rapidly decreases thereafter, particularly beyond 2 weeks,[58,72,243,250] although some risk persists indefinitely while vegetations remain present, particularly for very large vegetations.[113] For this reason, the benefits of surgery to prevent embolism are greatest during the first 2 weeks of antibiotic therapy, when embolic risk peaks.

8.3.3 Indications and timing of surgery to prevent embolism in infective endocarditis (*Table 22*)

Avoiding embolic events is difficult since the majority occur before admission.[222] The best means to reduce the risk of an embolic event is the prompt institution of appropriate antibiotic therapy.[38] While promising,[256,257] the addition of antiplatelet therapy did not reduce the risk of embolism in the only published randomized study.[258]

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The exact role of early surgery in preventing embolic events remains controversial. In the Euro Heart Survey, vegetation size was one of the reasons for surgery in 54% of patients with NVE and in 25% of those with PVE,[54] but was rarely the only reason. The value of early surgery in an isolated large vegetation is controversial. A recent randomized trial demonstrated that early surgery in patients with large vegetations significantly reduced the risk of death and embolic events compared with conventional therapy.[9] However, the patients studied were at low risk and there was no significant difference in all-cause mortality at 6 months in the early surgery and conventional-treatment groups.

Finally, the decision to operate early for prevention of embolism must take into account the presence of previous embolic events, other complications of IE, the size and mobility of the vegetation, the likelihood of conservative surgery and the duration of antibiotic therapy.[115] The overall benefits of surgery should be weighed against the operative risk and must consider the clinical status and co-morbidity of the patient.

The main indications and timing of surgery to prevent embolism are given in *Table 22*. Surgery is indicated in patients with persisting vegetations >10 mm after one or more clinical or silent embolic events despite appropriate antibiotic treatment.[58] Surgery may be considered in patients with large (>15 mm) isolated vegetations on the aortic or mitral valve, although this decision is more difficult and must be very carefully individualized according to the probability of conservative surgery.[58]

Surgery undertaken for the prevention of embolism must be performed very early, during the first few days following initiation of antibiotic therapy (urgent surgery), as the risk of embolism is highest at this time.[58,72]

In summary, embolism is very frequent in IE, complicating 20–50% of cases of IE, but falling to 6–21% after initiation of antibiotic therapy. The risk of embolism is highest during the first 2 weeks of antibiotic therapy and is clearly related to the size and mobility of the vegetation, although other risk factors exist. The decision to operate early to prevent embolism is always difficult and specific for the individual patient. Governing factors include the size and mobility of the vegetation, previous embolism, type of microorganism and duration of antibiotic therapy.

9. Other complications of infective endocarditis

9.1 Neurological complications

Symptomatic neurological complications occur in 15–30% of patients with IE and are mainly the consequence of embolism from vegetations.[110,113,259] Neurological manifestations occur before or at IE diagnosis in a majority of cases, but new or recurrent events can also take place later in the course of IE. Clinical presentation is variable and may include multiple symptoms or signs in the same patient, but focal signs predominate and ischaemic strokes are most commonly diagnosed. Transient ischaemic attack, intracerebral or subarachnoidal haemorrhage, brain abscess, meningitis and toxic encephalopathy are also seen, and firm evidence supports that additional clinically silent cerebral embolisms occur in 35–60% of IE patients.[83,85,90] *S. aureus* IE is more frequently associated with neurological complications compared with IE caused by other bacteria. Vegetation length and mobility also correlate with embolic tendency.[88,242] Neurological complications are associated with an excess mortality, as well as sequelae, particularly in the case of stroke.[113,259] Rapid diagnosis and initiation of appropriate antibiotics are of major importance to prevent a first or recurrent neurological complication.[250] Early surgery in high-risk patients is the second mainstay of embolism prevention, while antithrombotic drugs have no role (see section 12.7).

Successful management of IE requires a combined medical and surgical approach in a substantial proportion of patients. Following a neurological event, the indication for cardiac surgery often remains or is strengthened, but must be balanced with perioperative risk and postoperative prognosis. Randomized studies are not possible and cohort studies suffer from bias that can only be partly compensated for by statistical methods.[115,260–262] However, the risk of postoperative neurological deterioration is low after a silent cerebral emboli or transient ischaemic attack, and surgery is recommended without delay if an indication remains.[105] After an ischaemic stroke, cardiac surgery is not contraindicated unless the neurological prognosis is judged too poor.[263] Evidence regarding the optimal time interval between stroke and cardiac surgery is conflicting, but recent data favour early surgery.[9,115] If cerebral haemorrhage has been excluded by cranial CT and neurological damage is not severe (i.e. coma), surgery indicated for HF, uncontrolled infection, abscess or persistent high embolic risk should not be delayed and can be performed with a low neurological risk (3–6%) and good probability of complete neurological recovery.[105,263] Conversely, in cases with intracranial haemorrhage, neurological prognosis is worse and surgery should generally be postponed for at least 1 month,[264,265] although one recent study has reported a relatively low risk of neurological deterioration in IE patients undergoing surgery within 2 weeks after an intracranial haemorrhage.[266] The Task Force has thus decided to adapt the level of evidence to a class IIa. If urgent cardiac surgery is needed, close cooperation with the neurosurgical team and the Endocarditis Team is mandatory. *Table 23* and *Figure 4* summarize the recommended management of neurological complications in IE.

Cerebral imaging is mandatory for any suspicion of neurological complication of IE. CT scanning, with or without contrast agent, is most often performed. The higher sensitivity of MRI, with or without contrast gadolinium enhancement, allows for better detection and analysis of cerebral lesions in patients with neurological symptoms, and this may have an impact on the timing of surgery[89] (see section 5). In patients without neurological symptoms, cerebral MRI often detects lesions that may change the therapeutic strategy; in particular, the indications and timing of surgery.[85,90] Cerebral MRI often detects microbleeds (round T2* hypointensities with a diameter ≤10 mm) in patients with IE. The lack of association with parenchymal haemorrhage and the absence of postoperative neurological complications in patients with microbleeds suggest that microbleeds should not be interpreted as active bleeding and should not lead to postponed surgery when this is indicated.[89,90]

In summary, symptomatic neurological events develop in 15–30% of all patients with IE and additional silent events are frequent. Stroke (ischaemic and haemorrhagic) is associated with excess mortality. Rapid diagnosis and initiation of appropriate antibiotics are of major importance to prevent a first or recurrent neurological complication. After a first neurological event, cardiac surgery, if

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Table 23 Management of neurological complications of infective endocarditis

Recommendations	Class[a]	Level[b]	Ref.[c]
After a silent embolism or transient ischaemic attack, cardiac surgery, if indicated, is recommended without delay	I	B	105, 263
Neurosurgery or endovascular therapy is recommended for very large, enlarging or ruptured intracranial infectious aneurysms	I	C	
Following intracranial haemorrhage, surgery should generally be postponed for ≥1 month	IIa	B	264–266
After a stroke, surgery indicated for HF, uncontrolled infection, abscess, or persistent high embolic risk should be considered without any delay as long as coma is absent and the presence of cerebral haemorrhage has been excluded by cranial CT or MRI	IIa	B	9,263
Intracranial infectious aneurysms should be looked for in patients with IE and neurological symptoms. CT or MR angiography should be considered for diagnosis. If non-invasive techniques are negative and the suspicion of intracranial aneurysm remains, conventional angiography should be considered	IIa	B	267, 268

CT = computed tomography; HF = heart failure; IE = infective endocarditis; MR = magnetic resonance; MRI = magnetic resonance imaging.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

indicated, is generally not contraindicated, except when extensive brain damage or intracranial haemorrhage is present.

9.2 Infectious aneurysms

Infectious (mycotic) aneurysms result from septic arterial embolism to the intraluminal space or vasa vasorum or from subsequent spread of infection through the intimal vessels. Infectious aneurysms are typically thin walled and friable and, as such, exhibit a high tendency to rupture and haemorrhage. No predictor of rupture has been identified and, in contrast to non-infectious aneurysms, size does not appear to be a reliable predictor of potential rupture.[268,269]

An intracranial location is most common and the reported frequency of 2–4% is probably an underestimation since some infectious aneurysms are clinically silent.[267,270] Early detection and treatment of infectious aneurysms is essential given the high morbidity and mortality rate secondary to rupture. Clinical presentation is highly variable (i.e. focal neurological deficit, headache, confusion, seizures), so imaging should be systematically performed to detect intracranial infectious aneurysms in any case of IE with neurological symptoms.[268]

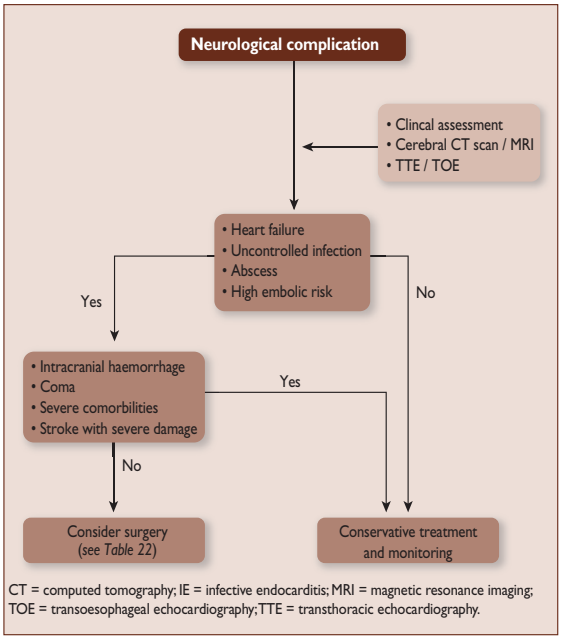

Figure 4 Therapeutic strategies for patients with infective endocarditis and neurological complications.

Cerebral CT and MRI both reliably diagnose infectious aneurysms with good sensitivity and specificity.[271] However, conventional angiography remains the gold standard and should be performed when non-invasive techniques are negative and suspicion remains.[267]

Owing to the lack of randomized trials, there is no widely accepted standard management for infectious aneurysms. Thus management should be provided by an Endocarditis Team and tailored to the individual patient. Some infectious aneurysms may resolve during antibiotic treatment, while others require surgical or endovascular intervention depending on the occurrence of rupture and the location in the artery bed, as well as the clinical status of the patient.[268,269]

Regarding intracranial infectious aneurysms, ruptured aneurysms must be treated immediately by surgical or endovascular procedures. Unruptured infectious aneurysms should be followed by serial cerebral imaging under antibiotic therapy. If the size of the aneurysm decreases or resolves completely, surgical or endovascular intervention is usually unnecessary. However, if the size of the aneurysm increases or remains unchanged, it is likely that the patient will require intervention. On the other hand, if the infectious aneurysm is voluminous and symptomatic, neurosurgery or endovascular therapy is recommended.[272] Finally, if early cardiac surgery is required, preoperative endovascular intervention might be considered before the procedure, depending on associated cerebral lesions, the haemodynamic status of the patient and the risk of the procedure.

9.3 Splenic complications

Splenic infarcts are common and very often asymptomatic. Persistent or recurrent fever, abdominal pain and bacteraemia suggest the presence of complications (splenic abscess or rupture). Although

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splenic emboli are common, splenic abscesses are rare. Persistent or recurrent fever and bacteraemia suggest the diagnosis. These patients should be evaluated by abdominal CT, MRI or ultrasound. Recently PET has proved useful for the diagnosis of splenic metastasic infection in patients with IE.[273] Treatment consists of appropriate antibiotic regimens. Splenectomy may be considered for splenic rupture or large abscesses, which respond poorly to antibiotics alone, and should be performed before valvular surgery unless the latter is urgent. Rarely, splenectomy and valvular surgery are performed during the same operative time. Percutaneous drainage is an alternative for high-risk surgical candidates.[274,275]

9.4 Myocarditis and pericarditis

Cardiac failure may be due to myocarditis, which is frequently associated with abscess formation or immune reaction. Ventricular arrhythmias may indicate myocardial involvement and imply a poor prognosis. Myocardial involvement is best assessed using TTE and cardiac MRI.

The inflammatory response, HF, periannular complications or infection itself can cause pericardial effusion, which could be a sign of more severe IE. Rarely, ruptured pseudoaneurysms or fistulae may communicate with the pericardium, with dramatic and often fatal consequences. Purulent pericarditis is rare and may necessitate surgical drainage.[276,277]

9.5 Heart rhythm and conduction disturbances

Conduction disorders are uncommon complications of IE. According to data from patient registries, their frequency is between 1% and 15% of cases and their presence is associated with worse prognosis and higher mortality.[278]

Conduction abnormalities (mainly first-, second-, and third-degree atrio-ventricular blocks, rarely bundle branch blocks) are due to spread of the infection beyond the endocardium, from valves to the conduction pathways, and are generally associated with perivalvular complications. Complete atrio-ventricular block is most often associated with involvement of the left-sided valves (aortic, 36%; mitral, 33%).[278] This is because of the anatomical relationship with the atrio-ventricular node, which is close to the non-coronary aortic cusp and the anterior mitral leaflet. In a study of patients with IE and complete atrio-ventricular block, pathology workup revealed the presence of an infection, frequently accompanied by abscesses and fistulae, affecting the conduction pathways; in cases of paroxysmal atrio-ventricular block, inflammation was observed at this level, which would explain the reversibility of the event.[279]

The occurrence of conduction abnormalities during electrocardiographic monitoring in patients with endocarditis can therefore alert physicians to the appearance of perivalvular complications.

In the case of embolization of vegetation fragments into a coronary artery, the resulting myocardial ischaemia can be the substrate for the onset of tachyarrhythmias.[280]

Atrial fibrillation can be observed in patients with IE and may be present before IE or occur as a complication of IE. Atrial fibrillation has been reported to be more frequent in the elderly and to be associated with a poor prognosis.[281] More recently, in a large prospective series of IE, atrial fibrillation was found to be associated with an increased embolic risk, as were other factors (age, diabetes, previous embolism, vegetation length and *S. aureus* infection).[222] Consequently, atrial fibrillation has the potential to increase the risk of both congestive HF and embolism in IE. However, there is no specific study on this situation and no international consensus for the care of these patients. The management of anticoagulation therapy in these patients should be taken on an individual basis by the Endocarditis Team.

9.6 Musculoskeletal manifestations

Musculoskeletal symptoms (arthralgia, myalgia, back pain) are frequent during IE.[282,283] Rheumatological manifestations may be the first manifestations of IE and can delay its diagnosis, especially when classic manifestations are less evident and a variety of antibodies (i.e. positive antineutrophil cytoplasmic antibody test) induced by infections[284,285] are present. Arthralgia occurs in about 10% of patients, while myalgia is present in 12–15%.[282,286] Back pain is observed in about 13% of cases, and lumbar pain is the most common symptom in patients with IE and vertebral osteomyelitis.[282,283,287,288] Peripheral arthritis occurs in about 14% of cases.[282] The prevalence of spondylodiscitis in patients with IE is about 1.8–15%.[282] Pyogenic vertebral osteomyelitis occurs in 4.6–19% of IE patients with a high incidence of streptococcal and staphylococcal bacteraemia.[283,287] IE can complicate or be complicated by pyogenic osteomyelitis. The prevalence of IE in vertebral osteomyelitis is higher[288,289] in the presence of *Streptococcus viridans* IE. CT, but preferably MRI, of the spine or whole-body ^{18}F-FDG-PET/CT[290] should be performed in IE patients with back or bone pain. Conversely, echocardiography should be performed in patients with a definite diagnosis of pyogenic spondylodiscitis/osteomyelitis and underlying cardiac conditions predisposing to IE.

In definite spondylodiscitis and osteomyelitis, prolonged antibiotic therapy is generally required until no signs of inflammatory activity are detected by ^{18}FDG PET/CT or MRI. Other musculoskeletal manifestations are less common in IE and include sacroiliitis in about 1% of cases, a condition mimicking polymyalgia rheumatica with pain and morning stiffness of the shoulders and hips, proximal muscle weakness in about 0.9% of cases and cutaneous leucocytoclastic vasculitis (purpuric skin lesions) in 3.6% of cases.[282,289]

9.7 Acute renal failure

Acute renal failure is a common complication of IE and may worsen the prognosis of IE. The onset of renal dysfunction is independently associated with increased risk of in-hospital death[291,292] and postoperative events.[293]

Acute renal dysfunction occurs in about 6–30% of patients.[291,292,294,295] Causes are often multifactorial:[296,297] (i) immune complex and vasculitic glomerulonephritis; (ii) renal infarction, mostly due to septic emboli, occurring at any time during the course of the disease; (iii) haemodynamic impairment in cases with HF or severe sepsis or after cardiac surgery; (iv) antibiotic toxicity (acute interstitial nephritis), notably related to aminoglycosides, vancomycin (synergistic toxicity with aminoglycosides) and even high-dose penicillin; and (v) nephrotoxicity of contrast agents used for imaging purposes.

Haemodialysis may be required in some patients with advanced renal failure and is associated with high mortality.[295] Acute renal

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failure of a milder degree is often reversible.[295] To mitigate this complication, antibiotic doses should be adjusted for creatinine clearance with careful monitoring of serum levels (aminoglycosides and vancomycin). Imaging with nephrotoxic contrast agents should be avoided when possible in patients with haemodynamic impairment or previous renal insufficiency.

10. Surgical therapy: principles and methods

10.1 Operative risk assessment

Few studies have evaluated the utility of operative risk scores in the setting of IE. Although EuroSCORE II is frequently used,[298] it was developed and validated predominantly for coronary artery bypass grafting and valve surgery. Risk scores specific to IE surgery have been developed: (i) from the Society of Thoracic Surgeons database using 13 617 patients[299] and (ii) an additional NVE risk score from a single centre using 440 patients by De Feo *et al.*[300] A study compared the prognostic utility of these contemporary risk scores for mortality and morbidity after IE surgery in 146 patients.[301] Here, although EuroSCORE II discriminated mortality and postoperative morbidity (in particular, stroke), the Society of Thoracic Surgeons endocarditis score and the De Feo *et al.* score[300] performed better at predicting operative mortality after surgery for active IE. However, the relevance of these findings is limited by the small number of patients involved. Similar to previous studies, preoperative use of inotropes or an intra-aortic balloon pump, prior coronary artery bypass surgery and renal failure requiring dialysis were independent predictors of operative and long-term mortality.

Finally, although no single operative risk score is perfect, preoperative assessment of operative risk is of utmost importance. Although the theoretical indications for surgery in IE are clear (*Table 22*), their practical application relies largely on the clinical status of the patient, the patient's co-morbidities and the patient's operative risk.

10.2 Preoperative and perioperative management

10.2.1 Coronary angiography

Coronary angiography is recommended according to the ESC Guidelines on the management of valvular heart disease[55] in men >40 years, in post-menopausal women and in patients with at least one cardiovascular risk factor or a history of coronary artery disease. Exceptions arise when there are aortic vegetations that may be dislodged during catheterization or when emergency surgery is necessary. In these situations, high-resolution CT may be used to rule out significant coronary artery disease in haemodynamically stable patients.[55]

10.2.2 Extracardiac infection

If a primary focus of infection likely to be responsible for IE has been identified, it must be eradicated before cardiac surgical intervention unless valve surgery is urgent. In any case, it should be eradicated before the end of antibiotic therapy.

10.2.3 Intraoperative echocardiography

Intraoperative TOE is most useful to determine the exact location and extent of infection, guide surgery, assess the result and help in early postoperative follow-up.[73]

10.3 Surgical approach and techniques

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

Where infection is confined to the valve cusps or leaflets, any method to repair or replace the valve may be used. However, valve repair is favoured whenever possible, particularly when IE affects the mitral or tricuspid valve without significant destruction.[302] Perforations in a single valve cusp or leaflet may be repaired with an untreated or glutaraldehyde-treated autologous or bovine pericardial patch. Isolated or multiple ruptured chordae may be replaced by polytetrafluoroethylene neo-chordae.

More extensive destruction of a single leaflet or the presence of an abscess is not necessarily a contraindication for valve repair.[302] Rather, intraoperative assessment of the valve after debridement is of paramount importance in order to evaluate whether the remaining tissue is of sufficient quality to achieve a durable repair. The need for a patch to achieve a competent valve, whether pericardial, tricuspid autograft or a flipped-over mitral patch, has not been associated with worse results in terms of recurrence of IE or mitral regurgitation when performed by experienced surgeons.[303]

To avoid paravalvular leaks in complex cases with locally uncontrolled infection, total excision of infected and devitalized tissue should be followed by valve replacement and repair of associated defects to secure valve fixation.[304]

Mechanical and biological prostheses have similar operative mortality.[305] Therefore the Task Force does not favour any specific valve substitute but recommends a tailored approach for each individual patient and clinical situation. The use of foreign material should be kept to a minimum. Small abscesses can be closed directly, but larger cavities should be allowed to drain into the pericardium or circulation.

In mitral valve IE, successful valve repair can be achieved by experienced teams in up to 80% of patients, but such results may not be matched in non-specialist centres.[306] Moreover, although surgery may be deferred if control of the infection by antibiotic therapy appears evident in the absence of cardiac failure, early operation has been associated in recent reports with a repair rate of 61–80% and improved in-hospital and long-term survival.[209,210,302,303,307] Residual mitral regurgitation should be assessed using intraoperative TOE. Mitral subannular, annular or supraannular tissue defects are preferably repaired with autologous or bovine pericardium, a prosthetic valve then being secured to the reconstructed/reinforced annulus, if necessary. The choice of technique depends on the vertical extension of the lesion/tissue defect.[308–310] The use of mitral valve homografts and pulmonary autografts (Ross II procedure) has been suggested,[311,312] but their application is limited by poor availability and difficulty of the surgical technique, and the results have not been consistent.

In aortic IE, replacement of the aortic valve using a mechanical or biological prosthesis is the technique of choice. Nevertheless, in

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centres with great expertise, aortic valve repair in IE can be achieved in up to 33% of patients. However, experience with aortic valve repair in this setting is still very limited and there is no evidence that repair is associated with improved outcomes compared with replacement.[313,314] Owing to their natural biocompatibility, the use of cryopreserved or sterilized homografts has been suggested to reduce the risk of persistent or recurrent infection, especially in the presence of annular abscesses.[315,316] It is expert opinion and standard strategy in many institutions that the use of a homograft is to be favoured over valve prostheses, particularly in the presence of root abscess.[316,317] However, mechanical prostheses and xenografts have led to similar results in terms of persistent or recurrent infection and survival if associated with complete debridement of annular abscesses.[313,318] Homografts or stentless xenografts may be preferred in PVE or in cases where there is extensive aortic root destruction with aorto-ventricular discontinuity.[315,319] The anterior mitral leaflet of the aortic homograft can be effectively used for reconstruction of the outflow tract. A monoblock aorto-mitral homograft has been suggested as a surgical option for extensive bivalvular IE.[320] In experienced hands, the Ross procedure may be used in children or adolescents to facilitate growth and in young adults for extended durability.[321,322]

Cardiac transplantation may be considered in extreme cases where repeated operative procedures have failed to eradicate persistent or recurrent PVE.[323]

10.4 Postoperative complications

Postoperative patient management should follow the usual recommendations after valvular surgery[324] but should also take into account the specificities of IE. Postoperative follow-up should be particularly cautious given the in-hospital mortality of patients operated on for acute IE on an emergency or urgent basis, which ranges from 10% to 20% in most series,[1] and the increased risk of postoperative complications.

Among the most frequent complications are severe coagulopathy requiring treatment with clotting factors, re-exploration of the chest for bleeding or tamponade, acute renal failure requiring haemodialysis, stroke, low cardiac output syndrome, pneumonia and atrioventricular block following radical resection of an aortic root abscess with the need for pacemaker implantation.[325] A preoperative electrocardiogram demonstrating left bundle branch block predicts the need for a postoperative permanent pacemaker.[23] When a patient does not survive surgery, the cause of death is often multifactorial.[325]

11. Outcome after discharge: follow-up and long-term prognosis

Following in-hospital treatment, the main complications include recurrence of infection, HF, need for valve surgery and death.[57,326,327]

11.1 Recurrences: relapses and reinfections

The actual risk of recurrence among survivors of IE varies between 2% and 6%.[57,326–332] Two main types of recurrence are distinguishable: relapse and reinfection. Although not systematically differentiated in the literature, the term 'relapse' refers to a repeat episode of IE caused by the same microorganism, while 'reinfection' describes an infection caused by a different microorganism.[38] When the same species is isolated during a subsequent episode of IE, there is often uncertainty as to whether the repeat infection is a relapse of the initial infection or a new infection (reinfection). In these cases, molecular methods including strain-typing techniques should be employed.[8,38] When these techniques or the identity of both isolates is unavailable, the timing of the second episode of IE may be used to distinguish relapse from reinfection. Thus, although variable, the time between episodes is usually shorter for relapse than for reinfection. Generally speaking, a recurrence caused by the same species within 6 months following the initial infection represents relapse, whereas later events suggest reinfection.[38] For these purposes, storage of IE isolates for at least 1 year is recommended.[8,38]

Factors associated with an increased rate of relapse are listed in *Table 24*. Relapses are most often due to insufficient duration of original treatment, suboptimal choice of initial antibiotics or a persistent focus of infection. When the duration of therapy has been insufficient or the choice of antibiotic incorrect, relapse should be treated for a further 4–6 weeks depending on the causative microorganism and its antibiotic susceptibility (remembering that resistance may develop in the meantime).

Patients with previous IE are at risk of reinfection,[332] and prophylactic measures should be very strict. Reinfection is more frequent in IVDAs (especially in the year after the initial episode),[332,333] in PVE,[334] in patients undergoing chronic dialysis[326,332] and in those with multiple risk factors for IE.[8] Patients with reinfection are at higher risk of death and need for valve replacement.[325,332] Paravalvular destruction is associated with a higher rate of recurrence and a higher operative mortality.[331] In a large series of surgically managed NVE (358 cases), 21% had paravalvular destruction, and freedom from recurrent PVE at 15 years was 78.9%.[331]

The type of valve implanted has no effect on the risk of recurrent IE.[325,331] Aortic valve and root replacement with a prosthetic

Table 24 Factors associated with an increased rate of relapse

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

BCNIE = blood culture-negative infective endocarditis; IE = infective endocarditis; IVDA = intravenous drug abuser.

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conduit yields results similar to those for homograft root replacement.[335,336]

11.2 Short-term follow-up

A first episode of IE should not be seen as an ending once the patient has been discharged. Residual severe valve regurgitation may decompensate left ventricular function, or valve deterioration may progress despite bacteriological cure, usually presenting with acute HF. After completion of treatment, recommendations for surgery follow conventional guidelines.[55] As a consequence of increasing rates of surgery during the active phase of infection, the need for late valve surgery is low, ranging from 3% to 8% in recent series.[326–328]

Patients should be educated about the signs and symptoms of IE after discharge. They should be aware that recurrence could occur in IE and that new onset of fever, chills or other signs of infection mandate immediate evaluation, including procurement of blood cultures before empirical use of antibiotics. To monitor the development of secondary HF, an initial clinical evaluation and baseline TTE should be performed at the completion of antimicrobial therapy and repeated serially, particularly during the first year of follow-up.

Clinical follow-up should be done by the Endocarditis Team or by a Heart Valve Clinic specialist.[11,337] Regular clinical and echocardiographic follow-up should be performed during the first year following completion of treatment.[8,12] This Task Force also recommends to take blood samples (i.e. white cell count, CRP, etc.), and blood cultures systematically at the initial visit, and otherwise if there is clinical suspicion.

Good oral health maintenance, preventive dentistry and advice about skin hygiene, including tattoos and skin piercing, are mandatory. Deficiencies in dental surveillance contribute to the continuous gradual increase in the incidence of IE.[30,337] This increase underlines the need for repeating the principles of IE prevention at each follow-up visit.

11.3 Long-term prognosis

In recent series, the crude long-term survival rates after the completion of treatment were estimated to be 80–90% at 1 year, 70–80% at 2 years and 60–70% at 5 years.[57,326–332] The main predictors of long-term mortality are older age, co-morbidities, recurrences and HF, especially when cardiac surgery cannot be performed.[57,327,330]

Compared with an age- and sex-matched general population, patients surviving a first episode of IE have a significantly worse survival.[57] This excess mortality is especially high within the first few years after hospital discharge and can be explained by late complications such as HF, higher risk of recurrences and higher patient vulnerability.[57,329] In fact, most recurrences and late cardiac surgeries occurred during this period of time.[57,328,329]

In summary, recurrences are rare following IE and may be associated with inadequate initial antibiotic therapy, resistant microorganisms, persistent focus of infection, i.v. drug abuse and chronic dialysis. Patients with IE must be informed of the risk of recurrence and educated about how to diagnose and prevent a new episode of IE. The need for late valve surgery is low.

12. Management of specific situations

12.1 Prosthetic valve endocarditis

PVE is the most severe form of IE and occurs in 1–6% of patients with valve prostheses,[338] with an incidence of 0.3–1.2% per patient-year.[216,233,339,340] PVE accounts for 10–30% of all cases of IE[341] and affects mechanical and bioprosthetic valves equally. PVE was observed in 16% of cases of IE in a French survey,[122] in 26% of cases in the Euro Heart Survey[54] and in 20% of 2670 patients with definite IE in the ICE Prospective Cohort Study.[340] PVE is still associated with difficulties in diagnosis, determination of the optimal therapeutic strategy and poor prognosis.

12.1.1 Definition and pathophysiology

Early PVE is defined as IE occurring within 1 year of surgery and late PVE as IE occurring beyond 1 year, because of significant differences between the microbiological profiles observed before and after this time point.[3,342] However, this is an artificial distinction. What is important is not the time from the valve replacement procedure to the onset of IE, but whether IE is acquired perioperatively and which microorganism is involved. A recent large, prospective, multicentre, international registry reported that 37% of PVE cases were associated with nosocomial infection or non-nosocomial healthcare-associated infections in outpatients with extensive healthcare contact.[340]

The pathogenesis of PVE differs according to both the type of contamination and the type of prosthetic valve. In cases with perioperative contamination, the infection usually involves the junction between the sewing ring and the annulus, leading to perivalvular abscess, dehiscence, pseudo-aneurysms and fistulae.[339,343,344] In late PVE, additional mechanisms may exist. For example, in late bioprosthetic PVE, infection is frequently located on the leaflets of the prosthesis, leading to vegetations, cusp rupture and perforation. PVE has recently been reported after transcatheter aortic bioprosthetic valve implantation, which should be managed in the same manner as other prosthetic valves.[345,346] The risk of prosthetic valve implantation endocarditis increases with the use of orotracheal intubation and a self-expandable valve system.

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

12.1.2 Diagnosis

Diagnosis is more difficult in PVE than in NVE. Clinical presentation is frequently atypical, particularly in the early postoperative period, in which fever and inflammatory syndromes are common in the absence of IE. However, persistent fever should trigger the suspicion of PVE. As in NVE, diagnosis of PVE is based mainly on the results of echocardiography and blood cultures. However, both are more frequently negative in PVE.[100] Although TOE is mandatory in suspected PVE (*Figure 3*), its diagnostic value is lower than in NVE. A negative echocardiogram is frequently observed in PVE[2] and does not rule out the diagnosis, but identification of a new periprosthetic leak is a major criterion, in which case an additional imaging modality could be considered (such as CT or nuclear imaging).

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In PVE, staphylococcal and fungal infections are more frequent and streptococcal infection less frequent than in NVE. Staphylococci, fungi and Gram-negative bacilli are the main causes of early PVE, while the microbiology of late PVE mirrors that of NVE, with staphylococci, oral streptococci, *S. bovis* and enterococci being the most frequent organisms, more likely due to community-acquired infections. Staphyloccoci and enteroccoci are the most common agents in prosthetic valve implantation endocarditis.[345,346]

The Duke criteria have been shown to be helpful for the diagnosis of NVE, with a sensitivity of 70–80%,[100,347] but are less useful in PVE because of their lower sensitivity in this setting.[348,349] Recently, nuclear techniques, particularly ^{18}F-FDG PET/CT, have been shown to be useful for the diagnosis of PVE.[93] The addition of abnormal FDG uptake as a novel major criterion for PVE has thus been pointed out. An algorithm for evaluation of patients with suspected PVE, including echocardiography and PET/CT has been suggested (see *Figure 3*).[93]

12.1.3 Prognosis and treatment

A very high in-hospital mortality rate of 20–40% has been reported in PVE.[338,341] As in NVE, prognostic assessment is of crucial importance in PVE, as it allows identification of high-risk subgroups of patients in whom an aggressive strategy may be necessary. Several factors have been associated with poor prognosis in PVE,[161,216,350–353] including older age, diabetes mellitus, healthcare-associated infections, staphylococcal or fungal infection, early PVE, HF, stroke and intracardiac abscess. Among these, complicated PVE and staphylococcal infection are the most powerful markers. These patients need aggressive management, consisting of antibiotic therapy and early radical surgery.

Antimicrobial therapy for PVE is similar to that for NVE. An exception is *S. aureus* PVE, which requires a more prolonged (≥6 weeks) antibiotic regimen (particularly in association with aminoglycosides) and frequent use of rifampin.

Surgery for PVE follows the general principles outlined for NVE. Radical debridement in these cases means removal of all infected foreign material, including the original prosthesis, and any calcium remaining from previous surgery. Homografts, stentless xenografts or autografts may be considered in aortic PVE, and homograft or xenograft root replacement is indicated for any abnormality of the aortic root that distorts the aortic sinuses. Alternatively, a valved Dacron conduit[336] can be used.

The best therapeutic option in PVE is still debated.[221,354–359] Although surgery is generally considered the best option when PVE causes severe prosthetic dysfunction or HF,[220] it was performed in only 50% of patients with PVE in the Euro Heart Survey,[54] a similar rate as for patients with NVE. Other groups have reported similar data.[221,340] Early surgery was associated with lower in-hospital and 1-year mortality in a large cohort of 4166 patients including both native and prosthetic valve IE complicated by HF.[216] Conversely, after adjustment for differences in clinical characteristics and survival bias, early valve replacement was not associated with lower mortality compared with medical therapy in a large international cohort.[37] However, in these series, surgery was beneficial in the subgroup of patients with the greatest need for surgery, including valve regurgitation, vegetation and dehiscence or paravalvular abscess/fistula.[37]

Therefore a surgical strategy is recommended for PVE in high-risk subgroups identified by prognostic assessment, i.e. PVE complicated by HF, severe prosthetic dysfunction, abscess or persistent fever (*Table 22*). Emergency surgery is indicated only in cases with refractory congestive HF leading to pulmonary oedema or shock, as in NVE. Conversely, patients with uncomplicated non-staphylococcal and non-fungal late PVE can be managed conservatively.[350,357,358] However, patients who are initially treated medically require close follow-up because of the risk of late events.

In summary, PVE represents 20% of all cases of IE, with an increasing incidence. The diagnosis of PVE is more difficult than for NVE. Complicated PVE and staphylococcal PVE are associated with a worse prognosis if treated without surgery. These forms of PVE must be managed aggressively. Patients with uncomplicated, non-staphylococcal late PVE can be managed conservatively with close follow-up.

12.2 Infective endocarditis affecting cardiac implantable electronic devices

12.2.1 Introduction

Infection of cardiac implantable electronic devices (CIEDs) is a severe disease associated with high mortality.[360] The increased rates of CIED implantation coupled with increased implantation in older patients with more co-morbidities have set the stage for higher rates of CIED infection and the increasing frequency of IE in these patients.[361] The reported incidence of permanent pacemaker infection varies widely among studies.[362,363] A population-based study found an incidence of CIED infection of 1.9 per 1000 device-years and a higher probability of infection after implantable cardioverter defibrillators compared with permanent pacemakers.[364] Both diagnosis and therapeutic strategy are particularly difficult in these patients.[365]

12.2.2 Definitions of cardiac device infections

A distinction should be made between local device infection and cardiac device-related IE (CDRIE). Local device infection is defined as an infection limited to the pocket of the cardiac device and is clinically suspected in the presence of local signs of inflammation at the generator pocket, including erythema, warmth, fluctuance, wound dehiscence, erosion, tenderness or purulent drainage.[366] CDRIE is defined as an infection extending to the electrode leads, cardiac valve leaflets or endocardial surface. However, differentiating local device infection and CDRIE is frequently difficult. In one study,[367] culture of intravascular lead segments was positive in 72% of 50 patients with manifestations strictly limited to the implantation site. However, the possibility of intraoperative contamination of the lead tip cannot be excluded in these patients.

12.2.3 Pathophysiology

The pocket may become infected at the time of implantation, during subsequent surgical manipulation of the pocket or if the generator or subcutaneous electrodes erode through the skin. Pocket infection may track along the intravascular portion of the electrode to involve the intracardiac portion of the pacemaker or implantable cardioverter defibrillator. Alternatively, the pocket or intracardiac portion of the electrode may become infected as a result of haematogenous seeding during a bacteraemia secondary to a distant infected focus. The consequence may be formation of vegetations, which can be found anywhere from the insertion vein to the superior vena cava, on the lead or on the tricuspid valve, as well as on the

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right atrial and ventricular endocardium. Septic pulmonary embolism is a very frequent complication of CDRIE.

12.2.4 Risk factors

Several factors have been associated with CIED infections.[366,367] Patient factors include renal failure, corticosteroid use, congestive HF, haematoma formation, diabetes mellitus and anticoagulation use.[368–370] In addition, procedural characteristics may also play an important role in the development of CIED infection. The factors associated with an increased risk of infection include the type of intervention,[371,372] device revisions, the site of intervention, the amount of indwelling hardware, the use of pre-procedural temporary pacing, failure to administer perioperative antimicrobial prophylaxis,[373] fever within the 24 h before implantation and operator experience.[374]

12.2.5 Microbiology

Staphylococci, and especially CoNS, account for 60–80% of cases in most reported series.[375,376] A variety of CoNS species have been described.[366,377] Methicillin resistance among staphylococci varies among studies,[376,378] but a low frequency of methicillin-resistant CoNS has been reported among individuals with no healthcare contact, whereas a high rate of methicillin resistance in CoNS is associated with a healthcare environment source.[379] Polymicrobial infection sometimes involves more than one species of CoNS.[376,380,381] *Corynebacterium* spp., *Propionibacterium acnes*, Gram-negative bacilli and *Candida* spp. are rarely identified as pathogens in CIED infection.[366,376,377]

12.2.6 Diagnosis

Clinical presentation is frequently misleading, with predominant respiratory and rheumatological symptoms as well as local signs of infection.[382] CDRIE must be suspected in the presence of unexplained fever in a patient with a CIED. Fever is frequently blunted, particularly in elderly patients. As in other forms of IE, echocardiography and blood cultures are the cornerstones of diagnosis. *S. aureus* bacteraemia might be the sole manifestation of device infection.

Echocardiography plays a key role in CDRIE and is helpful for the diagnosis of both lead vegetations and tricuspid involvement, quantification of tricuspid regurgitation, sizing of vegetations and follow-up after lead extraction. Several prognostic features may be better defined on TTE than on TOE, such as pericardial effusion, ventricular dysfunction and pulmonary vascular pressure estimations. TOE has superior sensitivity and specificity to TTE for diagnosis of lead-related endocarditis.[381–385] TOE allows visualization of the lead in atypical locations, such as the proximal superior vena cava, and of regions that are difficult to visualize by TTE. In addition, the sensitivity of TOE for left-sided involvement and for perivalvular extension of infection is superior to that of TTE. Considering their complementary role, it is recommended to perform both investigations in suspected CDRIE.

In the presence of infective material along the lead course not providing typical vegetations of measurable size, both TTE and TOE may be falsely negative in CDRIE. Intracardiac echocardiography was recently found to be feasible and effective in cardiac device patients[386] and to have a superior sensitivity for the detection of vegetations in cardiac devices.[386–388]

A normal echographic examination does not rule out CDRIE. In difficult cases, other modalities such as radiolabelled leucocyte scintigraphy[389] and ^{18}F-FDG PET/CT scanning[108,390] have been described as additive tools in the diagnosis of CDRIE and related complications, including pulmonary septic embolism.

The Duke criteria are difficult to apply in these patients because of lower sensitivity.[347] Modifications of the Duke criteria have been proposed,[382,391] including local signs of infection and pulmonary embolism as major criteria.[382]

12.2.7 Treatment

CDRIE must be treated by prolonged antibiotic therapy associated with complete hardware removal.[360,391]

12.2.8 Antimicrobial therapy

Antimicrobial therapy for CDRIE should be individualized and based on culture and susceptibility results if possible (see section 7). Because most CDRIE infections are secondary to staphylococcal species and, of those, up to 50% are methicillin-resistant,[376,392] vancomycin should be administered initially as empirical antibiotic coverage until microbiological results are known. Daptomycin, approved for right-side IE and bacteraemia attributable to *S. aureus*,[168] is a promising molecule to treat CIED infection.[393–395] Before hardware removal, but after blood cultures, i.v. antibiotics should be initiated. There are no clinical trial data to define the optimal duration of antimicrobial therapy. The duration of therapy should be 4–6 weeks in most cases.[362] At least 2 weeks of parenteral therapy is recommended after extraction of an infected device for patients with bloodstream infection. Patients with sustained (>24 h) positive blood cultures despite CIED removal and appropriate antimicrobial therapy should receive parenteral therapy for at least 4 weeks.[362,366]

12.2.9 Complete hardware removal (device and lead extraction)

In the case of definite CDRIE, medical therapy alone has been associated with high mortality and risk of recurrence.[360,363,391] For this reason, CIED removal is recommended in all cases of proven CDRIE and should also be considered when CDRIE is only suspected in the case of occult infection without any apparent source other than the device.[396]

Complete removal of the system is the recommended treatment for patients with established CDRIE.[363,391,396] Considering the inherent risk of an open surgical procedure,[380] transvenous lead extraction has become the preferred method. It is essential to remove all hardware to avoid the recurrence of infection.[368,397] In experienced centres, procedural mortality rates have been shown to be between 0.1% and 0.6%.[396,398] Long-term mortality varies among subgroups, but rates are higher in systemic infections.[399] Transvenous extractions are not without risk, and procedural complexity may vary significantly according to lead type and features. Typically ICD leads are more difficult to remove than coronary sinus leads, which are usually removed by simple manual traction.[400–402] Transvenous lead extraction should be performed only in centres committed to a procedural volume allowing the maintenance of skills of adequately trained teams and able to provide immediate cardiothoracic surgery backup in the event of emergency thoracotomy or sternotomy.[396,403]

Pulmonary embolism as a result of vegetation displacement during extraction occurs frequently, particularly when vegetations are

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large.[367,404] However, these episodes are frequently asymptomatic, and percutaneous extraction remains the recommended method even in cases of large vegetations,[360,391,404] as overall risks are even higher with surgical extraction.[367,380]

Some authors recommend surgery in patients with very large vegetations.[405] Until additional data are available, decisions regarding percutaneous versus surgical removal of leads with vegetations >2 cm in diameter should be individualized.

Other indications for a surgical approach to lead removal include patients who need a contemporary valve replacement or repair for IE or patients who have significant retained hardware after attempts at percutaneous removal. However, mortality associated with surgical removal is high in these frequently elderly patients with associated co-morbidities.[380]

12.2.10 Reimplantation

The first step before reimplantation is a re-evaluation of the indication for CIED implantation.[377,403] In a significant number of cases, reimplantation is not necessary.[366,398] The device should be reimplanted on the contralateral side. There is no clear recommendation concerning the optimal timing of reimplantation. Factors such as persistent bacteraemia, persistent vegetation and pacemaker and implantable cardioverter defibrillator dependency should be considered and the decision adapted to the individual patient. Immediate reimplantation should be avoided, owing to the risk of new infection.[366,377,398,403] Blood cultures should be negative for at least 72 h before placement of a new device. In cases of evidence of remnant valvular infection, implantation should be delayed for at least 14 days.[366,406]

Temporary pacing is a risk factor for subsequent cardiac device infection[367] and should be avoided if possible. In pacing-dependent patients, temporary use of active fixation leads connected to external devices is described as a 'bridge',[407] permitting earlier mobilization with a reduced risk of pacing-related adverse events.[408–410]

12.2.11 Prophylaxis

Although there are no large controlled studies on this topic, antibiotic prophylaxis is recommended before implantation.[367,368,373] A first-generation cephalosporin, such as cefazolin (6 g/day for 24–36 h after the intervention), is usually used as prophylaxis and should be parenterally administered 1 h before the procedure.

Vancomycin, teicoplanin and daptomicin may be considered instead of cefazolin in centres where oxacillin resistance among staphylococci is high, in high-risk patients or in patients with contraindications to cephalosporins. They should always be started before the procedure according to the drug pharmacokinetics.

In summary, CDRIE is one of the most difficult forms of IE to diagnose and must be suspected in the presence of frequently misleading symptoms, particularly in elderly patients. Prognosis is poor, probably because of its frequent occurrence in elderly patients with associated co-morbidities. In the majority of patients, CDRIE must be treated by prolonged antibiotic therapy and device removal. Table 25 summarizes the main features concerning diagnosis, treatment and prevention of CDRIE.

Table 25 Cardiac device-related infective endocarditis: diagnosis, treatment and prevention

Recommendations	Class[a]	Level[b]	Ref.[c]
A. Diagnosis			
1. Three or more sets of blood cultures are recommended before prompt initiation of antimicrobial therapy for CIED infection	I	C	
2. Lead-tip culture is indicated when the CIED is explanted	I	C	
3. TOE is recommended in patients with suspected CDRIE with positive or negative blood cultures, independent of the results of TTE, to evaluate lead-related endocarditis and heart valve infection	I	C	
4. Intracardiac echocardiography may be considered in patients with suspected CDRIE, positive blood cultures and negative TTE and TOE results	IIb	C	
5. Radiolabelled leucocyte scintigraphy and ^{18}F-FDG PET/CT scanning may be considered additive tools in patients with suspected CDRIE, positive blood cultures and negative echocardiography	IIb	C	
B. Principles of treatment			
1. Prolonged (i.e. before and after extraction) antibiotic therapy and complete hardware (device and leads) removal are recommended in definite CDRIE, as well as in presumably isolated pocket infection	I	C	
2. Complete hardware removal should be considered on the basis of occult infection without another apparent source of infection	IIa	C	
3. In patients with NVE or PVE and an intracardiac device with no evidence of associated device infection, complete hardware extraction may be considered	IIb	C	
C. Mode of device removal			
1. Percutaneous extraction is recommended in most patients with CDRIE, even those with vegetations >10 mm	I	B	382, 391, 405

Continued

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Table 25 ***Continued***

Recommendations	Class[a]	Level[b]	Ref.[c]
2. Surgical extraction should be considered if percutaneous extraction is incomplete or impossible or when there is associated severe destructive tricuspid IE	IIa	C	
3. Surgical extraction may be considered in patients with large vegetations (>20 mm)	IIb	C	
D. Reimplantation			
1. After device extraction, reassessment of the need for reimplantation is recommended	I	C	
2. When indicated, definite reimplantation should be postponed if possible, to allow a few days or weeks of antibiotic therapy	IIa	C	
3. A 'temporary' ipsilateral active fixation strategy may be considered in pacemaker-dependent patients requiring appropriate antibiotic treatment before reimplantation	IIb	C	
4. Temporary pacing is not routinely recommended	III	C	
E. Prophylaxis			
1. Routine antibiotic prophylaxis is recommended before device implantation	I	B	367, 368, 373
2. Potential sources of sepsis should be eliminated ≥2 weeks before implantation of an intravascular/ cardiac foreign material, except in urgent procedures	IIa	C	

CDRIE = cardiac device-related infective endocarditis; CIED = cardiac implantable electronic device; FDG = fluorodeoxyglucose; IE = infective endocarditis; NVE = native valve endocarditis; PET = positron emission tomography; PVE = prosthetic valve endocarditis; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

12.3 Infective endocarditis in the intensive care unit

Admission to the intensive care unit (ICU) is frequently a part of the normal patient pathway following surgery for IE. In addition, patients with IE may be admitted to the ICU due to haemodynamic instability related to severe sepsis, overt HF and/or severe valvular pathology or organ failure from IE-related complications.[411,412] The incidence of nosocomial infection is increasing and patients may develop IE as a result of healthcare-associated infection acquired during hospital or intensive care admission. Finally, the diagnosis of IE can be challenging, being made only post-mortem in a number of patients.[413] Despite advances in diagnosis and treatment, mortality remains particularly high in critically ill patients, ranging from 29% to 84%.[411,414,415]

Estimation of the number of patients requiring ICU admission for IE is challenging. In a retrospective, multicentre, observational study of 4106 patients admitted to four medical ICUs, IE was identified in 0.8% of admissions.[416] Reasons for admission to the ICU were congestive cardiac failure (64%), septic shock (21%), neurological deterioration (15%) and cardiopulmonary resuscitation (9%).[416] Critical care morbidity is high, with up to 79% of patients requiring mechanical ventilation, 73% inotropic support and 39% developing renal failure.

12.3.1 Organisms

Limited data are available regarding causative organisms for IE in the ICU. Case series have revealed *Staphylococci* spp. to be the most common causative agent, accounting for 74% of all nosocomial IE cases. Streptococci are the second most common causative organisms. Fungal IE is an increasing problem in the ICU, with *Candida* IE occurring significantly more often in ICU than non-ICU hospitalized patients.[417] There should be a high index of suspicion for fungal IE in the ICU setting, in particular where there is failure to respond to empirical antimicrobial therapy.

12.3.2 Diagnosis

The diagnostic criteria for IE in the ICU are identical to those for the non-ICU patient population. However, clinical manifestations may be atypical and the classic features may be masked by concomitant pathology and critical care interventions. Thus pyrexia may be attributed to co-existing hospital-acquired infections, neurological manifestations masked by the confounding factors of sedation, ICU-related delirium, concomitant multiple pathologies and acute kidney injury ascribed to co-existing pathologies. Echocardiography can be challenging in the intensive care setting, with a reduced sensitivity of TTE for the diagnosis of IE. There should be a relatively low threshold for TOE in critically ill patients with *S. aureus* catheter-related bloodstream infection because of its high propensity to cause IE, and also, if negative, this may allow short antibiotic treatment.

12.3.3 Management

Patients with severe sepsis or septic shock should be managed according to protocolised international guidelines.[418] Antimicrobial management and indications for surgery in patients with IE are described in sections 7 and 10, respectively. However, emergency/salvage status accounts for the highest mortality rates in registry data for patients operated on for IE,[299] and patients with SOFA scores >15 on the day of surgery have extremely poor outcomes.[125] Decision making in this most critically ill patient population where indications and contraindications for cardiac surgery co-exist is challenging and should be undertaken in the context of the multiprofessional, multidisciplinary Endocarditis Team environment.

12.4 Right-sided infective endocarditis

Right-sided IE accounts for 5–10% of IE cases.[419,420] Although it may occur in patients with a pacemaker, ICD, central venous catheter or CHD, this situation is most frequently observed in IVDAs, especially in patients with concomitant human immunodeficiency virus (HIV) seropositivity or in immunosuppressed patients.[420–422] *S. aureus* is the predominant organism (60–90% of cases),[419,423] with methicillin-resistant strains becoming more prevalent.[414] The frequency of polymicrobial infections is also rising.[424] The tricuspid valve is most

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frequently affected, but other valves—including left-sided—may also become infected.[425] In-hospital mortality is approximately 7%.[426–429]

12.4.1 Diagnosis and complications

The usual manifestations of right-sided IE are persistent fever, bacteraemia and multiple septic pulmonary emboli, which may manifest as chest pain, cough or haemoptysis. When systemic emboli occur, paradoxical embolism or associated left-sided IE should be considered. Isolated right HF is rare, but can be caused by pulmonary hypertension or severe right-sided valvular regurgitation or obstruction.[425] Pulmonary hypertension can be secondary to left-sided IE.

TTE usually allows assessment of tricuspid involvement because of the anterior location of this valve and usual large vegetations.[430,431] Eustachian and pulmonary valves should always be assessed. TOE is more sensitive in the detection of pulmonary vegetations[432] and associated left-sided involvement.

12.4.2 Prognosis and treatment

Vegetation length >20 mm and fungal aetiology were the main predictors of death in a large retrospective cohort of right-sided IE in IVDAs.[433] In HIV-infected patients, a CD4 count <200 cells/μL has a high prognostic value.[420,421]

12.4.2.1 Antimicrobial therapy

The choice of empiric antimicrobial therapy depends on the suspected microorganism, type of drug and solvent used by the addict and the infection location.[424] In any case, *S. aureus* must always be covered. Initial treatment includes penicillinase-resistant penicillins, vancomycin or daptomycin, depending on the local prevalence of MRSA,[424] in combination with gentamicin. If the patient is a pentazocine addict, an antipseudomonas agent should be added.[434] If an IVDA uses brown heroin dissolved in lemon juice, *Candida* spp. (not *Candida albicans*) should be considered and antifungal treatment added.[435] Once the causative organisms have been isolated, therapy has to be adjusted.

Consistent data show that 2-week treatment may be sufficient and that the addition of an aminoglycoside may be unnecessary.[436] Two-week treatment with oxacillin (or cloxacillin) without gentamicin is effective for most patients with isolated tricuspid IE if all the following criteria are fulfilled:

- MSSA,
- Good response to treatment,
- Absence of metastatic sites of infection or empyema,
- Absence of cardiac and extracardiac complications,
- Absence of associated prosthetic valve or left-sided valve infection,
- <20 mm vegetation, and
- Absence of severe immunosuppression (<200 CD4 cells/μL) with or without acquired immune deficiency syndrome (AIDS).

Because of limited bactericidal activity, poor penetration into vegetations and increased drug clearance in IVDAs, glycopeptides (vancomycin) should not be used in a 2-week treatment. The standard 4–6-week regimen must be used in the following situations:

- Slow clinical or microbiological response (> 96 h) to antibiotic therapy;[426]
- Right-sided IE complicated by right HF, vegetations >20 mm, acute respiratory failure, septic metastatic foci outside the lungs (including empyema) or extracardiac complications, e.g. acute renal failure;[426]
- Therapy with antibiotics other than penicillinase-resistant penicillins;[437]
- IVDA with severe immunosuppression (CD4 count <200 cells/μL) with or without AIDS;[438] or
- Associated left-sided IE.

Alternatively, when conventional i.v. route therapy is not possible, right-sided *S. aureus* IE in IVDAs may also be treated with oral ciprofloxacin [750 mg bis in die (b.i.d.)] plus rifampicin (300 mg b.i.d.) provided that the strain is fully susceptible to both drugs, the case is uncomplicated and patient adherence is monitored carefully.[439] One randomized controlled study has demonstrated the non-inferiority of daptomycin compared with standard therapy in the treatment of *S. aureus* infections, including right-sided IE.[168] When using daptomycin, most authors recommend using high doses (10 mg/kg/24 h) and combining it with cloxacillin or fosfomycin to avoid the development of resistance to this drug.[174] Glycopeptides (e.g. vancomycin) or daptomycin are the agents of choice for MRSA infections. Vancomycin may have a lower efficacy in infections caused by MRSA strains with a vancomycin MIC >1 μg/mL.[171,172,440] In these cases, daptomycin would be the drug of choice. For organisms other than *S. aureus*, therapy in IVDAs does not differ from that in non-IVDAs.

12.4.2.2 Surgery

Given the high recurrence rate of IE due to continued drug abuse, surgery should generally be avoided in IVDAs with right-

Table 26 Indications for surgical treatment of right-sided infective endocarditis

Recommendation	Class[a]	Level[b]
Surgical treatment should be considered in the following scenarios: • Microorganisms difficult to eradicate (e.g. persistent fungi) or bacteraemia for > 7 days (e.g. *S. aureus*, *P. aeruginosa*) despite adequate antimicrobial therapy or • Persistent tricuspid valve vegetations > 20 mm after recurrent pulmonary emboli with or without concomitant right heart failure or • Right HF secondary to severe tricuspid regurgitation with poor response to diuretic therapy	IIa	C

HF = heart failure.
[a]Class of recommendation.
[b]Level of evidence.

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sided native IE, but it has to be considered in the following situations (*Table 26*):

- Right HF secondary to severe tricuspid regurgitation with poor response to diuretic therapy;
- IE caused by organisms that are difficult to eradicate (e.g. persistent fungi) or bacteraemia for at least 7 days (e.g. *S. aureus*, *Pseudomonas aeruginosa*) despite adequate antimicrobial therapy;[441] and
- Tricuspid valve vegetations >20 mm that persist after recurrent pulmonary emboli with or without concomitant right HF.[426,433]

Cardiac surgery in HIV-infected IVDAs with IE does not worsen the prognosis of either the IE or the HIV.

Recent nationwide data have shown that the three most frequent surgical strategies for tricuspid valve IE are valvectomy, valve repair and valve replacement.[429] Tricuspid valve replacement accounted for the majority of cases, with most receiving a bioprosthetic valve. Some authors prefer valve repair (avoiding artificial material whenever possible) over valve replacement, but the former did not improve outcomes over valve replacement or valvectomy.[429] Valvectomy without prosthetic replacement can be done in extreme cases, but may be associated with severe postoperative right HF, particularly in patients with pulmonary hypertension. In these cases, the valve can be subsequently replaced once infection has been cured and drug use discontinued. Pulmonary valve replacement should be avoided, but if judged necessary, use of a pulmonary homograft (or, if unavailable, a xenograft valve) is preferred.

In summary, right-sided IE is primarily a disease that affects IVDAs and patients with CHD. Diagnostic features include respiratory symptoms and fever. S. aureus is responsible for most cases. TTE is of major value in these patients. Despite relatively low in-hospital mortality, right-sided IE has a high risk of recurrence in IVDAs and surgery is recommended only for intractable symptoms, failure of medical therapy, recurrent septic emboli to the lungs or paradoxical emboli.

12.5 Infective endocarditis in congenital heart disease

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

The reported incidence of IE in CHD is 15–140 times higher than that in the general population (the highest estimate originating from a highly specialized unit).[442,443] The incidence is lower in children (0.04% per year) than in adults with CHD (0.1% per year).[444,445] The reported proportion of CHD in patients with IE varies (probably due to selection bias) by between 2% and 60%,[446–450] with a consistent minor male dominance.[443,451,452]

Some simple lesions, such as secundum atrial septal defect and pulmonary valve disease, carry a low risk of IE, while others, such as bicuspid aortic valve, carry higher risk. However, CHD often consists of multiple cardiac lesions, each contributing to the total risk of IE. For example, the incidence of IE is considerably higher in patients with a ventricular septal defect when there is associated aortic regurgitation.[453]

The distribution of causative organisms does not differ from the pattern found in acquired heart disease, with streptococci and staphylococci being the most common strains.[443,451,452]

As in other groups, the diagnosis of IE is often made too late, highlighting the need to consider the diagnosis of IE in any patient with CHD presenting with ongoing fever or other signs of ongoing infection. Blood cultures should be taken before starting antibiotic treatment. The principal symptoms, complications and basis for diagnosis do not differ from IE in general. However, right-sided IE is more frequent in CHD than in acquired cardiac disease. The superiority of TOE over TTE has not been systematically studied in this setting. Nevertheless, complex anatomy and the presence of artificial material may reduce the rate of detection of vegetations and other features of IE, thus favouring the addition of TOE, particularly in the adult group.[443] However, a negative study does not exclude the diagnosis.

Care of CHD patients with IE, from diagnosis to treatment, is best provided by specialized CHD centres with expertise in imaging, surgery and intensive care. Cardiac surgery is appropriate when medical therapy fails, when serious haemodynamic complications arise and when there is a high risk of devastating septic embolism.

IE in CHD carries a mortality rate of 4–10%.[443,451,452,454] This better prognosis compared with acquired heart disease may reflect the higher proportion of right-heart IE or the better care in CHD centres.

Primary prevention is vital.[455] The importance of good oral, dental and skin hygiene has already been emphasized, and antibiotic prophylaxis is indicated in high-risk groups as defined in section 3. However, there is also an educational problem, especially in patients not followed in specialist CHD centres, and awareness of the risk of IE and the need for preventive measures are not satisfactorily highlighted in the population with CHD.[456] Cosmetic tattooing and piercing, at least involving the tongue and mucous membranes, should be discouraged in this group.

Surgical repair of CHD often reduces the risk of IE, provided there is no residual lesion.[447,457] However, in other cases when artificial valve substitutes are implanted, the procedure may increase the overall risk of IE. There are no scientific data justifying cardiac surgery or percutaneous interventions (e.g. closure of a patent ductus arteriosus) with the sole purpose of eliminating the risk of IE.[458] Cardiac repair as a secondary preventive measure to reduce the risk of recurrent IE has been described but not systematically studied.

In summary, IE in CHD is rare and more frequently affects the right heart. Care of CHD patients with IE, from diagnosis to treatment, is best provided by specialist CHD centres with expertise in imaging, surgery and intensive care. This applies to most patients with CHD. Complex anatomy makes echocardiographic assessment difficult. However, the diagnosis should be considered in all CHD patients with ongoing infection or fever. Prognosis is better than in other forms of IE, with a mortality rate of <10%. Preventive measures and patient education are of particular importance in this population.

12.6 Infective endocarditis during pregnancy

A challenge for the physician during pregnancy in the cardiac patient is the changing cardiovascular physiology, which can mimic cardiac disease and confuse the clinical picture.[459,460] The incidence of IE during pregnancy has been reported to be 0.006%.[196] The incidence of IE in patients with cardiac disease is 0–1.2% and is higher in women with a mechanical prosthetic valve.[461–464] Therefore IE in pregnancy is extremely rare and is either a complication of a pre-existing cardiac lesion or the result of i.v. drug abuse. Maternal mortality approaches 33%, with most deaths relating to HF or an embolic event, while foetal

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Table 27 Recommendations for the use of antithrombotic therapy

Recommendations	Class[a]	Level[b]	Ref.[c]
Interruption of antiplatelet therapy is recommended in the presence of major bleeding	I	B	257
In intracranial haemorrhage, interruption of all anticoagulation is recommended	I	C	
In ischaemic stroke without haemorrhage, replacement of oral anticoagulant (anti-vitamin K) therapy by unfractionated or low molecular weight heparin for 1–2 weeks should be considered under close monitoring[d]	IIa	C	
In patients with intracranial haemorrhage and a mechanical valve, unfractionated or low molecular weight heparin should be reinitiated as soon as possible following multidisciplinary discussion	IIa	C	
In the absence of stroke, replacement of oral anticoagulant therapy by unfractionated or low molecular weight heparin for 1–2 weeks should be considered in the case of *Staphylococcus aureus* IE under close monitoring	IIa	C	
Thrombolytic therapy is not recommended in patients with IE	III	C	

IE = infective endocarditis.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]There is very limited experience with new oral anticoagulant treatment in the field of IE.

mortality is reported to be about 29%.[196] Close attention should be paid to any pregnant woman with unexplained fever and a cardiac murmur.

Rapid detection of IE and appropriate treatment is important in reducing the risk of both maternal and foetal mortality.[196] Despite the high foetal mortality, urgent surgery should be performed during pregnancy in women who present with HF due to acute regurgitation.

12.7 Antithrombotic therapy in infective endocarditis

Indications for anticoagulant and antiplatelet therapy are the same in IE patients as in other patients, and evidence does not support the initiation of medications interfering with the coagulation system as adjunctive therapy for IE.[258] Thrombolytic therapy is generally contraindicated and has sometimes resulted in severe intracranial haemorrhage,[465] but thrombectomy could be an alternative in selected patients with ischaemic stroke related to IE (see section 9.1).

The risk of intracranial haemorrhage may be increased in patients already on oral anticoagulants when IE is diagnosed, especially in patients with *S. aureus* PVE.[113,466] On the other hand, ongoing oral anticoagulants during IE development may diminish early embolic tendencies.[467]

The recommendations for management of anticoagulant therapy in IE patients are based on a low level of evidence, and decisions should be made on an individual basis by the Endocarditis Team. The role of bridging therapy with unfractionated or low molecular weight heparin has not been studied in patients with IE, but may have reasonable advantages in special situations (i.e. in unstable patients) before surgical decisions are made or to avoid drug interactions.

Evidence does not support initiation of antiplatelet therapy in patients diagnosed with IE,[258] despite promising results in experimental studies.[468] Some cohort studies indicate a possible reduction in the rate of embolic complications[257] or IE development in subgroups of patients already on antiplatelet therapy,[469] but the data are contradictory.[470,471]

12.8 Non-bacterial thrombotic endocarditis and endocarditis associated with cancers

12.8.1 Non-bacterial thrombotic endocarditis

Non-bacterial thrombotic endocarditis (NBTE) (i.e. marantic endocarditis, Libman–Sacks endocarditis or verrucous endocarditis) is characterized by the presence of sterile vegetations consisting of fibrin and platelet aggregates on cardiac valves. These vegetations are associated with neither bacteraemia nor with destructive changes of the underlying valve.[472] It is also quite relevant to differentiate true NBTE versus patients with negative blood cultures due to previous antibiotic therapy.[473]

NBTE is a condition associated with numerous diseases such as cancer, connective tissue disorders (i.e. systemic lupus erythematosus patients possessing antiphospholipid antibodies, called Libman–Sacks endocarditis), autoimmune disorders, hypercoagulable states, septicaemia, severe burns or chronic diseases such as tuberculosis, uraemia or AIDS. It is a potentially life-threatening source of thromboembolism, its main clinical manifestation.

It is essential to differentiate NBTE from IE. The same initial diagnostic workup used for IE is recommended. The diagnosis of NBTE is difficult and relies on strong clinical suspicion in the context of a disease process known to be associated with NBTE, the presence of a heart murmur, the presence of vegetations not responding to antibiotic treatment and evidence of multiple systemic emboli.[474]

The presence of a new murmur or a change in a pre-existing murmur, although infrequent, in the setting of a predisposing disease should alert the clinician to consider NBTE.

Valvular vegetations in NBTE are usually small, broad based and irregularly shaped. They have little inflammatory reaction at the site of attachment, which make them more friable and detachable. Following embolization, small remnants on affected valves ($\leq$3 mm) may result in false-negative echocardiography results. TOE should be ordered when there is a high suspicion of NTBE. Left-sided (mitral more than aortic) and bilateral vegetations are more consistent with NTBE than with IE.[475] When an early TOE examination is performed, the prognosis of NTBE is improved.[476]

Comprehensive haematological and coagulation studies should be performed to search for a potential cause. Multiple blood cultures should be undertaken to rule out IE, although negative blood cultures

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can be observed in IE (i.e. previous antibiotic therapy, HACEK group, fungi, etc.). Immunological assays for antiphospholipid syndrome (i.e. lupus anticoagulant, anticardiolipin antibodies, and anti-β_2-glycoprotein 1 antibodies; at least one must be positive for the diagnosis of antiphospholipid syndrome on at least two occasions 12 weeks apart) should be undertaken in patients presenting with recurrent systemic emboli or known systemic lupus erythematous.[477]

NTBE is first managed by treating the underlying pathology. If there is no contraindication, these patients should be anticoagulated with unfractioned or low molecular weight heparin or warfarin, although there is little evidence to support this strategy. In NTBE, the use of direct thrombin or factor Xa inhibitors has not been evaluated. In antiphospholipid syndrome, lifelong anticoagulation is indicated. A trial comparing rivaroxaban (a factor Xa inhibitor) and warfarin in patients with thrombotic antiphospholipid syndrome is currently in progress.[478] However, anticoagulation is associated with a risk of haemorrhagic conversion of embolic events. CT of the brain should be performed in patients with NBTE and cerebral attack before anticoagulation to rule out intracranial haemorrhage.

Surgical intervention, valve debridement and/or reconstruction are often not recommended unless the patient presents with recurrent thromboembolism despite well-controlled anticoagulation. Other indications for valve surgery are the same as for IE. In the context of cancer, a multidisciplinary approach is recommended (Endocarditis Team).

12.8.2 Infective endocarditis associated with cancer

IE may be a potential marker of occult cancers. In a large, Danish, nationwide, population-based cohort study, 997 cancers were identified among 8445 IE patients with a median follow-up of 3.5 years. The risk of abdominal and haematological cancers was high soon after IE diagnosis (within the first 3 months) and remained higher than expected in the long-term follow-up (>12 months) for abdominal cancer.[479]

Several bacteria have been reported in association with colonic cancer, with the strongest and best-documented relationship with *S. bovis* infection, specifically the *S. gallolyticus* subspecies; *S. bovis* infection *has* been related to the presence of gastrointestinal neoplasia, which in most cases is colonic adenoma or carcinoma.[480] However, it is still a source of debate whether the association of *S. bovis*/*S. gallolyticus* IE with colorectal tumours is merely a consequence of the gastrointestinal lesion or could trigger or promote colorectal cancer.[481]

In the setting of *S. bovis* IE, there is a need for proper microbiological classification. In case of *S. bovis*/*S. gallolyticus* IE, it is recommended to rule out occult colon cancer during hospitalization. In the absence of any tumour, scheduling an annual colonoscopy is highly suggested.[482]

As for other tests (i.e. faecal occult blood), the serology-based detection of colorectal cancer—serum IgG concentrations against *S. bovis* antigens—is neither sensitive (not all colorectal tumours are colonized by *S. bovis*) nor specific.[483]

FDG PET/CT is increasingly used in the diagnostic workup of IE. It may play an interesting role in detecting gastrointestinal pathological activity and guide colonoscopy. However, negative PET/CT does not rule out significant colonic pathology. No study has examined its clinical value for the detection of occult colorectal cancer in patients with *S. bovis*/*S. gallolyticus* IE.

13. To do and not to do messages from the guidelines

Recommendations	Class[a]	Level[b]
1. Prophylaxis/prevention		
Antibiotic prophylaxis should be considered for patients at highest risk for IE: a. Patients with any prosthetic valve, including transcatheter valve, or those in whom any prosthetic material was used for cardiac valve repair b. Patients with a previous episode of IE c. Patients with congenital heart disease (i.e. any type of cyanotic congenital heart disease or any type of congenital heart disease repaired with a prosthetic material)	IIa	C
Antibiotic prophylaxis is not recommended in other forms of valvular or congenital heart disease	III	C
Dental procedures		
Antibiotic prophylaxis should only be considered for dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa	IIa	C
Antibiotic prophylaxis is not recommended for local anaesthetic injections in non-infected tissues, treatment of superficial caries, removal of sutures, dental X-rays, placement or adjustment of removable prosthodontic or orthodontic appliances or braces, or following the shedding of deciduous teeth or trauma to the lips and oral mucosa	III	C
Other procedures		
Antibiotic prophylaxis is not recommended for respiratory tract procedures, including bronchoscopy or laryngoscopy, transnasal or endotracheal intubation, gastroscopy, colonoscopy, cystoscopy, vaginal or caesarean delivery, TOE or skin and soft tissue procedures	III	C
2. Recommendations for referring patients to the Reference Centre		
Patients with complicated IE should be evaluated and managed at an early stage in a reference centre with immediate surgical facilities and the presence of a multidisciplinary Endocarditis Team, including an ID specialist, a microbiologist, a cardiologist, imaging specialists, a cardiac surgeon and, if needed, a specialist in CHD	IIa	B
For patients with non-complicated IE managed in a non-reference centre, there should be early and regular communication with the reference centre and, when needed, visits to the reference centre, should be made	IIa	B
3. Diagnosis		
TTE is recommended as the first-line imaging modality in suspected IE	I	B
TOE is recommended in all patients with clinical suspicion of IE and a negative or non-diagnostic TTE	I	B

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Recommendations	Class[a]	Level[b]
TOE is recommended in patients with clinical suspicion of IE when a prosthetic heart valve or an intracardiac device is present	I	B
Repeat TTE and/or TOE within 5–7 days is recommended in case of initially negative examination when clinical suspicion of IE remains high	I	C
Repeat TTE and/or TOE are recommended as soon as a new complication of IE is suspected (new murmur, embolism, persisting fever, HF, abscess, atrioventricular block)	I	B
Intra-operative echocardiography is recommended in all cases of IE requiring surgery	I	B
4. Treatment		
Aortic or mitral NVE or PVE with severe regurgitation or obstruction causing symptoms of HF or echocardiographic signs of poor haemodynamic tolerance must by treated by urgent surgery	I	B
Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation) must by treated by urgent surgery	I	B
Infection caused by fungi or multiresistant organisms must by treated by urgent surgery	I	C
Aortic or mitral NVE or PVE with persistent vegetations >10 mm after ≥1 embolic episodes despite appropriate antibiotic therapy must by treated by urgent surgery	I	B
5. Neurological complications		
After a silent embolism or transient ischaemic attack, cardiac surgery, if indicated, is recommended without delay	I	B
Neurosurgery or endovascular therapy are indicated for very large, enlarging or ruptured intracranial infectious aneurysms	I	C
Following intracranial haemorrhage, surgery should generally be postponed for ≥1 month	IIa	B
6. Cardiac device-related infective endocarditis		
Prolonged (i.e. before and after extraction) antibiotic therapy and complete hardware (device and leads) removal are recommended in definite CDRIE, as well as in presumably isolated pocket infection	I	C
Percutaneous extraction is recommended in most patients with CDRIE, even those with vegetations >10 mm	I	B
After device extraction, reassessment of the need for reimplantation is recommended	I	C
Temporary pacing is not routinely recommended	III	C
Routine antibiotic prophylaxis is recommended before device implantation	I	B
7. Recommendations for the use of antithrombotic therapy		
Interruption of antiplatelet therapy is recommended in the presence of major bleeding	I	B
In intracranial haemorrhage, interruption of all anticoagulation is recommended	I	C
Thrombolytic therapy is not recommended in patients with IE	III	C

14. Appendix

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