ESC European Society of Cardiology

European Heart Journal (2023) **00**, 1–95
https://doi.org/10.1093/eurheartj/ehad193

ESC GUIDELINES

2023 ESC Guidelines for the management of endocarditis

Developed by the task force on the management of endocarditis of the European Society of Cardiology (ESC)

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

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All experts involved in the development of these guidelines have submitted declarations of interest. These have been compiled in a report and simultaneously published in a supplementary document to the guidelines. The report is also available on the ESC website www.escardio.org/Guidelines

See the *European Heart Journal* online for supplementary documents that include background information and evidence tables.

Keywords Guidelines • Antibiotics • Cardiac imaging • Cardiac implantable electronic device • Cardiac surgery • Complications • Computed tomography • Congenital heart disease • Diagnosis • Echocardiography • Endocarditis • Infection • Nuclear imaging • Positron emission tomography • Prevention • Prognosis • Prosthetic heart valve • Valve disease

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Abbreviations and acronyms

[18F]FDG	^{18}F-fluorodeoxyglucose
99mTc-HMPAO	^{99m}Technetium-hexamethylpropyleneamine oxime
AIDS	Acquired immune deficiency syndrome
AEPEI	Association for the Study and Prevention of Infective Endocarditis Study
ANCLA	Anaemia, NYHA class IV, critical state, large intracardiac destruction, surgery of thoracic aorta
APLs	Antiphospholipid syndrome
AUC	Area under the curve
AVB	Atrioventricular block
AVN	Atrioventricular node
BCNIE	Blood culture-negative infective endocarditis
BMI	Body mass index
CAD	Coronary artery disease
CHD	Congenital heart disease
CI	Confidence interval
CIED	Cardiovascular implanted electronic device
CNS	Central nervous system
CoNS	Coagulase-negative staphylococci
CPB	Cardio-pulmonary bypass
CRT	Cardiac resynchronization therapy
CT	Computed tomography
CTA	Computed tomography angiography
DIC	Disseminated intravascular coagulation
DNA	Deoxyribonucleic acid
DSA	Digital subtraction angiography
ECG	Electrocardiogram
EHRA	European Heart Rhythm Association
ESC	European Society of Cardiology
EUCAST	European Committee on Antimicrobial Susceptibility Testing
EURO-ENDO	European Infective Endocarditis Registry
HACEK	*Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, and *Kingella*
HF	Heart failure
HIV	Human immunodeficiency virus
HLAR	High-level aminoglycoside resistance
i.m.	Intramuscular
i.v.	Intravenous
ICD	Implantable cardioverter defibrillator
ICE-PCS	International Collaboration on Endocarditis-Prospective Cohort Study
ICU	Intensive care unit
IE	Infective endocarditis
Ig	Immunoglobulin
MALDI-TOF MS	Matrix-assisted laser desorption ionization time-of-flight mass spectrometry
MIC	Minimum inhibitory concentration
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
NBTE	Non-bacterial thrombotic endocarditis
NIHSS	National Institutes of Health Stroke Scale Score
NVE	Native valve endocarditis
NYHA	New York Heart Association
OPAT	Outpatient parenteral antibiotic therapy
PADIT	Previous procedure on same pocket; Age; Depressed renal function; Immunocompromised; Type of procedure
PALSUSE	Prosthetic valve, age ≥70, large intracardiac destruction, *Staphylococcus* spp., urgent surgery, sex (female), EuroSCORE ≥10
PBP	Penicillin-binding protein
PCR	Polymerase chain reaction
PET/CT	Positron emission tomography/computed tomography
POET	Partial Oral Treatment of Endocarditis (trial)
PPV	Positive predictive value
PVE	Prosthetic valve endocarditis
PWID	People who inject drugs
RCT	Randomized clinical trial
RHD	Rheumatic heart disease
rRNA	Ribosomal ribonucleic acid
SAPS	Simplified Acute Physiology Score
SLE	Systemic lupus erythematous
SOT	Solid organ transplantation
SPECT/CT	Single photon emission tomography/computed tomography
STS	Society of Thoracic Surgeons
TAVI	Transcatheter aortic valve implantation
TOE	Transoesophageal echocardiography
TPVI	Transcatheter pulmonary valve implantation
TTE	Transthoracic echocardiography
WBC	White blood cell
WRAP-IT	Worldwide Randomized Antibiotic Envelope Infection Prevention Trial

1. Preamble

Guidelines evaluate and summarize available evidence, with the aim of assisting health professionals in proposing the best diagnostic or therapeutic approach for an individual patient with a given condition. Guidelines are intended for use by health professionals and the European Society of Cardiology (ESC) makes its Guidelines freely available.

ESC Guidelines do not override 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 or the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable in each country to drugs and devices at the time of prescription, and, where appropriate, to respect the ethical rules of their profession.

ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated. ESC Policies and Procedures for formulating and issuing ESC Guidelines can be found on the ESC website (https://www.escardio.org/Guidelines).

The Members of this Task Force were selected by the ESC to represent professionals involved with the medical care of patients with this

Table 1 **Classes of recommendations**

Classes of recommendations	Definition	Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or 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

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.

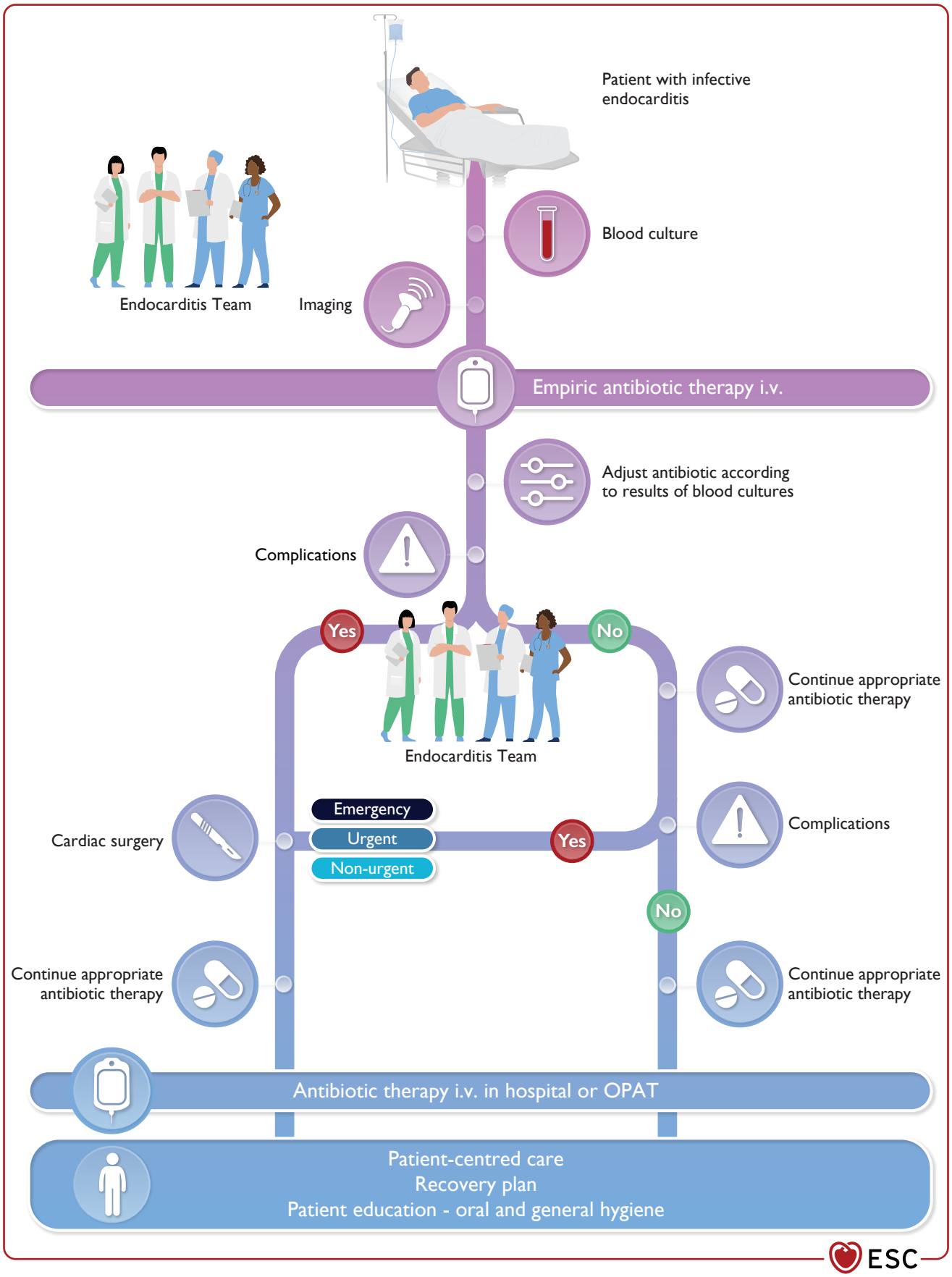

Figure 1 Management of patients with infective endocarditis. i.v., intravenous; OPAT, outpatient parenteral antibiotic therapy.

pathology. The selection procedure aimed to include members from across the whole of the ESC region and from relevant ESC Subspecialty Communities. Consideration was given to diversity and inclusion, notably with respect to gender and country of origin. The Task Force performed a critical evaluation of diagnostic and therapeutic approaches, including assessment of the risk-benefit ratio. The strength of every recommendation and the level of evidence supporting them were weighed and scored according to predefined scales as outlined below. The Task Force followed ESC voting procedures, and all approved recommendations were subject to a vote and achieved at least 75% agreement among voting members.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. Their declarations of interest were reviewed according to the ESC declaration of interest rules and can be found on the ESC website (http://www.escardio.org/Guidelines) and have been compiled in a report published in a supplementary document with the guidelines. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.

The ESC Clinical Practice Guidelines (CPG) Committee supervises and co-ordinates the preparation of new guidelines and is responsible for the approval process. ESC Guidelines undergo extensive review by the CPG Committee and external experts, including members from across the whole of the ESC region and from relevant ESC Subspecialty Communities and National Cardiac Societies. After appropriate revisions, the guidelines are signed off by all the experts involved in the Task Force. The finalized document is signed off by the CPG Committee 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 writing. Tables of evidence summarizing the findings of studies informing development of the guidelines are included. The ESC warns readers that the technical language may be misinterpreted and declines any responsibility in this respect.

Off-label use of medication may be presented in this guideline if a sufficient level of evidence shows that it can be considered medically appropriate for a given condition. However, the final decisions concerning an individual patient must be made by the responsible health professional giving special consideration to:

- The specific situation of the patient. Unless otherwise provided for by national regulations, off-label use of medication should be limited to situations where it is in the patient's interest with regard to the quality, safety, and efficacy of care, and only after the patient has been informed and has provided consent.
- Country-specific health regulations, indications by governmental drug regulatory agencies, and the ethical rules to which health professionals are subject, where applicable.

2. Introduction

Infective endocarditis (IE) is a major public health challenge.[1] In 2019, the estimated incidence of IE was 13.8 cases per 100 000 subjects per year, and IE accounted for 66 300 deaths worldwide.[2] Due to the associated high morbidity and mortality (1723.59 disability-adjusted life years and 0.87 death cases per 100 000 population, respectively), identification of the best preventive strategies has been the focus of research.[2,3] Since the publication of the *2015 ESC Guidelines for the management of infective endocarditis*,[4] important new data have been published mandating an update of recommendations. First, the population at risk of IE has increased and new data on IE in different clinical scenarios have arisen.[5–11] Furthermore, the emerging and increasing antibiotic resistance among oral streptococci is of concern. The rate of resistance to azythromycin and clarithromycin is higher than that to penicillin.[12] Whether changes in national guidelines on the use of antibiotic prophylaxis have resulted in an increase in the incidence of IE remains unclear.[13–18] It is likely that the increased use of diagnostic tools to diagnose IE is an important contributor to the increase in the incidence of IE. The use of echocardiography has probably increased in patients with positive blood cultures for *Enteroccus faecalis*, *Staphylococcus aureus*, or streptococci due to the associated increased risk of IE.[19] In addition, computed tomography (CT) and nuclear imaging techniques have increased the number of definite IE cases particularly among patients with prosthetic valves and implantable cardiac devices.[20–22]

Data on the contemporary characterization of patients with IE have been taken into consideration to update the recommendations on the diagnosis and management of patients with IE.[5,19,23–41] Furthermore, the recommendations on antibiotic therapy have been updated based on the susceptibility of various microorganisms defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints.[42] Recommendations on outpatient parenteral antibiotic therapy (OPAT) or oral antibiotic treatment have been included based on the results of the Partial Oral Treatment of Endocarditis (POET) randomized trial and other trials.[43–46]

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 (see Supplementary data, evidence tables online). An evidence-based scoring system was used, based on a classification of the strength of recommendations and the levels of evidence.

2.1. What is new

Table 3 New recommendations

Recommendation	Class	Level
Section 3. Recommendation Table 1 — Recommendations for antibiotic prophylaxis in patients with cardiovascular diseases undergoing oro-dental procedures at increased risk of infective endocarditis		
General prevention measures are recommended in individuals at high and intermediate risk of IE.	I	C
Antibiotic prophylaxis is recommended in patients with ventricular assist devices.	I	C
Antibiotic prophylaxis may be considered in recipients of heart transplant.	IIb	C
Section 3. Recommendation Table 2 — Recommendations for infective endocarditis prevention in high-risk patients		
Systemic antibiotic prophylaxis may be considered for high-risk patients undergoing an invasive diagnostic or therapeutic procedure of the respiratory, gastrointestinal, genitourinary tract, skin, or musculoskeletal systems.	IIb	C
Section 3. Recommendation Table 3 — Recommendations for infective endocarditis prevention in cardiac procedures		
Optimal pre-procedural aseptic measures of the site of implantation is recommended to prevent CIED infections.	I	B

Continued

Surgical standard aseptic measures are recommended during the insertion and manipulation of catheters in the catheterization laboratory environment.	I	C
Antibiotic prophylaxis covering for common skin flora including *Enterococcus* spp. and *S. aureus* should be considered before TAVI and other transcatheter valvular procedures.	IIa	C
Section 5. Recommendation Table 5 — Recommendations for the role of echocardiography in infective endocarditis		
TOE is recommended when the patient is stable before switching from intravenous to oral antibiotic therapy.	I	B
Section 5. Recommendation Table 6 — Recommendations for the role of computed tomography, nuclear imaging, and magnetic resonance in infective endocarditis		
Cardiac CTA is recommended in patients with possible NVE to detect valvular lesions and confirm the diagnosis of IE.	I	B
[18F]FDG-PET/CT(A) and cardiac CTA are recommended in possible PVE to detect valvular lesions and confirm the diagnosis of IE.	I	B
[18F]FDG-PET/CT(A) may be considered in possible CIED-related IE to confirm the diagnosis of IE.	IIa	B
Cardiac CTA is recommended in NVE and PVE to diagnose paravalvular or periprosthetic complications if echocardiography is inconclusive.	I	B
Brain and whole-body imaging (CT, [18F]FDG-PET/CT, and/or MRI) are recommended in symptomatic patients with NVE and PVE to detect peripheral lesions or add minor diagnostic criteria.	I	B
WBC SPECT/CT should be considered in patients with high clinical suspicion of PVE when echocardiography is negative or inconclusive and when PET/CT is unavailable.	IIa	C
Brain and whole-body imaging (CT, [18F]FDG-PET/CT, and MRI) in NVE and PVE may be considered for screening of peripheral lesions in asymptomatic patients.	IIb	B
Section 7. Recommendation Table 11 — Recommendations for outpatient antibiotic treatment of infective endocarditis		
Outpatient parenteral antibiotic treatment should be considered in patients with left-sided IE caused by *Streptococcus* spp., *E. faecalis*, *S. aureus*, or CoNS who were receiving appropriate i.v. antibiotic treatment for at least 10 days (or at least 7 days after cardiac surgery), are clinically stable, and who do not show signs of abscess formation or valve abnormalities requiring surgery on TOE.	IIa	A
Outpatient parenteral antibiotic treatment is not recommended in patients with IE caused by highly difficult-to-treat microorganisms, liver cirrhosis (Child–Pugh B or C), severe cerebral nervous system emboli, untreated large extracardiac abscesses, heart valve complications, or other severe conditions requiring surgery, severe post-surgical complications, and in PWID-related IE.	III	C

Continued

Section 9. Recommendation Table 13 — Recommendations for the treatment of neurological complications of infective endocarditis		
In embolic stroke, mechanical thrombectomy may be considered if the expertise is available in a timely manner.	IIb	C
Thrombolytic therapy is not recommended in embolic stroke due to IE.	III	C
Section 9. Recommendation Table 14 — Recommendations for pacemaker implantation in patients with complete atrioventricular block and infective endocarditis		
Immediate epicardial pacemaker implantation should be considered in patients undergoing surgery for valvular IE and complete AVB if one of the following predictors of persistent AVB is present: pre-operative conduction abnormality, *S. aureus* infection, aortic root abscess, tricuspid valve involvement, or previous valvular surgery.	IIa	C
Section 9. Recommendation Table 15 — Recommendations for patients with musculoskeletal manifestations of infective endocarditis		
MRI or PET/CT is recommended in patients with suspected spondylodiscitis and vertebral osteomyelitis complicating IE.	I	C
TTE/TOE is recommended to rule out IE in patients with spondylodiscitis and/or septic arthritis with positive blood cultures for typical IE microorganisms.	I	C
More than 6-week antibiotic therapy should be considered in patients with osteoarticular IE-related lesions caused by difficult-to-treat microorganisms, such as *S. aureus* or *Candida* spp., and/or complicated with severe vertebral destruction or abscesses.	IIa	C
Section 10. Recommendation Table 16 — Recommendations for pre-operative coronary anatomy assessment in patients requiring surgery for infective endocarditis		
In haemodynamically stable patients with aortic valve vegetations who require cardiac surgery and are high risk of CAD, a high-resolution multislice coronary CTA is recommended.	I	B
Invasive coronary angiography is recommended in patients requiring heart surgery who are high risk of CAD, in the absence of aortic valve vegetations.	I	C
In emergency situations, valvular surgery without pre-operative coronary anatomy assessment regardless of CAD risk should be considered.	IIa	C
Invasive coronary angiography may be considered despite the presence of aortic valve vegetations in selected patients with known CAD or at high risk of significant obstructive CAD.	IIb	C
Section 10. Recommendation Table 17 — Indications and timing of cardiac surgery after neurological complications in active infective endocarditis		
In patients with intracranial haemorrhage and unstable clinical status due to HF, uncontrolled infection, or persistent high embolic risk, urgent or emergency surgery should be considered weighing the likelihood of a meaningful neurological outcome.	IIa	C

Continued

Section 11. Recommendation Table 18 — Recommendations for post-discharge follow-up		
Patient education on the risk of recurrence and preventive measures, with emphasis on dental health, and based on the individual risk profile, is recommended during follow-up.	I	C
Addiction treatment for patients following PWID-related IE is recommended.	I	C
Cardiac rehabilitation including physical exercise training should be considered in clinically stable patients based on an individual assessment.	IIa	C
Psychosocial support may be considered to be integrated in follow-up care, including screening for anxiety and depression, and referral to relevant psychological treatment.	IIb	C
Section 12. Recommendation Table 19 — Recommendations for prosthetic valve endocarditis		
Surgery is recommended for early PVE (within 6 months of valve surgery) with new valve replacement and complete debridement.	I	C
Section 12. Recommendation Table 20 — Recommendations for cardiovascular implanted electronic device-related infective endocarditis		
Complete system extraction without delay is recommended in patients with definite CIED-related IE under initial empirical antibiotic therapy.	I	B
Extension of antibiotic treatment of CIED-related endocarditis to (4–)6 weeks following device extraction should be considered in the presence of septic emboli or prosthetic valves.	IIa	C
Use of an antibiotic envelope may be considered in select high-risk patients undergoing CIED reimplantation to reduce risk of infection.	IIb	B
In non-*S. aureus* CIED-related endocarditis without valve involvement or lead vegetations, and if follow-up blood cultures are negative without septic emboli, 2 weeks of antibiotic treatment may be considered following device extraction.	IIb	C
Removal of CIED after a single positive blood culture, with no other clinical evidence of infection, is not recommended.	III	C
Section 12. Recommendation Table 21 — Recommendations for the surgical treatment of right-sided infective endocarditis		
Tricuspid valve repair should be considered instead of valve replacement, when possible.	IIa	B
Surgery should be considered in patients with right-sided IE who are receiving appropriate antibiotic therapy and present persistent bacteraemia/sepsis after at least 1 week of appropriate antibiotic therapy.	IIa	C
Prophylactic placement of an epicardial pacing lead should be considered at the time of tricuspid valve surgical procedures.	IIa	C
Debulking of right intra-atrial septic masses by aspiration may be considered in select patients who are high risk of surgery.	IIb	C

[18F]FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; AVB, atrioventricular block; CAD, coronary artery disease; CIED, cardiovascular implanted electronic device; CoNS, coagulase-negative staphylococci; CT, computed tomography; CTA, computed tomography angiography; HF, heart failure; IE, infective endocarditis; i.v., intravenous; MRI, magnetic resonance imaging; NVE, native valve endocarditis; PET, positron emission tomography; PVE, prosthetic valve endocarditis; PWID, people who inject drugs; TAVI, transcatheter aortic valve implantation; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography; WBC SPECT/CT, white blood cell single photon emission tomography/computed tomography.

Continued

Table 4 Revised recommendations

Recommendations in 2015 version	Class	Level	Recommendations in 2023 version	Class	Level
Section 3. Recommendation Table 1 — Recommendations for antibiotic prophylaxis in patients with cardiovascular diseases undergoing oro-dental procedures at increased risk of infective endocarditis					
Antibiotic prophylaxis should be considered for patients at highest risk of 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	IIa	C	Antibiotic prophylaxis is recommended in patients with previous IE.	I	B
			Antibiotic prophylaxis is recommended in patients with surgically implanted prosthetic valves and with any material used for surgical cardiac valve repair.	I	C
			Antibiotic prophylaxis is recommended in patients with transcatheter implanted aortic and pulmonary valvular prostheses.	I	C
			Antibiotic prophylaxis should be considered in patients with transcatheter mitral and tricuspid valve repair.	IIa	C

Continued

percutaneous techniques, up to 6 months after the procedure or lifelong if residual shunt.			Antibiotic prophylaxis is recommended in patients with untreated cyanotic CHD, and patients treated with surgery or transcatheter procedures with post-operative palliative shunts, conduits, or other prostheses. After surgical repair, in the absence of residual defects or valve prostheses, antibiotic prophylaxis is recommended only for the first 6 months after the procedure.	I	C
Section 4. Recommendation Table 4 — Recommendations for the Endocarditis Team					
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 infectious disease specialist, a microbiologist, a cardiologist, imaging specialists, a cardiac surgeon and, if needed, a specialist in CHD.	IIa	B	Diagnosis and management of patients with complicated IE are recommended to be performed at an early stage in a Heart Valve Centre, with immediate surgical facilities and an 'Endocarditis Team' to improve the outcomes.	I	B
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	For patients with uncomplicated IE managed in a Referring Centre, early and regular communication between the local and the Heart Valve Centre Endocarditis Teams is recommended to improve the outcomes of the patients.	I	B
Section 5. Recommendation Table 5 — Recommendations for the role of echocardiography in infective endocarditis					
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 finding.	IIa	C	TOE is recommended 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.	I	C
Section 8. Recommendation Table 12 — Recommendations for the main indications of surgery in infective endocarditis (native valve endocarditis and prosthetic valve endocarditis)					
Aortic or mitral NVE with vegetations >10 mm, associated with severe valve stenosis or regurgitation, and low operative risk (urgent surgery should be considered).	IIa	B	Urgent surgery is recommended in IE with vegetation ≥10 mm and other indications for surgery.	I	C
Aortic or mitral NVE or PVE with isolated large vegetations (>15 mm) and no other indication for surgery (urgent surgery may be considered).	IIb	C	Urgent surgery may be considered in aortic or mitral IE with vegetation ≥10 mm and without severe valve dysfunction or without clinical evidence of embolism and low surgical risk.	IIb	B
Section 9. Recommendation Table 13 — Recommendations for the treatment of neurological complications of infective endocarditis					
Intracranial infectious aneurysms should be looked for in patients with IE and neurological symptoms. CT or MRA 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	Brain CT or MRA is recommended in patients with IE and suspected infective cerebral aneurysms.	I	B
			If non-invasive techniques are negative and the suspicion of infective aneurysm remains, invasive angiography should be considered.	IIa	B
Section 12. Recommendation Table 20 — Recommendations for cardiovascular implanted electronic device-related infective endocarditis					
Routine antibiotic prophylaxis is recommended before device implantation.	I	B	Antibiotic prophylaxis covering *S. aureus* is recommended for CIED implantation.	I	A
TOE is recommended in patients with suspected cardiac device-related infective endocarditis with positive or negative blood cultures, independent of the results of TTE, to evaluate lead-related endocarditis and heart valve infection.	I	C	TTE and TOE are both recommended in case of suspected CIED-related IE to identify vegetations.	I	B
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	Complete CIED extraction should be considered in case of valvular IE, even without definite lead involvement, taking into account the identified pathogen and requirement for valve surgery.	IIa	C

Continued

Complete hardware removal should be considered on the basis of occult infection without another apparent source of infection.	IIa	C	In cases of possible CIED-related IE or occult Gram-positive bacteraemia or fungaemia, complete system removal should be considered in case bacteraemia/fungaemia persists after a course of antimicrobial therapy.	IIa	C
			In cases of possible CIED-related IE with occult Gram-negative bacteraemia, complete system removal may be considered in case of persistent/relapsing bacteraemia after a course of antimicrobial therapy.	IIb	C
When indicated, definite reimplantation should be postponed if possible, to allow a few days or weeks of antibiotic therapy.	IIa	C	If CIED reimplantation is indicated after extraction for CIED-related IE, it is recommended to be performed at a site distant from the previous generator, as late as possible, once signs and symptoms of infection have abated and until blood cultures are negative for at least 72 h in the absence of vegetations, and negative for at least 2 weeks if vegetations were visualized.	I	C
Section 12. Recommendation Table 21 — Recommendations for the surgical treatment of right-sided infective endocarditis					
Surgical treatment should be considered in the following scenarios:			Surgery is recommended in patients with right-sided IE who are receiving appropriate antibiotic therapy for 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 HF; or • Right HF secondary to severe tricuspid regurgitation with poor response to diuretic therapy.	IIa	C	Right ventricular dysfunction secondary to acute severe tricuspid regurgitation non-responsive to diuretics.	I	B
			Persistent vegetation with respiratory insufficiency requiring ventilatory support after recurrent pulmonary emboli.	I	B
			Large residual tricuspid vegetations (>20 mm) after recurrent septic pulmonary emboli.	I	C
			Patients with simultaneous involvement of left-heart structures.	I	C
Section 12. Recommendation Table 22 — Recommendations for the use of antithrombotic therapy in infective endocarditis					
Interruption of antiplatelet therapy is recommended in the presence of major bleeding.	I	B	Interruption of antiplatelet or anticoagulant therapy is recommended in the presence of major bleeding (including intracranial haemorrhage).	I	C

CHD, congenital heart disease; CIED, cardiovascular implanted electronic device; CT, computed tomography; HF, heart failure; IE, infective endocarditis; MRA, magnetic resonance angiography; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

3. Prevention

3.1. Rationale

The development of IE usually requires several conditions, including the presence of predisposing risk factors (i.e. a surface/structure that could be colonized by bacteria), pathogens entering the bloodstream, and the competence of the host's immune response. The role of predisposing risk factors has been recently underscored by Thornhill *et al.*[47] Predisposing risk factors conveying a moderate and high risk of IE had an incidence of 280 and 497 cases per 100 000 subjects per year, respectively.[47]

The portals of entry of bacteria/fungi are variable and include: (i) infections of the skin, oral cavity, gastrointestinal, or genitourinary system; (ii) direct inoculation in people who inject drugs (PWID), or by any unsafe or unprotected vascular puncture; (iii) healthcare exposure (including a variety of invasive diagnostic or therapeutic procedures, such as transcatheter or surgical techniques).[6,11,48–50]

The oral cavity is colonized by relevant commensal flora, including oral group streptococci, and represents an important entry port. Oral surgery procedures (including all extractions, periodontal surgery, implant surgery, and oral biopsies) and dental procedures that involve manipulation of the gingival or periapical region of the teeth are considered at high risk of causing bacteraemia.[11,48,49,51]

Successful antibiotic prophylaxis assumes that reducing the bacteraemia associated with medical procedures will lead to a reduced risk of IE. This concept was supported by a few animal models and observational studies that led to the recommendation for antibiotic prophylaxis in a large number of patients with predisposing cardiac conditions undergoing a wide range of procedures.[4,14,52–60]

However, systematic use of antibiotic prophylaxis has been questioned based on several considerations, the most important being the lack of randomized clinical trials (RCTs) demonstrating the efficacy of antibiotic prophylaxis prior to medical procedures in preventing IE. Such trials would entail enrolment of a very large number of individuals and prolonged follow-up, making the feasibility of such studies improbable. Furthermore, since the standard of care for high-risk individuals is antibiotic prophylaxis (to date, mostly before invasive oro-dental procedures), there may not be sufficient equipoise to perform such RCTs. Finally, the costs of performing such trials have been considered unacceptable.[61] To overcome these limitations, population-based studies

have evaluated the efficacy of antibiotic prophylaxis using bacteraemia as a surrogate of IE.[16–18,52,62] However, the relationship between bacteraemia and IE is not straightforward. Bacteraemia may be caused by daily activities such as tooth brushing, flossing, and chewing, and although these constitute low-level bacteraemia, they occur repetitively and may therefore outweigh the risk of bacteraemia associated with dental procedures.[48,49] A meta-analysis of 36 studies, including 21 trials that investigated the effect of antibiotic prophylaxis on the incidence of bacteraemia following dental procedures, demonstrated that antibiotic prophylaxis is effective in reducing the incidence of bacteraemia, but did not lead to a statistically significant protective effect against IE in case-control studies.[52] Additionally, the potential risk of anaphylaxis,[63] or other adverse side effects in a small minority of patients, and the fact that a widespread use of antibiotics may be associated with antibiotic resistance, are areas of concern.[57,58,64–67] While some studies did not demonstrate significant increases in IE-related hospitalizations and death rates after scaling down antibiotic prophylaxis indications,[68–77] others showed an increase in the incidence of IE among individuals at moderate and high risk of IE.[13,26,59,78–81] A meta-analysis including 16 studies reporting over 1.3 million cases of IE has shown that restricting antibiotic prophylaxis to only high-risk individuals has not resulted in an increase in the incidence of streptococcal IE in a North American population (despite the fact that it was unable to draw that conclusion for other populations).[18] In contrast, a systematic review including multiple nationwide population-based studies in Europe has shown a 4% per year rise in the incidence of IE.[82] These contrasting results may be explained by differences in the methodology of the studies (retrospective, population- or health-system-based studies that relied on claims data or epidemiological observations to estimate the incidence of IE), greater disease diagnosis with the use of newer imaging technologies, lack of microbiological data, and the lack of specific International Classification of Diseases codes for oral streptococci.[83] Recently, it has been shown that antibiotic prophylaxis in high-risk individuals was associated with a significant reduction of IE after invasive dental procedures (particularly extractions and oral surgical procedures).[11,51] After careful consideration of all the new studies published after 2015, the present Task Force decided to revise and update the risk categories for IE, strengthening the recommendation of antibiotic prophylaxis, clarifying the definition of the population at risk, and considering the advances in transcatheter valve interventions.

3.2. Populations at risk of infective endocarditis

The groups of individuals at high risk of IE in whom antibiotic prophylaxis is recommended or should be considered include the following:

(i) Patients with previous IE: the highest risk of IE is observed in patients with previous history of IE who have an ominous prognosis during IE-related hospitalization. Patients with recurrent IE more frequently have prosthetic valves or prosthetic material, are more commonly PWID, or have staphylococcal IE.[47,84–86]

(ii) Patients with surgically implanted prosthetic valves, with transcatheter implanted prosthetic valves, and with any material used for cardiac valve repair: the increased risk of IE in these patients, combined with the ominous outcomes as compared with patients with native IE (NVE), make antibiotic prophylaxis advisable in this patient group. Patients with prosthetic valve endocarditis (PVE) have an in-hospital mortality rate that is twice as high with more complications (e.g. heart failure [HF], conduction disturbances) as compared with patients with NVE, regardless of the pathogen.[87,88] Furthermore, mitral and aortic bioprostheses may be associated with increased risk of IE as compared with mechanical prostheses,[89,90] and bioprostheses are being implanted in an ever-increasing proportion of patients requiring valve replacement therapy. The indication for prophylaxis also expands to transcatheter aortic and pulmonic prosthetic valves, since IE is also associated with a high risk of morbidity and mortality in these patients.[91–94] In terms of transcatheter mitral and tricuspid valve interventions, the data on the risk of IE are limited.[95] Patients with septal defect closure devices, left atrial appendage closure devices, vascular grafts, vena cava filters, and central venous system ventriculo-atrial shunts are considered within this risk category in the first 6 months after implantation.[96]

(iii) Patients with congenital heart disease (CHD) (not including isolated congenital valve abnormalities) are at increased risk of IE.[8,47,97–99] The cumulative incidence over time is influenced strongly by the improved long-term survival of children with CHD into adulthood.[98] Indeed, there are now more adults living with CHD than children with CHD.[100] The overall incidence rate of IE among adult patients with CHD is 27–44 times that reported for contemporary adults of the general population (1.33 cases per 1000 persons per year)[8] while in children with CHD the incidence of IE is 0.41 cases per 1000 persons per year.[101] CHD groups at increased risk include those with untreated cyanotic CHD, and those whose surgery includes prosthetic material, including valved conduits or systemic to pulmonary shunts.[8,47,97] The risk of post-operative IE for CHD patients undergoing transcatheter atrial or ventricular septal defect closure with devices or surgery with non-valve-related prosthetic material is also increased, but predominantly for the first 6 months after surgery.[8]

(iv) Patients with ventricular assist devices as destination therapy are also considered at high risk because of associated morbidity and mortality, and prophylaxis is also recommended in such patients.[102]

Patients at intermediate risk of IE include those with: (i) rheumatic heart disease (RHD); (ii) non-rheumatic degenerative valve disease; (iii) congenital valve abnormalities including bicuspid aortic valve disease; (iv) cardiovascular implanted electronic devices (CIEDs); and (v) hypertrophic cardiomyopathy.[47,103,104] Some epidemiological data suggest that certain conditions stratified as intermediate risk are associated

Table 5 General prevention measures to be followed in patients at high and intermediate risk of infective endocarditis

Patients should be encouraged to maintain twice daily tooth cleaning and to seek professional dental cleaning and follow-up at least twice yearly for high-risk patients and yearly for others.
Strict cutaneous hygiene, including optimized treatment of chronic skin conditions.
Disinfection of wounds.
Curative antibiotics for any focus of bacterial infection.
No self-medication with antibiotics.
Strict infection control measures for any at-risk procedure.
Discouragement of piercing and tattooing.
Limitation of infusion catheters and invasive procedures. when possible. Strict adherence to care bundles for central and peripheral cannulae should be performed.

with a higher risk of IE compared with the background population,[47,90,103] but further studies are required. In patients at intermediate risk of IE, antibiotic prophylaxis is not routinely recommended and may be considered on an individual basis. However, prevention measures (*Table 5*) are strongly encouraged in these patients.[7]

Most of the IE in recipients of solid organ transplant is nosocomial. A recent systematic review of patient-level data including 57 heart transplant patients has shown that IE occurs frequently during the first year post-transplant, and the most common pathogen is *S. aureus* followed by *Aspergillus fumigatus*.[105] Oral streptococci are a very infrequent cause of IE, making the value of antibiotic prophylaxis after invasive oro-dental procedures questionable. However, IE in this group of patients is associated with very high mortality, particularly in patients with fungal IE. In contrast, other series that include a larger proportion of non-cardiac solid organ transplant patients have shown that the pathogens are more frequently from the *Staphylococcus* spp. and the mortality seems to be similar to that of patients without solid organ transplant.[106,107]

Recommendation Table 1 — Recommendations for antibiotic prophylaxis in patients with cardiovascular diseases undergoing oro-dental procedures at increased risk for infective endocarditis

Recommendations	Class[a]	Level[b]
General prevention measures are recommended in individuals at high and intermediate risk for IE.	I	C
Antibiotic prophylaxis is recommended in patients with previous IE.[47,84,86]	I	B
Antibiotic prophylaxis is recommended in patients with surgically implanted prosthetic valves and with any material used for surgical cardiac valve repair.[47,87–89]	I	C
Antibiotic prophylaxis is recommended in patients with transcatheter implanted aortic and pulmonary valvular prostheses.[91–94]	I	C
Antibiotic prophylaxis is recommended in patients with untreated cyanotic CHD, and patients treated with surgery or transcatheter procedures with post-operative palliative shunts, conduits, or other prostheses. After surgical repair, in the absence of residual defects or valve prostheses, antibiotic prophylaxis is recommended only for the first 6 months after the procedure.[8,47,97,101]	I	C
Antibiotic prophylaxis is recommended in patients with ventricular assist devices.[102]	I	C
Antibiotic prophylaxis should be considered in patients with transcatheter mitral and tricuspid valve repair.[95]	IIa	C
Antibiotic prophylaxis may be considered in recipients of heart transplant.[105–107]	IIb	C
Antibiotic prophylaxis is not recommended in other patients at low risk for IE.[11,51]	III	C

CHD, congenital heart disease; IE, infective endocarditis.
[a]Class of recommendation.
[b]Level of evidence.

3.3. Situations and procedures at risk

3.3.1. Dental procedures

Antibiotic prophylaxis is recommended in patients at high risk of IE undergoing at-risk dental procedures and is not currently recommended in other situations. At-risk dental procedures include dental extractions, oral surgery procedures (including periodontal surgery, implant surgery, and oral biopsies), and dental procedures involving manipulation of the gingival or periapical region of the teeth (including scaling and root canal procedures).[49,108] The use of dental implants raises concerns about potential risk due to foreign material at the interface between the buccal cavity and blood, but available data remain very limited.[109] So far there is no evidence to contraindicate implants in all patients at risk and the indication should be discussed on an individual basis. Implant placement procedures, and invasive dental procedures on established implants, however, should be covered by antibiotic prophylaxis in those at high risk of IE. Once dental implants are placed in high-risk patients, professional dental hygiene and follow-up should be performed at least twice yearly under antibiotic cover, when indicated.

The main target for antibiotic prophylaxis is oral streptococci. *Table 6* summarizes the main regimens of antibiotic prophylaxis recommended before dental procedures. The risk of adverse fatal/non-fatal events appear to be extremely low for amoxicillin but high for clindamycin (mainly related to *Clostridioides difficile* infections).[63,110–112] Accordingly, this Task Force does not recommend the use of clindamycin for antibiotic prophylaxis.

Table 6 Prophylactic antibiotic regime for high-risk dental procedures

Situation	Antibiotic	Single-dose 30–60 min before procedure	
		Adults	Children
No allergy to penicillin or ampicillin	Amoxicillin	2 g orally	50 mg/kg orally
	Ampicillin	2 g i.m. or i.v.	50 mg/kg i.v. or i.m.
	Cefazolin or ceftriaxone	1 g i.m. or i.v.	50 mg/kg i.v. or i.m.
Allergy to penicillin or ampicillin	Cephalexin[a,b]	2 g orally	50 mg/kg orally
	Azithromycin or clarithromycin	500 mg orally	15 mg/kg orally
	Doxycycline	100 mg orally	<45 kg, 2.2 mg/kg orally >45 kg, 100 mg orally
	Cefazolin or ceftriaxone[b]	1 g i.m. or i.v.	50 mg/kg i.v. or i.m.

i.m., intramuscular; i.v., intravenous.
[a]Or other first- or second-generation oral cephalosporin in equivalent adult or paediatric dosing.
[b]Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticarial with penicillin or ampicillin.

3.3.2. Non-dental procedures

No convincing evidence has been brought forward on the relationship between bacteraemia resulting from a non-dental procedure and risk of subsequent IE. However, observational studies reported that, compared with patients with IE not undergoing an invasive procedure,

several invasive non-dental medical procedures were associated with increased risk of IE, including cardiovascular interventions, skin procedures and wound management, transfusion, dialysis, bone marrow puncture, and endoscopic procedures.[6,11,51] For this reason, an aseptic operational environment should be ensured during all these procedures to minimize the risk of IE. As previously indicated, it is very unlikely that an RCT on antibiotic prophylaxis for IE will be performed in the foreseeable future. However, at-risk patients have longer survival due to the advent of newer medical and device-based medical therapies. In addition, the ageing general population with their accumulating number of co-morbidities has an increased risk of surgical therapy, if IE occurs. For these reasons, this Task Force no longer felt that a class III recommendation for antibiotic prophylaxis in high-risk patients undergoing non-dental medical procedures (see Recommendation Table 2) was appropriate, despite the limitations of observational data used to support this class IIb recommendation.

3.3.3. Cardiac or vascular interventions

In all patients undergoing implantation of a prosthetic valve, any type of prosthetic graft/occluder device or CIED, peri-operative antibiotic prophylaxis is recommended due to the increased risk and adverse outcome of an infection.[6] The most frequent microorganisms underlying early (1 year after surgery) surgical PVE are coagulase-negative staphylococci (CoNS) and *S. aureus*. Pre-operative screening of nasal carriage for *S. aureus* is recommended before elective cardiac surgery or transcatheter valve implantation to treat carriers using local mupirocin and chlorhexidine.[113,114] 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. For specific prophylactic measures in other cardiac and vascular interventions (i.e. CIED, transcatheter aortic valve implantation [TAVI]), please see the Supplementary data online, *Section S1.1*.

3.4. Patient education

Preventing IE also depends on preventive measures other than antibiotic prophylaxis. People at risk should be educated to maintain good dental and skin hygiene, to look out for signs of infection and, when

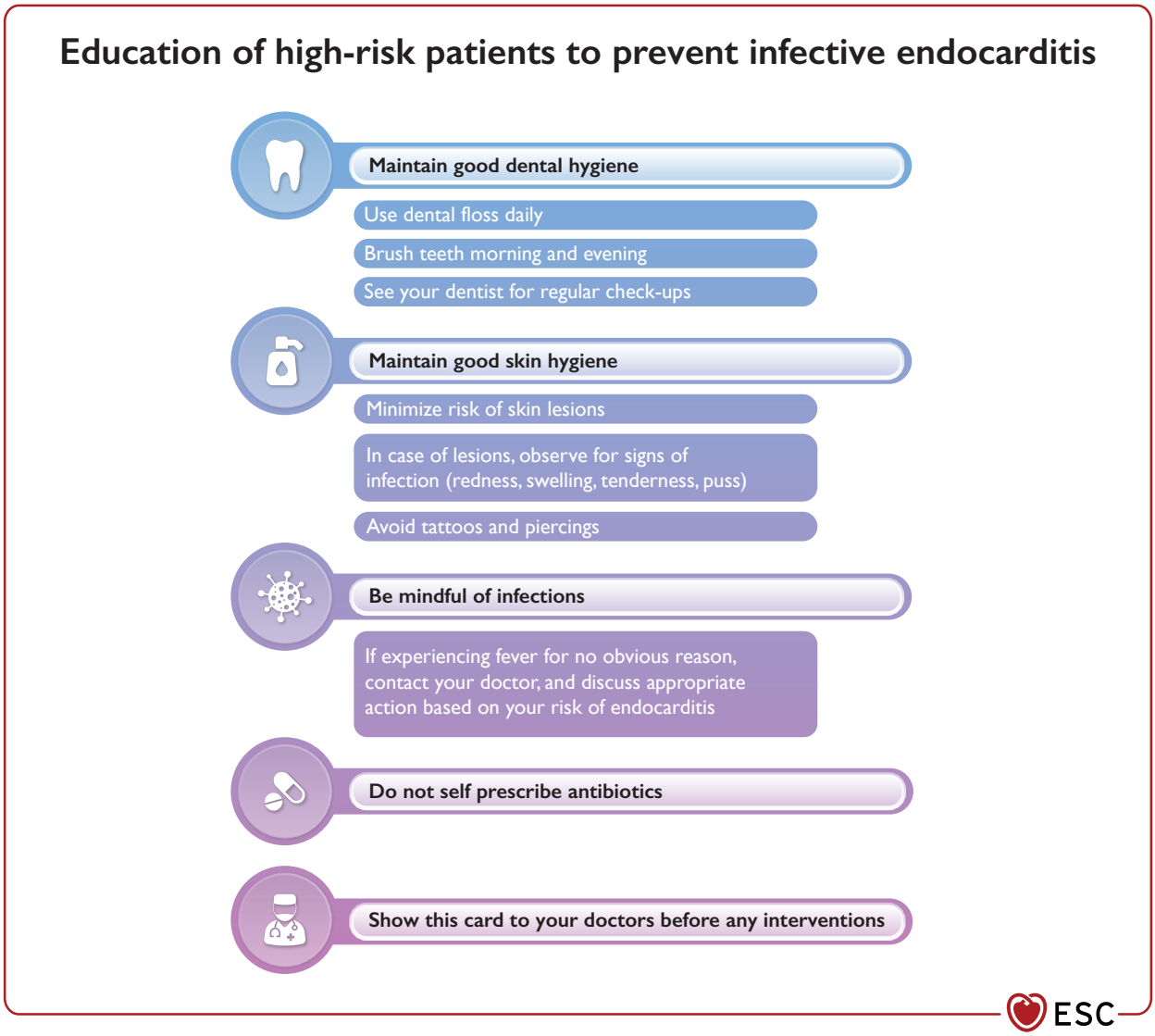

Figure 2 Education of high-risk patients to prevent infective endocarditis.

experiencing fever of unknown origin, report to their physician that they are at risk, in which case clinicians should consider screening for IE before initiating antibiotics.

Use of non-medical language, visual aids, digital tools, repetition, and teach back methods all aid the patients' comprehension and is encouraged.[115] National cardiology societies should be encouraged to develop specific IE cards for patient awareness (*Figure 2*).

Recommendation Table 2 — Recommendations for infective endocarditis prevention in high-risk patients

Recommendations	Class[a]	Level[b]
Antibiotic prophylaxis is recommended in dental extractions, oral surgery procedures, and procedures requiring manipulation of the gingival or periapical region of the teeth.[11,49,51,108]	I	B
Systemic antibiotic prophylaxis may be considered for high-risk[c] patients undergoing an invasive diagnostic or therapeutic procedure of the respiratory, gastrointestinal, genitourinary tract, skin, or musculoskeletal systems.[6,11]	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
[c]This recommendation does not apply to patients with intermediate risk for IE or to the general population.

Recommendation Table 3 — Recommendations for infective endocarditis prevention in cardiac procedures

Recommendations	Class[a]	Level[b]
Pre-operative screening for nasal carriage of *S. aureus* is recommended before elective cardiac surgery or transcatheter valve implantation to treat carriers.[113,114]	I	A
Peri-operative antibiotic prophylaxis is recommended before placement of a CIED.[116–118]	I	A
Optimal pre-procedural aseptic measures of the site of implantation is recommended to prevent CIED infections.[119]	I	B
Periprocedural antibiotic prophylaxis is recommended in patients undergoing surgical or transcatheter implantation of a prosthetic valve, intravascular prosthetic, or other foreign material.[120]	I	B
Surgical standard aseptic measures are recommended during the insertion and manipulation of catheters in the catheterization laboratory environment.	I	C
Elimination of potential sources of sepsis (including of dental origin) should be considered ≥2 weeks before implantation of a prosthetic valve or other intracardiac or intravascular foreign material, except in urgent procedures.	IIa	C
Antibiotic prophylaxis covering for common skin flora including *Enterococcus* spp. and *S. aureus* should be considered before TAVI and other transcatheter valvular procedures.[121]	IIa	C
Systematic skin or nasal decolonization without screening for *S. aureus* is not recommended.	III	C

Continued

CIED, cardiac implantable electronic device; TAVI, transcatheter aortic valve implantation.
[a]Class of recommendation.
[b]Level of evidence.

4. The Endocarditis Team

The importance of an Endocarditis Team in the diagnosis, management, and clinical outcomes of patients with IE has been demonstrated in several observational studies.[36–41,122–126] Establishing multidisciplinary endocarditis teams according to the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association Guidelines[4,127,128] has resulted in earlier and more accurate diagnosis of the primary disease and its complications,[5,22,31,40,129] uniform antibiotic treatment,[36,40,123] and optimized timing for surgical intervention.[36,37,40,123] A variety of scenarios of patients presenting with IE justifies a multidisciplinary approach.[5,25,27,28,130–135] Furthermore, the clinical presentation may vary significantly depending on the characteristics of the host and virulence of the microorganism. Accordingly, the concept of the Endocarditis Team needs to embrace a multidisciplinary approach that must adapt according to the patient's clinical needs and the local epidemiology to ensure prompt diagnosis and treatment.

The members of the Endocarditis Team should include the specialists with direct involvement in the diagnostic and therapeutic processes (*Table 7*), and may vary depending on the type of centre. In the

Table 7 Members of the Endocarditis Team

	Heart Valve Centre
Core members	• Cardiologists. • Cardiac imaging experts. • Cardiovascular surgeons. • Infectious disease specialist (or internal medicine specialist with expertise in infectious diseases). • Microbiologist. • Specialist in outpatient parenteral antibiotic treatment.
Adjunct specialities	• Radiologist and nuclear medicine specialist. • Pharmacologist. • Neurologist and neurosurgeon. • Nephrologist. • Anaesthesiologists. • Critical care. • Multidisciplinary addiction medicine teams. • Geriatricians. • Social worker. • Nurses. • Pathologist.

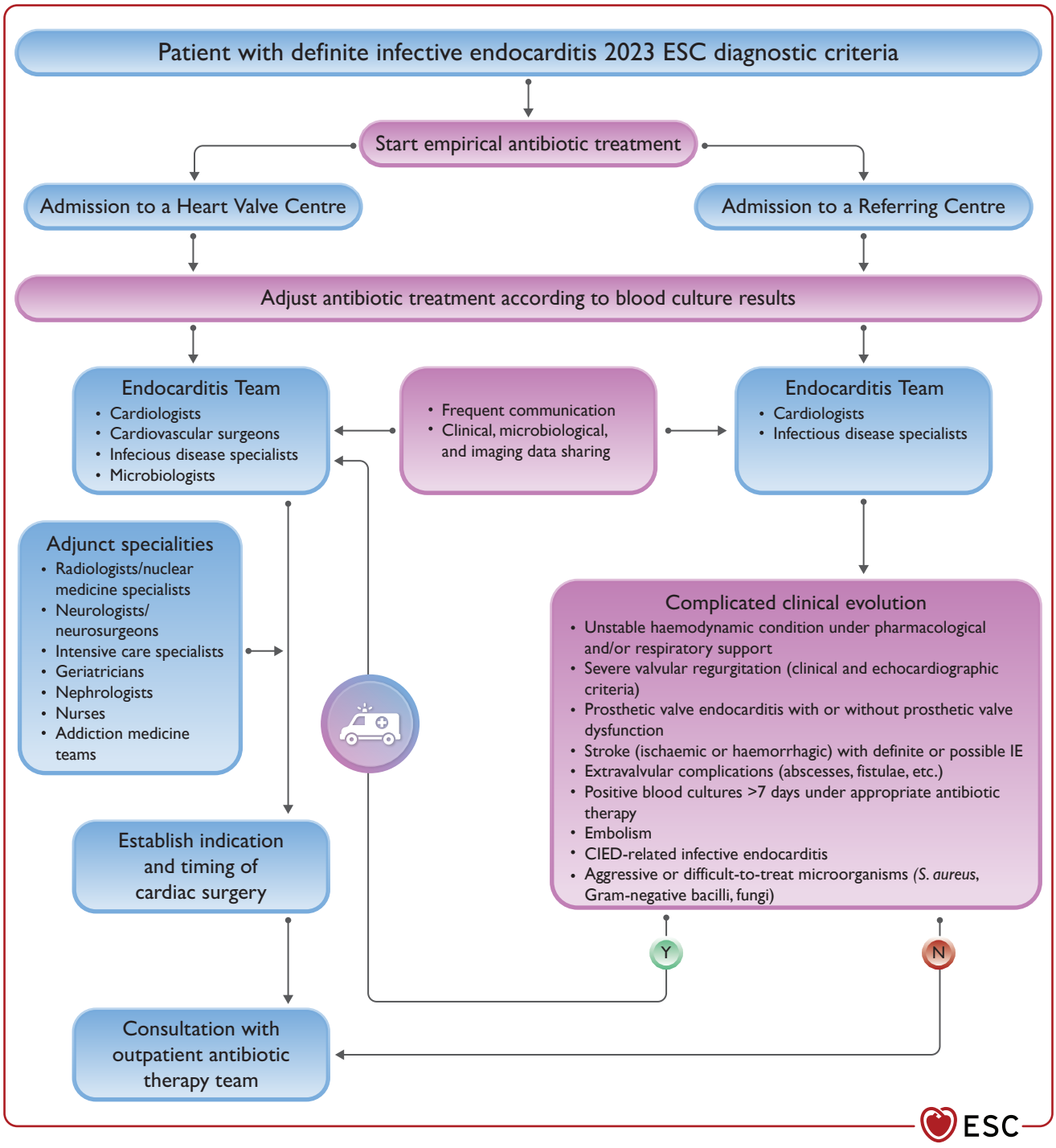

Figure 3 Management of patients with infective endocarditis: positioning of the Endocarditis Team. CIED, cardiovascular implanted electronic device; ESC, European Society of Cardiology.

Heart Valve Centre, a centre having all diagnostic and therapeutic resources to treat IE, the core members of the Endocarditis Team should include cardiologists, cardiovascular surgeons, infectious disease specialists (or internal medicine specialists with expertise in infectious diseases), and microbiologists. Furthermore, for specific clinical questions, cardiologists/surgeons with expertise in CIED extraction, HF, and CHD; pathologists; critical care specialists; cardiac anaesthesiologists; interventional cardiologists; neurologists and neurosurgeons; pharmacologists; radiologists and nuclear medicine specialists; nephrologists; geriatricians; and multidisciplinary addiction medicine teams (psychiatrists, nurses, and social work specialists providing counselling) are crucial adjuncts that should be available onsite for consultation. Specific subgroups of complex and high-risk patients are frequently assessed by the Endocarditis Team. The decision-making process may involve difficult decisions regarding continuation of therapy, and legal counsel may therefore be required.

Cardiovascular imaging has achieved such an advanced sophistication in the diagnosis of IE that the cardiologists with expertise in

multimodality imaging are key in the Endocarditis Team. In addition, radiology and nuclear medicine specialists with expertise on clinical cardiovascular imaging should be available whenever indicated.[22,31,129] The Endocarditis Team must meet on a frequent basis and work with standard operating procedures and the clinical governance arrangements defined locally.[128,136] Although the decision of timing is left to the discretion of the local team, a weekly meeting is to be considered.

In Referring Centres, i.e. those without a cardiovascular surgical team, the treating physician diagnosing IE should consult with a specialist in infectious diseases (or an internal medicine specialist with expertise in infectious diseases) and the microbiologist.[136] In addition, a cardiologist with expertise in valvular heart disease and cardiac imaging should be present to provide the initial and subsequent evaluations with echocardiography. Information of the strains of the isolated microorganisms, usually kept for 7–15 days, should be provided to the Heart Valve Centre if requested.

Communication between Referring Centres and the Heart Valve Centres should be facilitated with digital solutions that enable reliable data sharing. Early referral to the Heart Valve Centre for further diagnostic testing and clinical management should be available when deemed necessary (*Figure 3*). When there is evidence of failure to respond to the antibiotic therapy or there are complications related to valvular tissue destruction, the Referring Centre should consult the Heart Valve Centre. The Endocarditis Team of the Heart Valve Centre should share protocols with the physicians from the referring hospitals and should facilitate their continuing education.[136]

A critical aspect of the Endocarditis Team decision-making process is defining when a patient must be transferred to a Heart Valve Centre to expedite advanced diagnostics and therapy. The indications for transfer are comprehensive, to facilitate interhospital communication and avoid delaying therapy to improve prognosis.

Recommendation Table 4 — Recommendations for the Endocarditis Team

Recommendations	Class[a]	Level[b]
Diagnosis and management of patients with complicated IE are recommended to be performed at an early stage in a Heart Valve Centre, with immediate surgical facilities and an 'Endocarditis Team' to improve the outcomes.[36–41,122,123,125,126]	I	B
For patients with uncomplicated IE managed in a Referring Centre, early and regular communication between the local and the Heart Valve Centre endocarditis teams is recommended to improve the outcomes of the patients.[36–41,122,123,125,126]	I	B

IE, infective endocarditis.
[a]Class of recommendation.
[b]Level of evidence.

5. Diagnosis

The diagnosis of IE is based on a clinical suspicion supported by consistent microbiological data and the documentation of IE-related cardiac lesions by imaging techniques. Evidence of involvement of cardiac valves (native or prosthetic) or prosthetic intracardiac material is a major diagnostic criterion of IE. Echocardiography is the first-line diagnostic imaging technique. Other imaging modalities such as CT, nuclear imaging, and magnetic resonance imaging (MRI) are currently part of the diagnostic strategy of suspected IE, given their ability to provide key information to confirm IE diagnosis, to assess local IE complications as well as IE-related distant lesions, and to identify the original source of bacteraemia in patients who develop secondary IE.[137] Beyond diagnosis of IE, imaging findings also have prognostic implications.

5.1. Clinical features

Infective endocarditis remains a diagnostic challenge due to its variable clinical presentation. In general, a diagnosis of IE should be considered in all patients with sepsis or fever of unknown origin in the presence of risk factors. Infective endocarditis may present as an acute, rapidly progressive infection, but also as a subacute or chronic disease with low-grade, or even no fever, and non-specific symptoms that may mislead or confuse initial assessment. Infective endocarditis can also present with a complication mimicking a wide range of medical conditions that may prompt evaluation of other diseases, such as rheumatological, neurological, and autoimmune disorders, or even malignancy, before reaching a diagnosis of IE. Therefore, high suspicion for IE is generally driven by fever and positive blood cultures in the absence of an alternative focus of infection, especially in patients with one or more risk factors. Early involvement of the Endocarditis Team to guide management is highly recommended.

The initial clinical assessment should include evaluation of cardiac and non-cardiac risk factors (*Table 8*), supportive clinical context, and physical examination findings including potential portals of entry. Physical examination may reveal a variety of clinical signs. However, the absence of clinical signs alone should not exclude IE since the overall sensitivity and specificity of the clinical signs are low.

In the European Infective Endocarditis Registry (EURO-ENDO), fever (77.7%), cardiac murmur (64.5%), and congestive HF (27.2%) were the most frequent clinical presentations.[5] Embolic complications were detected in 25.3% of patients and cardiac conduction abnormalities were found in 11.5%. Some classical signs, such as peripheral stigmata, are less frequently observed, but may still be observed in severe infections caused by *S. aureus* and in cases of subacute endocarditis (mainly caused by *Streptococcis* spp.). However, vascular and immunological phenomena, such as splinter haemorrhages,[138] Roth spots, and

Table 8 Cardiac and non-cardiac risk factors

Cardiac risk factors
Previous infective endocarditis
Valvular heart disease
Prosthetic heart valve
Central venous or arterial catheter
Transvenous cardiac implantable electronic device
Congenital heart disease
Non-cardiac risk factors
Central venous catheter
People who inject drugs
Immunosuppression
Recent dental or surgical procedures
Recent hospitalization
Haemodialysis

glomerulonephritis, remain common. The main symptoms and signs observed in the EURO-ENDO registry are shown in the Supplementary data online, *Table S1*. Atypical presentation is common in elderly or immunocompromised patients.[139–141] A high index of suspicion and low threshold for investigation are therefore essential to exclude IE or avoid delays in diagnosis in these and other high-risk groups, such as those with CHD or prosthetic valves.[142] It is important to inform those patients about the risk of IE who should be aware of compatible symptoms to ask for advice in referral centres.

5.2. Laboratory findings

Laboratory investigations and biomarkers typically yield non-specific results. A large number of potential biomarkers have been proposed, reflecting the complex pathophysiology of the pro- and anti-inflammatory processes, humoral and cellular reactions, and both circulatory and end-organ abnormalities involved in IE.[143] The degree of anaemia, leucocytosis/leucopaenia, the number of immature white cell forms, concentrations of C-reactive protein and procalcitonin, erythrocyte sedimentation rate, and markers of end-organ dysfunction (serum lactate, serum creatinine, bilirubin, thrombocytopaenia, cardiac troponin, and natriuretic brain peptides) can be used to estimate the severity of sepsis, but none is diagnostic of IE. C-reactive protein and procalcitonin are the most widely evaluated biomarkers in RCTs of antibiotic stewardship. Furthermore, several of these biomarkers are included in scores used for risk stratification in critically ill patients. Unfortunately, no biomarker has sufficient accuracy for the diagnosis of sepsis or specificity for IE.[144] Therefore, the main role of biomarkers is to facilitate initial risk stratification and monitor the response to antibiotic therapy.

5.3. Microbiological diagnosis

The aetiology of IE is described in the EURO-ENDO registry[5] and the International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS).[145] In 2009, the ICE-PCS showed that the most frequent microorganisms causing IE were *S. aureus* (31%), followed by oral streptococci (17%), and CoNS (11%).[145] Similar results were reported in the EURO-ENDO registry.[5,145] Other registries have highlighted the increasing incidence of IE caused by *E. faecalis* and CoNS, particularly in the elderly.[146–149] However, the results of these registries should be carefully interpreted due to inherent biases (type of participating centres, geographical differences, lack of complete granular data, etc.).

5.3.1. Blood culture-positive infective endocarditis

Positive blood cultures remain the cornerstone of IE diagnosis and provide live bacteria for both identification and susceptibility testing. At least three sets of blood cultures should be obtained at 30-minute intervals prior to antibiotic therapy, each containing 10 mL of blood, and should be incubated in both aerobic and anaerobic atmospheres.[150,151] 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. In the absence of previous antimicrobial therapy, 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 to coincide with peaks of fever; and (ii) nearly all blood cultures are positive during bacteraemia. As a result, a single positive blood culture should be regarded cautiously for establishing IE diagnosis. The microbiology laboratory should be aware of the clinical suspicion of IE. Automated machines perform continuous monitoring of bacterial growth, which ensures quick provision of reports to physicians. When a positive blood culture is identified, presumptive identification is based on Gram staining. This information is immediately given to clinicians in order to adapt empirical antibiotic therapy. Complete identification is routinely achieved the same day or the following day with current methodology (e.g. matrix-assisted laser desorption ionization time-of-flight mass spectrometry [MALDI-TOF MS]), but may require a longer time for fastidious or atypical organisms. Since there is a long delay between blood culture sampling and definitive identification of the organism responsible for the bacteraemia and antibiotic susceptibility testing, 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 MALDI-TOF MS.[152] However, despite technical developments and the progress toward rapid susceptibility testing using MALDI-TOF MS, the gold standard for susceptibility testing is still the determination of the minimal inhibitory concentrations (MICs) to select appropriate antibiotic therapy, which needs to be performed following validated, standardized methodology.[153]

5.3.2. Blood culture-negative infective endocarditis

Blood culture-negative infective endocarditis (BCNIE) refers to IE in which no causative microorganism can be grown using the usual blood culture methods. The frequency of BCNIE as the cause of IE is highly variable and often poses considerable diagnostic and therapeutic dilemmas.[154,155] Blood culture-negative IE most commonly arises as a consequence of previous antibiotic administration, underlying the importance of performing blood cultures prior to antibiotic therapy, particularly in patients with known risk factors for IE. Withdrawal of antibiotics and repeating blood cultures may be required in stable patients with subacute symptoms, no evidence of local or distant complications, and receiving a very short course of antibiotics. Blood culture-negative IE can also be caused by fungi or fastidious bacteria, notably obligatory intracellular bacteria. Isolation of these microorganisms requires culturing on specialized media, and their growth is relatively slow. Depending on local epidemiology,[156] systematic serological testing for *Coxiella burnetii*, *Bartonella* spp., *Aspergillus* spp., *Mycoplasma pneumoniae*, *Brucella* spp., and *Legionella pneumophila* should be proposed,[157] followed by specific polymerase chain reaction (PCR) assays for *Tropheryma whipplei*, *Bartonella* spp., and fungi (*Candida* spp., *Aspergillus* spp.) from blood and the tissue (*Table 9*).[158]

In addition, 16S and 18S ribosomal ribonucleic acid (rRNA) sequencing from tissue is routinely performed in most laboratories and may provide a microorganism diagnosis in BCNIE. For patients with prosthetic valve BCNIE, molecular imaging technique fluorescence *in situ* hybridization combined with 16S rRNA-gene PCR and sequencing improved the conventional cultural diagnostic methods in 30% of cases.[159] Next-generation sequencing of plasma microbial cell-free deoxyribonucleic acid (DNA) may facilitate a rapid diagnosis of IE in the future.[160]

When all microbiological assays are negative, the diagnosis of non-bacterial endocarditis should systematically be considered and assays

Table 9 Investigation of rare causes of blood culture-negative infective endocarditis

Pathogen	Diagnostic procedures
Brucella spp.	Serology, blood cultures, tissue culture, immunohistology, and 16S rRNA sequencing of tissue
C. burnetii	Serology (IgG phase I >1:800), tissue culture, immunohistology, and 16S rRNA sequencing of tissue
Bartonella spp.	Serology (IgG phase I >1:800), blood cultures, tissue culture, immunohistology, and 16S rRNA sequencing of tissue
T. whipplei	Histology and 16S rRNA sequencing of tissue
Mycoplasma spp.	Serology, tissue culture, immunohistology, and 16S rRNA sequencing of tissue
Legionella spp.	Serology, blood cultures, tissue culture, immunohistology, and 16S rRNA sequencing of tissue
Fungi	Serology, blood cultures, 18S rRNA sequencing of tissue
Mycobacteria (including *Mycobacterium chimaera*)	Specific blood cultures, 16S rRNA sequencing of tissue

Ig, immunoglobulin; rRNA, ribosomal ribonucleic acid.

for antinuclear antibodies as well as antiphospholipid syndrome (APLs) (anticardiolipin antibodies [immunoglobulin (Ig)G] and anti-β_2-glycoprotein 1 antibodies [IgG and IgM]) should be performed (although these antibodies may also be present in patients with proven IE).[161,162] Pathological examination of resected tissue or embolic fragments remains the gold standard for IE diagnosis. All tissue samples that are excised during surgical valve debridement/resection must be collected in a sterile container without fixative or culture medium. Samples should be sent to the pathology department and the microbiology laboratory for the identification of microorganisms. On histological examination of excised valve tissue, patterns, and degrees of inflammation will vary depending on the infecting organism. Stains for bacteria, mycobacteria, and fungi may identify the microorganisms, and organism-specific immunohistochemical stains can be very useful for the final diagnosis. Importantly, histopathological analysis may facilitate the diagnosis of non-infectious causes of endocarditis, such as neoplastic and autoimmune causes.[160]

5.3.3. Proposed strategy for a microbiological diagnostic algorithm in suspected infective endocarditis

A proposed diagnostic scheme is provided in *Figure 4*. When there is clinical suspicion of IE and blood cultures remain negative at 48 h, consultation with the microbiologist is necessary.[156,160] A suggested strategy is the use of a diagnostic kit including blood cultures for the suspected microorganism and when negative, systematic serological testing for *C. burnetii*, *Bartonella* spp., *Aspergillus* spp., *L. pneumophila*, *Brucella* spp., and *M. pneumoniae*, as well as rheumatoid factor, serological tests for APLs (anticardiolipin [IgG] and anti-β_2-glycoprotein 1 [IgG and IgM]), antinuclear antibodies, and anti-pork antibodies. Serological testing should be performed taking into consideration the clinical characteristics of the patients (i.e. *Aspergillus* spp. in severe immunocompromised patients), the local epidemiology, and being aware of the specificity of the tests. In addition, tissue or prosthetic material obtained at surgery must be subjected to systematic culture, histological examination, and 16S or 18S rRNA sequencing aimed at documenting the presence of organisms.

5.4. Imaging techniques

Evidence of lesions characteristic of IE are major diagnostic criterion. Echocardiography is the first-line imaging technique to diagnose IE and to assess the structural and functional damage of cardiac structures. Echocardiographic findings have prognostic implications, and help to guide decision-making and patient follow-up while receiving antibiotic therapy and during the peri-operative and post-operative periods.[163] In some clinical scenarios, other imaging modalities, such as CT, nuclear imaging, and MRI, are needed to confirm or exclude the diagnosis of IE, to characterize the extent of the cardiac lesions, and to diagnose extracardiac complications. They can also provide additional useful information for patient management.[137] Each of these techniques has its diagnostic strengths and weaknesses (see Supplementary data online, *Table S2*). The use of an optimal imaging strategy depends on the availability of, and expertise in, each technique, but when indicated a multimodality imaging approach is essential for patients with suspected IE and should be strongly encouraged by the Endocarditis Team.[21]

5.4.1. Echocardiography

Transthoracic echocardiography (TTE) and transoesophageal echocardiography (TOE) are the first and key imaging techniques used to diagnose IE. Although echocardiography is widely accessible, significant variation in the use of TOE still exists.[164] Three-dimensional TOE and intracardiac echocardiography have also been shown to be useful for the diagnosis of IE and its complications.[165] However, the availability of intracardiac echocardiography is limited. Vegetation characteristics and size, perivalvular complications (abscess, pseudoaneurysm, new partial dehiscence of prosthetic valve), intracardiac fistula, and leaflet perforation are the main echocardiographic findings for the diagnosis and evaluation of local complications of IE (see Supplementary data online, *Table S3*). Importantly, vegetation size is a key metric that guides surgical indication, and vegetation size is defined as the maximal length of the vegetation.[166] When evaluating IE on native or prosthetic valves, TTE had low sensitivity but good specificity as compared with TOE.[166] TOE is helpful in a wide range of clinical scenarios, due to limitations of TTE to diagnose perivalvular complications, small vegetations, PVE, and vegetations associated with CIED. TOE is strongly recommended in patients with an inconclusive TTE, in patients with a negative TTE and a high suspicion of IE, as well as in patients with a positive TTE, in order to document local complications. Repeating 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 repeated examination depend on the initial findings, type of microorganism, and initial response to therapy.

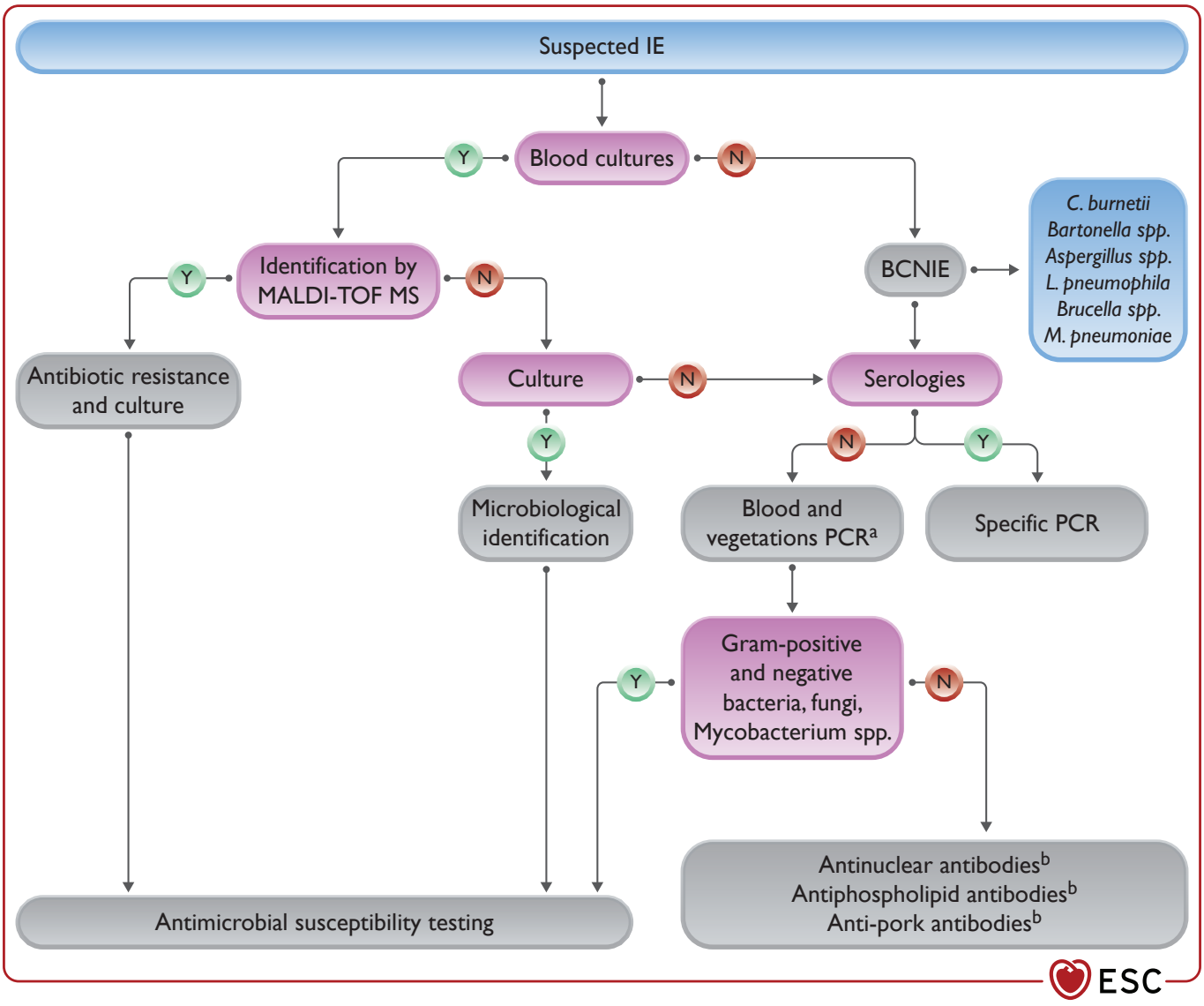

Figure 4 Microbiological diagnostic algorithm in culture-positive and culture-negative infective endocarditis. BCNIE, blood cultures negative endocarditis; IE, infective endocarditis; MALDI-TOF MS, matrix-assisted laser desorption ionization time-of-flight mass spectrometry; PCR, polymerase chain reaction. [a]Qualified microbiological laboratory. [b]Immunological laboratory.

Echocardiographic imaging should be performed as soon as the IE diagnosis is suspected. The degree of valvular damage, the rate of peripheral embolic events, and the need for valve surgery increase with increasing time to initial echocardiographic assessment.[167] Echocardiography should be repeated 5–7 days after an initial normal or inconclusive echocardiography, if the suspicion of IE remains high, and in patients with diagnosed IE at high risk of complications (e.g. aggressive microorganisms, prosthetic valves).[22,165,168,169]

There is uncertainty regarding whether echocardiography should be systematically performed in patients with bloodstream infections due to different bacterial species, or if there are strategies (microbiological or imaging) that allow the identification of patients at higher risk of IE. Scoring systems have been developed to help in the appropriate indication to perform echocardiography when bacteraemia of different microorganisms occurs (see Supplementary data online, *Table S4*).[60,170–173] The combination of microbiological parameters (type of microorganism and number of positive blood culture bottles) and cardiac-related risk factors (native valve disease, previous IE, prosthetic valve, and cardiac devices) may help identify the patients in whom echocardiography (TTE+TOE) is needed.[19,174] Three risk scores were recently developed to identify patients at high risk of IE caused by *S. aureus*, and those who should be evaluated with echocardiography (see Supplementary data online, *Section S2.2.1*).[170–173,175–178] The cut-off values of the various scores are provided in Supplementary data online, *Table S4*.

Recommendation Table 5 — Recommendations for the role of echocardiography in infective endocarditis

Recommendations	Class[a]	Level[b]
A. Diagnosis		
TTE is recommended as the first-line imaging modality in suspected IE.[166,179]	I	B
TOE is recommended in all patients with clinical suspicion of IE and a negative or non-diagnostic TTE.[166,178,179]	I	B
TOE is recommended in patients with clinical suspicion of IE, when a prosthetic heart valve or an intracardiac device is present.[166,178,179]	I	B
Repeating TTE and/or TOE within 5–7 days is recommended in cases of initially negative or inconclusive examination when clinical suspicion of IE remains high.[178]	I	C
TOE is recommended 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.[165,166,179]	I	C
Performing an echocardiography should be considered in *S. aureus*, *E. faecalis*, and some *Streptococcus* spp. bacteraemia.[19,149,174]	IIa	B
B. Follow-up under medical therapy		
Repeating TTE and/or TOE is recommended as soon as a new complication of IE is suspected (new murmur, embolism, persisting fever and bacteraemia, HF, abscess, AVB).[165,166,179]	I	B
TOE is recommended when patient is stable before switching from intravenous to oral antibiotic therapy.[43,180]	I	B
During follow-up of uncomplicated IE, repeat TTE and/or TOE should be considered to detect new silent complications. The timing of repeat TTE and/or TOE depends on the initial findings, type of microorganism, and initial response to therapy.[165,166,179]	IIa	B
C. Intra-operative echocardiography		
Intra-operative echocardiography is recommended in all cases of IE requiring surgery.[181]	I	C
D. Following completion of therapy		
TTE and/or TOE are recommended at completion of antibiotic therapy for evaluation of cardiac and valve morphology and function in patients with IE who did not undergo heart valve surgery.[182–184]	I	C

AVB, atrioventricular block; HF, heart failure; IE, infective endocarditis; PVE, prosthetic valve endocarditis; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography.
[a]Class of recommendation.
[b]Level of evidence.

5.4.2. Computed tomography

The indications for CT in patients with suspected or diagnosed IE include:

(i) Diagnosis of IE and cardiac complications. Cardiac CT is more accurate than TOE for diagnosing perivalvular and periprosthetic complications of IE (abscesses, pseudoaneurysms, and fistulae) and is recommended in both NVE and PVE if TOE is not conclusive or not feasible.[33,168,169] In addition, cardiac CT can significantly influence subsequent surgical decision-making.[20,185,186] Echocardiography continues to be superior for detecting valvular lesions, particularly small vegetations (<10 mm) which remain underdiagnosed by CT, but also leaflet perforations and fistulae (see Supplementary data online, *Table S3*).[35,168,169] Cardiac CT should be acquired according to the recommendations of cardiac CT guidelines to ensure high diagnostic accuracy, and can be performed alone or in combination with PET.[187]

(ii) Detection of distant lesions and sources of bacteraemia. Whole-body and brain CT are useful for assessing IE systemic complications, including septic emboli. The detection of distant lesions adds a minor diagnostic criterion leading to a more conclusive diagnosis of definite or rejected IE, and can be relevant for decision-making.[188] CT angiography can detect mycotic arterial aneurysms complicating IE in almost any site of the vascular tree,[189,190] including the central nervous system (CNS). Although MRI is superior to CT for diagnosing neurological complications,[191] CT may be more feasible in an emergency setting and is an acceptable alternative for the detection of neurological complications, with a sensitivity of 90% and specificity of 86% in the detection of ischaemic and haemorrhagic lesions.[192] Finally, CT can also detect the extracardiac sources of the bacteraemia, including early neoplastic lesions, that may be important for patient management, and which need to be ideally addressed prior to undergoing heart valve surgery. However, CT does not replace the specific test indicated for the diagnosis of the extracardiac source of bacteraemia (i.e. colonoscopy in colon neoplasms).

(iii) Pre-operative assessment. Cardiac CT is a valuable alternative for non-invasive assessment of coronary artery disease (CAD) before cardiac surgery in patients with IE.[193]

(iv) Alternative diagnosis. In patients in whom IE is ruled out, or even in doubtful patients with possible IE, an alternative diagnosis can be reached by whole-body CT, as it can help to detect alternative infectious foci. However, in these circumstances, an [18]FDG positron emission tomography/computed tomography (PET/CT) is the preferred imaging technique.[194]

5.4.3. Magnetic resonance imaging

The roles of MRI in the diagnostic work-up of IE include:

(i) Diagnosis of IE and cardiac complications. The role of cardiac MRI to diagnose IE is limited by the low spatial resolution (as compared with cardiac CT) and the signal void generated by some prostheses impairing the assessment of prosthetic valve anatomy and function.[195,196]

(ii) Diagnosis of neurological IE-related complications. MRI has higher sensitivity than CT for the diagnosis of neurological lesions and, hence, increases the likelihood of detecting neurological complications in patients with IE. Patients with IE might present CNS lesions in up to 60–80% of cases,[197] most of them corresponding to ischaemic lesions (50–80% of patients) that are often small and asymptomatic and do not impact on the decision-making.[198] Other lesions that may influence the decision-making, such as parenchymal or subarachnoid haemorrhages, abscesses, or mycotic aneurysms, are found in <10% of patients.[198–201] The systematic performance of brain MRI has shown to directly impact the

diagnosis of IE, as it can add a minor diagnostic criterion in patients without neurological symptoms with non-definitive IE diagnosis. Brain MRI can reclassify 25% of patients with an initially inconclusive diagnosis for IE to a more conclusive diagnosis, thereby leading to an earlier diagnosis.[151] Cerebral microbleeds, found in 50–60% of patients with IE, are detected at gradient echo T2* sequences.[200,202] Cerebral microbleeds should not be considered a minor criterion because there is no concordance with ischaemic lesions.[203–205]

(iii) Diagnosis of spine lesions. MRI is the diagnostic modality of choice of spondylodiscitis and vertebral osteomyelitis with a diagnostic accuracy of 89–94%. MRI findings include vertebrae and disc oedema, paravertebral/epidural inflammation or abscess, bone erosion, and gadolinium enhancement of vertebrae and discs.[32,206] It should be acknowledged that when MRI is performed too early, the rate of false-negative increases.[207]

5.4.4. Nuclear imaging positron emission tomography/computed tomography (angiography) and single photon emission tomography/computed tomography

Technical specifications of these imaging techniques are in the Supplementary data online, *Section S2.2.2*. The roles of nuclear imaging techniques in the diagnostic work-up of IE include:

(i) Diagnosis of IE and cardiac complications. [18F]FDG-PET/CT and white blood cell (WBC) single photon emission computed tomography (SPECT)/CT are recommended in suspected PVE in cases of inconclusive echocardiography. The most recent meta-analysis showed 86% sensitivity and 84% specificity for [18F]FDG-PET/CT in PVE.[129] Additional evidence demonstrating the incremental diagnostic value of [18F]FDG-PET/CT and WBC SPECT/CT is summarized in the Supplementary data online, *Section S2.2.2; Table S5*.[22,208–212]

White blood cell SPECT/CT is an alternative nuclear imaging technique for the diagnosis of IE, when PET/CT is unavailable and inexperienced centres. The sensitivity of WBC SPECT/CT has been reported as 64–90% and the specificity as 36–100%; diagnostic ability significantly increases with the presence of periprosthetic abscesses.[213–215] ^{99m}Technetium-hexamethylpropyleneamine oxime (99mTc-HMPAO)-SPECT/CT helped to reduce the number of misdiagnosed IE cases classified in the 'possible IE' category by the modified Duke criteria by 27%.[216]

In cases of NVE, the sensitivity of PET/CT and SPECT/CT is low (about 31%) but with a higher specificity (around 98%).[211] In NVE, the diagnosis of IE cannot be excluded in the absence of abnormal [18F]FDG uptake.[217] The more frequent presence of valve vegetations in comparison with paravalvular involvement in NVE compared with PVE leads to reduced inflammatory response and subsequently lower [18F]FDG and WBC uptake. The lower sensitivity of [18F]FDG-PET/CT is offset by other strengths of the technique, such as its ability to identify septic emboli when suspected.[211,218–220] Electrocardiogram (ECG)-gated PET may further improve the diagnostic accuracy.[221]

Combining PET/CT acquisition with a CT angiography (PET/CTA) allows the detection of metabolic findings ([18F]FDG uptake distribution and intensity) and anatomical findings (IE-related lesions) within a single imaging procedure, resulting in the clinical clarification of indeterminate findings and change in the management of the patients.[22,211] Such investigations may be particularly helpful in complex settings, such as patients with CHD[222,223] and/or aortic grafts.[22,224]

(ii) Detection of distant lesions and sources of bacteraemia. Whole-body [18F]FDG-PET/CT imaging is particularly useful in patients with a suspicion or proven IE to identify distant lesions, mycotic aneurysms, and the portal of entry of the infection.[225,226] Septic emboli are typically located in the spleen, lungs (in right-sided IE), and kidneys, and metastatic infections in the intervertebral discs and/or the vertebral bone (spondylodiscitis) as well as in muscles and joints (septic arthritis) and liver.[211,227,228] [18F]FDG-PET/CT is less suited to detect cerebral septic embolism and mycotic aneurysms of intracerebral arteries due to the high physiological uptake of [18F]FDG in the brain.

(iii) Monitoring response to antimicrobial treatment with [18F]FDG-PET/CT in patients with established IE and indication for surgery but who cannot be operated on due to unacceptable high risk and remain with long-term suppressive antibiotic treatment.[137,184,229–236]

Recommendation Table 6 — Recommendations for the role of computed tomography, nuclear imaging, and magnetic resonance in infective endocarditis

Recommendations	Class[a]	Level[b]
Cardiac CTA is recommended in patients with possible NVE to detect valvular lesions and confirm the diagnosis of IE.[33,168,169]	I	B
[18F]FDG-PET/CT(A) and cardiac CTA are recommended in possible PVE to detect valvular lesions and confirm the diagnosis of IE.[22,129,209,210,237–239]	I	B
Cardiac CTA is recommended in NVE and PVE to diagnose paravalvular or periprosthetic complications if echocardiography is inconclusive.[20,168,169,185,186]	I	B
Brain and whole-body imaging (CT, [18F]FDG-PET/CT, and/or MRI) are recommended in symptomatic[c] patients with NVE and PVE to detect peripheral lesions or add minor diagnostic criteria.[22,197–200,210,213,240,241]	I	B
WBC SPECT/CT should be considered in patients with high clinical suspicion of PVE when echocardiography is negative or inconclusive and when PET/CT is unavailable.[213–216]	IIa	C
[18F]FDG-PET/CT(A) may be considered in possible CIED-related IE to confirm the diagnosis of IE.[22,129,209,210,237,238]	IIb	B
Brain and whole-body imaging (CT, [18F]FDG-PET/CT, and MRI) in NVE and PVE may be considered for screening of peripheral lesions in asymptomatic patients.[188,197–201]	IIb	B

[18F]FDG-PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; CAD, coronary artery disease; CT, computed tomography; CTA, computed tomography angiography; IE, infective endocarditis; MRI, magnetic resonance imaging; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis; WBC SPECT/CT, white blood cell single photon emission tomography/computed tomography.
[a]Class of recommendation.
[b]Level of evidence.
[c]Symptomatic: symptoms suggesting septic embolic complications.

5.5. Diagnostic criteria

Since 2000, clinical, microbiological, and imaging findings have been integrated in the modified Duke criteria (see Supplementary data online, *Table S6*), which have demonstrated an overall sensitivity of 80% for IE.[151] However, the clinical presentation of IE can be highly variable and some major limitations of the modified Duke criteria have become clear, particularly when prosthetic material is present (PVE, aortic grafts, cardiac devices, CHD). In these situations, echocardiography can be normal or inconclusive in up to 30% of cases despite the presence of IE.[242–244] Therefore, the 2015 ESC diagnostic criteria introduced a multimodality imaging approach (echocardiography, cardiac/whole-body CT, cerebral MRI, [18F]FDG-PET/CT, and WBC SPECT/CT) to improve the diagnostic yield. This new approach has shown to be superior over the traditional diagnostic criteria.[36–41,122,123,125,126,212]

5.5.1. Modifications for the diagnosis of infective endocarditis

The current *2023 ESC Guidelines for the management of endocarditis* introduce the following modifications for IE diagnosis:

(i) Changes to the major and minor diagnostic criteria (*Table 10*).

Table 10 Definitions of the 2023 European Society of Cardiology modified diagnostic criteria of infective endocarditis

Major criteria
(i) Blood cultures positive for IE
(a) Typical microorganisms consistent with IE from two separate blood cultures: Oral streptococci, *Streptococcus gallolyticus* (formerly *S. bovis*), HACEK group, *S. aureus*, *E. faecalis*
(b) Microorganisms consistent with IE from continuously positive blood cultures: • ≥2 positive blood cultures of blood samples drawn >12 h apart. • All of 3 or a majority of ≥4 separate cultures of blood (with first and last samples drawn ≥1 h apart).
(c) Single positive blood culture for *C. burnetii* or phase I IgG antibody titre >1:800.
(ii) Imaging positive for IE:
Valvular, perivalvular/periprosthetic and foreign material anatomic and metabolic lesions characteristic of IE detected by any of the following imaging techniques: • Echocardiography (TTE and TOE). • Cardiac CT. • [18F]-FDG-PET/CT(A). • WBC SPECT/CT.
Minor criteria
(i) Predisposing conditions (i.e. predisposing heart condition at high or intermediate risk of IE or PWIDs)[a]
(ii) Fever defined as temperature >38°C
(iii) Embolic vascular dissemination (including those asymptomatic detected by imaging only): • Major systemic and pulmonary emboli/infarcts and abscesses. • Haematogenous osteoarticular septic complications (i.e. spondylodiscitis). • Mycotic aneurysms. • Intracranial ischaemic/haemorrhagic lesions. • Conjunctival haemorrhages. • Janeway's lesions.
(IV) Immunological phenomena: • Glomerulonephritis. • Osler nodes and Roth spots. • Rheumatoid factor.
(V) Microbiological evidence: • Positive blood culture but does not meet a major criterion as noted above. • Serological evidence of active infection with organism consistent with IE.
IE Classification (at admission and during follow-up)
Definite: • 2 major criteria. • 1 major criterion and at least 3 minor criteria. • 5 minor criteria.
Possible: • 1 major criterion and 1 or 2 minor criteria. • 3–4 minor criteria.
Rejected: • Does not meet criteria for definite or possible at admission with or without a firm alternative diagnosis.

[18F]-FDG-PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography; CT(A), computed tomography (angiography); HACEK, *Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, and *Kingella*; IE, infective endocarditis; Ig, immunoglobulin; PWID, people who inject drugs; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography; WBC SPECT/CT, white blood cell single photon emission tomography/computed tomography.

[a]For detailed explanation of predisposing conditions, please see *Section 3*.

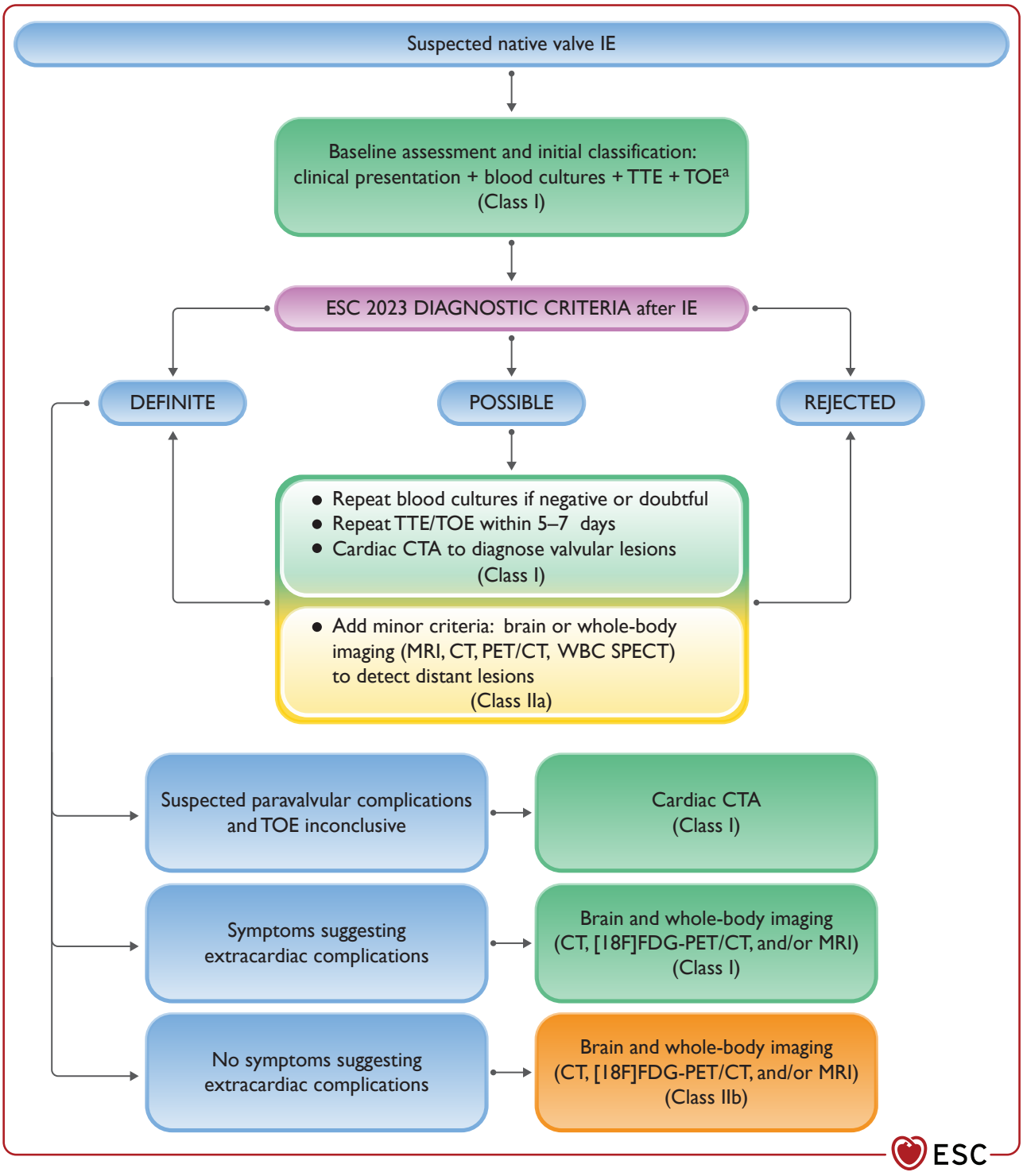

Figure 5 European Society of Cardiology 2023 algorithm for diagnosis of native valve infective endocarditis. [18F]FDG, ^{18}F-fluorodeoxyglucose; CT, computed tomography; CTA, computed tomography angiography; ESC, European Society of Cardiology; IE, infective endocarditis; MRI, magnetic resonance imaging; NVE, native valve endocarditis; PET, photon emission tomography; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography; WBC SPECT, white blood cell single photon emission tomography. [a]TOE for diagnosis and to detect perivalvular complications in all cases (unless right-sided NVE when TTE is good quality and conclusive).

(ii) Specific diagnostic algorithms to support decision-making, especially in the recommended sequence of imaging techniques (*Figures 5–7*).
(iii) CIED-related IE is considered a right-sided endocarditis for diagnostic purposes and is included in the diagnostic algorithms, but its definitions and recommendations for management can be found in *Section 12* and are in accordance with the specific European Heart Rhythm Association (EHRA) consensus on CIED infections.[130]

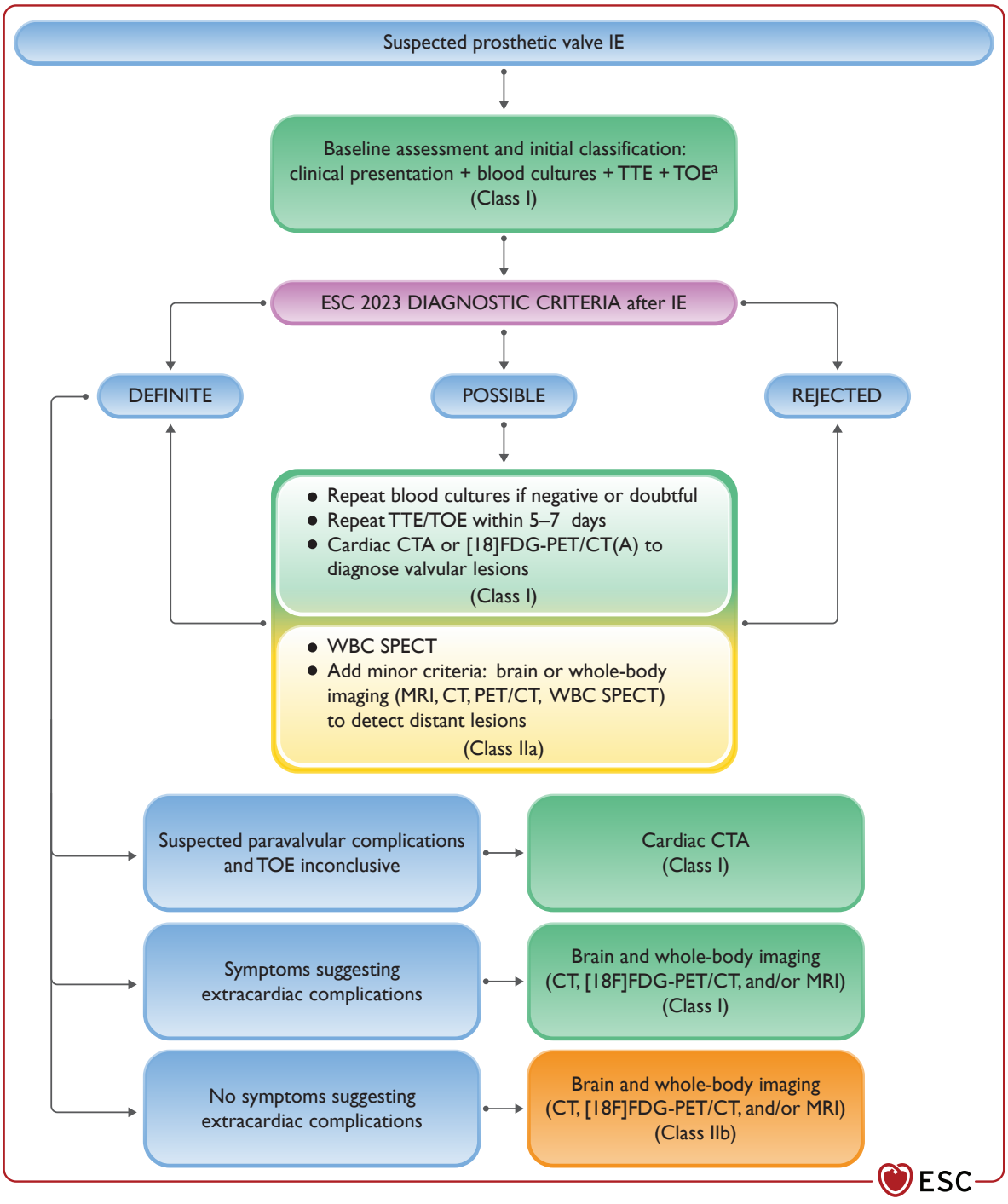

Figure 6 European Society of Cardiology 2023 algorithm for diagnosis of prosthetic valve infective endocarditis. [18F]FDG, ^{18}F-fluorodeoxyglucose; CT, computed tomography; CTA, computed tomography angiography; ESC, European Society of Cardiology; IE, infective endocarditis; MRI, magnetic resonance imaging; PET, positron emission tomography; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography; WBC SPECT, white blood cell single photon emission tomography. [a]TOE for diagnosis and to detect perivalvular complications in all cases (unless right-sided NVE when TTE is good quality and conclusive).

The reasons to justify the changes in the diagnostic criteria include:

5.5.1.1. Major criteria – microbiology

Enteroccus faecalis should be acknowledged as a typical endocarditis bacterium, regardless of the place of acquisition or the source of infection. Currently, the modified Duke criteria fail to identify 30% of *E. faecalis* definite IE. Using data from a prospective study of 344 patients with *E. faecalis* bacteraemia evaluated with echocardiography, Dahl *et al.* demonstrated that designating *E. faecalis* as a 'typical' endocarditis pathogen significantly improved the sensitivity to correctly identify definite IE, from 70% to 96%.[245]

5.5.1.2. Major criteria – imaging

(i) Diagnosis based on the presence of lesions characteristics of IE. Anatomic lesions and increased [18F]FDG uptake or WBC accumulation can be depicted by nuclear imaging techniques and add

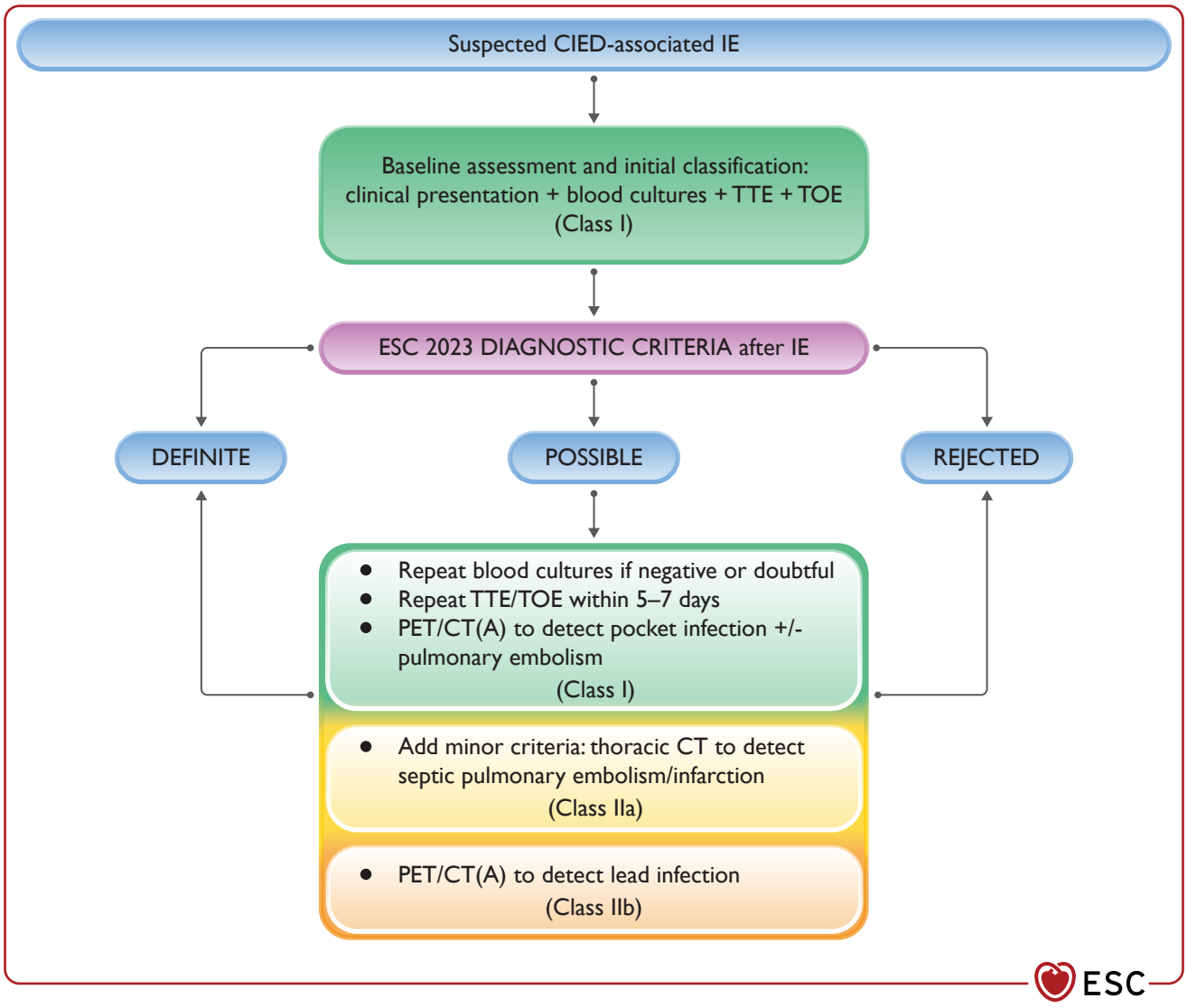

Figure 7 European Society of Cardiology 2023 algorithm for diagnosis of cardiac device-related infective endocarditis. CIED, cardiovascular implanted electronic device; CT, computed tomography; CTA, computed tomography angiography; ESC, European Society of Cardiology; IE, infective endocarditis; PET, positron emission tomography; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography; WBC SPECT, white blood cell single photon emission tomography.

a major diagnostic criterion. Definitions of the anatomic and metabolic features of the infective lesions can be found in the Supplementary data online, *Table S5*.

(ii) Abnormal prosthetic or periprosthetic uptake (intense focal or heterogeneous) detected by [18F]FDG-PET/CT or WBC SPECT/CT should be considered a major criterion for PVE, irrespective of the interval from surgery (see Supplementary data online, *Figure S1*). Published data support that intense focal or heterogeneous patterns is associated with a final diagnosis of infection, while post-operative inflammatory changes can be persistent more than 3 months after surgery, as noted in the previous guidelines. However, these inflammatory changes can be differentiated from infection even after recent valve implantation.[246] Therefore, a consensus of experts has concluded that the need for a time interval prior to investigation is questionable, but accurate imaging interpretation by proper interpretation criteria is mandatory.[233,236]

5.5.1.3. Minor criteria

Distant IE-related lesions include all lesions that can result from embolic events and from haematogenous seeding of bacteria. These lesions can be suspected due to specific symptoms or can be incidentally detected on imaging techniques. Spondylodiscitis is the most frequent osteoarticular infective complication in patients with IE.[247,248]

5.5.1.4. Microbiological criteria

Molecular biology (16S/18S rRNA PCR sequencing) in cardiac tissue or embolic material has increased the diagnostic performance of IE with negative blood culture. The sensitivity ranges between 41% and 96% and the specificity is very high, ranging between 90% and 100%.[249]

5.5.1.5. Infective endocarditis classification

Infective endocarditis classification has been added to the 2023 ESC criteria. Possible IE cases include the combination of 1 major and 1 or 2 minor criteria. Infective endocarditis classification should be applied by the Endocarditis Team at admission and later at follow-up, taking into account the complete clinical, microbiology, imaging, and surgical information to establish the final diagnosis.

It is important to acknowledge that these new criteria should be prospectively validated.

5.5.2. The new 2023 European Society of Cardiology diagnostic algorithms

The diagnosis of IE is based on clinical suspicion, blood cultures, and imaging findings. Echocardiography is usually the first imaging technique to diagnose IE, although the use of other techniques, either for the diagnosis of cardiac involvement (cardiac CT, [18F]FDG-PET/CT, or WBC SPECT/CT), or for the diagnosis of distant lesions (cerebral MRI, whole-body CT, and/or PET/CT), is encouraged. In the presence of prosthetic valves and CIED, echocardiography is particularly limited and the aforementioned imaging techniques are strongly recommended. Adapted diagnostic algorithms for suspected IE in NVE, PVE, and CIED are displayed in *Figures 5*–*7*, respectively.

6. Prognostic assessment at admission

The in-hospital mortality rate of patients with IE has remained largely unchanged over the past two decades, ranging from 15% to 30%.[5,145,250,251] Several patient characteristics, often occurring simultaneously, have been shown to confer an increased risk of death in IE. The rapid identification of patients at the highest risk may offer the opportunity to change the course of the disease (i.e. with urgent or emergency surgery) and improve prognosis. Predictors of poor outcome on admission of patients with IE are specified in the Supplementary data online, *Section S3.1; Table S7*.

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. Bactericidal regimens are more effective than bacteriostatic therapy, both in animal experiments and in humans.[252–254] 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. However, the side effects of aminoglycosides should be taken into consideration and currently the combination of ampicillin with ceftriaxone has demonstrated effective in treating IE caused by *E. faecalis* irrespective of the presence of high-level aminoglycoside resistance (HLAR) and minimizing the risk of nephrotoxicity.[255,256]

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 (complex communities of bacteria residing within an exopolysaccharide matrix that adheres to a surface, e.g. in PVE),[257] and justify the need for prolonged therapy to fully sterilize infected heart valves. Some bacteria carry mutations rendering them tolerant during both active growth and stationary (dormant) phases.[258,259] Bactericidal drug combinations are preferred to monotherapy against tolerant organisms (e.g. the combination of ampicillin and ceftriaxone in IE caused by *E. faecalis*).

Drug treatment of PVE should last longer (≥6 weeks) than that of NVE (2–6 weeks) but is otherwise similar. In staphylococcal PVE, the regimen should include rifampin whenever the strain is susceptible, even if some recent data have shown no differences in outcomes between patients with PVE treated with rifampin vs. those treated without.[260,261]

In NVE needing valve replacement by a prosthesis during antibiotic therapy, the post-operative antibiotic regimen should be that recommended for NVE, not for PVE. In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy (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.

Finally, there are important considerations in these recommendations:

(i) Only published antibiotic efficacy data from clinical trials and cohort studies in patients with IE (or bacteraemia if there are no IE data) have been considered in these guidelines. Data from experimental IE models have not been taken into account. A recent systematic review evaluating the existing evidence about clinical benefits and harms of different antibiotic regimens used to treat patients with IE has shown that there is limited and low- to very low-quality evidence to make strong conclusions on the comparative effects of different antibiotic regimens on cure rates or other relevant clinical outcomes and, therefore, there is not enough evidence to support or reject any regimen of antibiotic therapy for the treatment of IE.[262,263]

(ii) These guidelines have adopted the MIC breakpoints included in the 2022 EUCAST clinical breakpoint tables.[42] The EUCAST breakpoints are used to categorize results into three susceptibility categories:

- Susceptible, standard dosing regimen: a microorganism is categorized as such, when there is a high likelihood of therapeutic success using a standard dosing regimen of the agent.
- Susceptible, increased exposure: a microorganism is categorized as such when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.
- Resistant: a microorganism is categorized as such when there is a high likelihood of therapeutic failure even when there is increased exposure.

The term exposure is defined as a function of how the mode of administration, dose, dosing interval, infusion time, as well as distribution and excretion of the antimicrobial agent, will influence the infecting organism at the site of infection. The local laboratories are responsible for the use of appropriate methods and interpretative criteria and quality control of the test results (MIC) while the clinicians are responsible for adjusting the level of exposure by modifying the dosing strategy

(individual dose, frequency of dosing, mode of administration [oral or intravenous (i.v.)]).[42]

(iii) Oral antimicrobial therapy. The POET trial has changed the paradigm of i.v. antibiotic treatment for IE.[43] For more than 60 years it had been considered that antibiotics should always be given intravenously. The POET trial has shown that after an initial phase of i.v. treatment, up to 20% of patients could complete the treatment by oral antibiotic therapy (see *Section 7.13.1*).[43] Therefore, as indicated in *Figure 8*, the antibiotic treatment of IE has two phases. The first phase can last up to 2 weeks of hospital i.v. treatment using combinations of rapidly bactericidal antibiotics to destroy planktonic bacteria.[257] In this initial phase, cardiac surgery should be performed if indicated, infected foreign bodies should be removed, and cardiac as well as extracardiac abscesses should be drained. After this period, clinically stable patients can end the antibiotic treatment at home with i.v. (OPAT) or oral antibiotic regimens for up to 6 weeks in order to eliminate the dormant (resting) bacteria and prevent relapses.

(iv) Aminoglycosides are not recommended in staphylococcal NVE because their clinical benefits have not been demonstrated, but they can increase renal toxicity.[255,264] When they are indicated in other conditions (e.g. resistant oral streptococci),[265] aminoglycosides should be given for no longer than 2 weeks to reduce nephrotoxicity.[266]

(v) 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,[267] and the synergy seen against dormant bacteria within the biofilms and prevention of rifampin-resistant variants.[268] New evidence based on a small, retrospective study has questioned this approach and needs further validation.[260]

(vi) Daptomycin has been recommended for treating staphylococcal and enterococcal endocarditis.[269] When daptomycin is indicated, it must be given at high doses (10 mg/kg once daily)[270] and combined with a second antibiotic (beta-lactams or fosfomycin in beta-lactam allergic patients) to increase activity and avoid the development of resistance.[271] It should be noted the use of fosfomycin is associated with increased risk of acute HF and renal failure due to the high load of sodium while the use of daptomycin has been associated with eosinophilic syndromes in up to 15% of patients.[272,273]

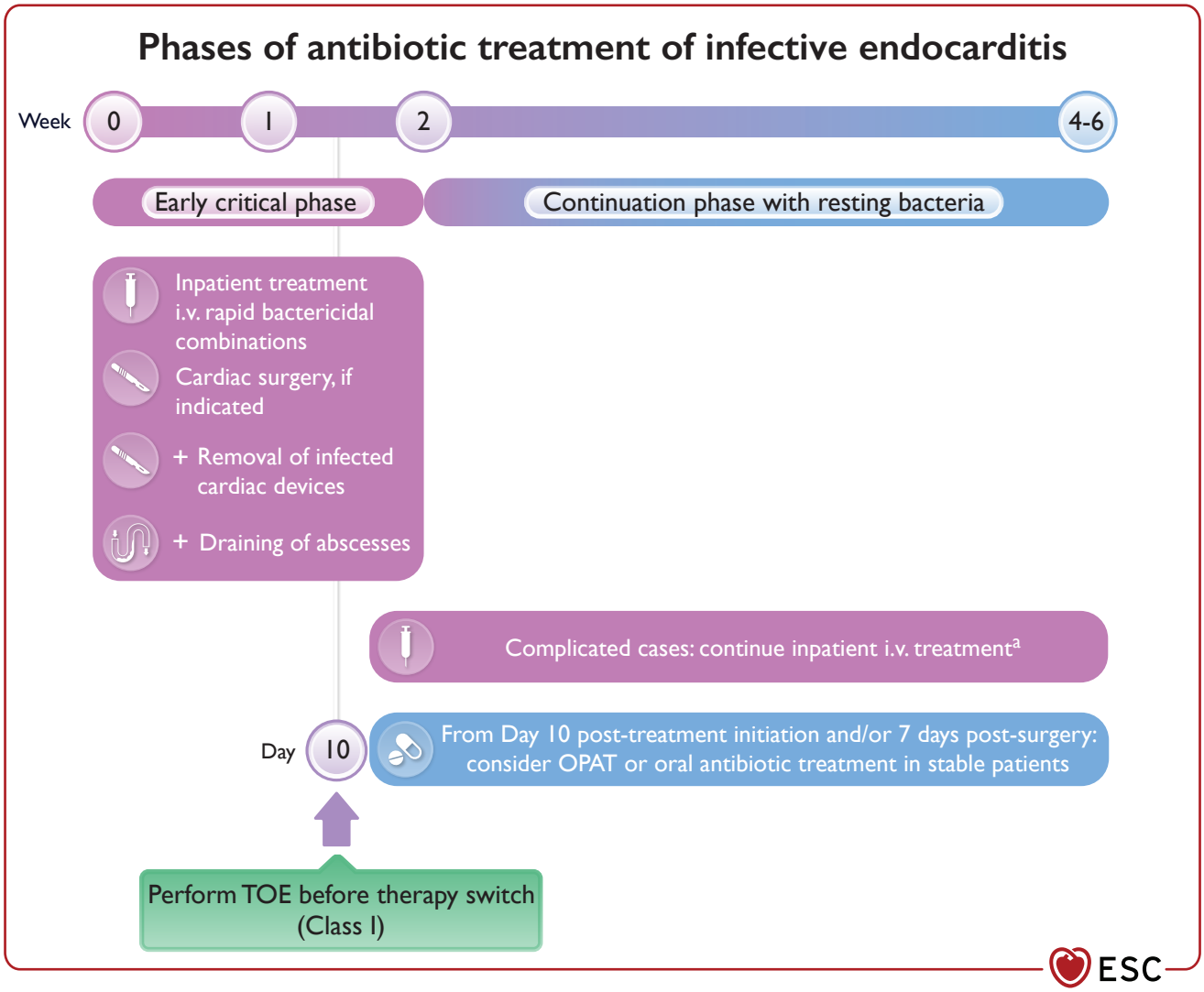

Figure 8 Phases of antibiotic treatment for infective endocarditis in relation to outpatient parenteral antibiotic therapy and partial oral endocarditis treatment. i.v., intravenous: OPAT, outpatient parenteral antibiotic treatment; TOE, transoesophageal echocardiography. [a]Criteria for switching to OPAT or partial oral treatment of endocarditis are given in the Supplementary data online, Table S8.

(vii) The antibiotic regimens need to adapt to the local circumstances and the availability of antibiotics.

(viii) Data on the efficacy of long-term antibiotic suppressive therapy in patients with IE who do not undergo cardiac surgery are limited to small and heterogeneous series with various antibiotic regimens.[184,274] In a small series of Gram-positive bloodstream infections and IE, dalbavancin (500 mg weekly or 1000 mg biweekly regimens) has been shown effective.[274,275] Relapses are not infrequent.[184]

7.2. Penicillin-susceptible oral streptococci and *Streptococcus gallolyticus* group

Oral streptococci include the groups *mitis*, *sanguinis*, *anginosus*, *salivarius*, *downei*, and *mutans* (see Supplementary data online, *Figure S2*).[276] The remaining streptococci isolated outside of the oral cavity are classified into either the *Streptococcus gallolyticus* (former bovis) or pyogenic groups. Recommended regimens against susceptible (susceptible standard dosing regimen and increased exposure) streptococci are summarized in Recommendation Table 7.[4,277–279] The cure rate is expected to be >95%. In uncomplicated cases of NVE, short-term 2-week therapy can be administered by combining penicillin or ceftriaxone with gentamicin or netilmicin.[280,281] Gentamicin and netilmicin can be given once daily in patients with IE due to susceptible streptococci and normal renal function. When outpatient antibiotic therapy is feasible, ceftriaxone alone or combined with gentamicin or netilmicin given once a day is particularly convenient.[280–282] In patients with documented allergy to penicillin, desensitization is recommended. If desensitization cannot be performed, patients allergic to beta-lactam should receive cephalosporins (in non-anaphylactic reaction) or vancomycin, keeping in mind that a beta-lactam is superior to glycopeptides. Teicoplanin has been proposed as an alternative,[4] starting with loading doses (6 mg/kg/12 h for 3 days) and 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.[283] However, only limited retrospective studies have assessed its efficacy in streptococcal IE.[284] After 10–14 days of therapy, OPAT or outpatient oral antibiotic therapy should be considered.

7.3. Oral streptococci and *Streptococcus gallolyticus* group susceptible, increased exposure or resistant to penicillin

The incidence of these resistant streptococci is increasing. Large strain collections have reported >30% of resistant *S. mitis* and *Streptococcus oralis*.[285]

Retrospective series provide the evidence for the recommendations on antibiotic treatment of IE caused by penicillin-resistant oral streptococci and *S. gallolyticus*. Compiling four of them, 47 of 60 patients (78%) were treated with penicillin or ceftriaxone, mostly combined with aminoglycosides.[285–290] In penicillin-resistant cases, aminoglycoside treatment must be given for ≥2 weeks and short-term therapy regimens are not recommended. There is very limited experience with daptomycin in IE caused by resistant isolates.[265,291] After 10–14 days of therapy, OPAT or outpatient oral antibiotic therapy should be considered if clinically stable (see *Section 7.13*).

Recommendation Table 7 — Recommendations for antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus gallolyticus* group

Recommendations		Class[a]	Level[b]
Penicillin-susceptible oral streptococci and *Streptococcus gallolyticus* group			
Standard treatment: 4-week duration in NVE or 6-week duration in PVE			
In patients with IE due to oral streptococci and *S. gallolyticus* group, penicillin G, amoxicillin, or ceftriaxone are recommended for 4 (in NVE) or 6 weeks (in PVE), using the following doses:[277,278]		I	B
Adult antibiotic dosage and route			
Penicillin G	12–18 million[c] U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Paediatric antibiotic dosage and route			
Penicillin G	200 000 U/kg/day i.v. in 4–6 divided doses		
Amoxicillin	100–200[c] mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg/day i.v. in 1 dose		
Standard treatment: 2-week duration (not applicable to PVE)			
2-week treatment with penicillin G, amoxicillin, ceftriaxone combined with gentamicin is recommended only for the treatment of non-complicated NVE due to oral streptococci and *S. gallolyticus* in patients with normal renal function using the following doses:[277,278]		I	B
Adult antibiotic dosage and route			
Penicillin G	12–18 million[c] U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose[d]		

Continued

Paediatric antibiotic dosage and route			
Penicillin G			
12–18 million[c] U/day i.v. either in 4–6 doses or continuously			
Amoxicillin	100–200 mg/kg/day[c] i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg i.v. in 1 dose		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose or 3 equally divided doses[d]		
Allergy to beta-lactams			
In patients allergic to beta-lactams and with IE due to oral streptococci and *S. gallolyticus*, vancomycin for 4 weeks in NVE or for 6 weeks in PVE is recommended using the following doses:[292]		I	C
Adult antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 doses[e]		
Paediatric antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 or 3 equally divided doses[e]		
Oral streptococci and *Streptococcus gallolyticus* group susceptible, increased exposure or resistant to penicillin			
In patients with NVE due to oral streptococci and *S. gallolyticus*, penicillin G, amoxicillin, or ceftriaxone for 4 weeks in combination with gentamicin for 2 weeks is recommended using the following doses:[285–290]		I	B
Adult antibiotic dosage and route			
Penicillin G	24 million U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	2 g/day i.v. in 6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose[d]		
In patients with PVE due to oral streptococci and *S. gallolyticus*, penicillin G, amoxicillin, or ceftriaxone for 6 weeks combined with gentamicin for 2 weeks is recommended using the following doses:[285–290]		I	B
Adult antibiotic dosage and route			
Penicillin G	24 million U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	2 g/day i.v. in 6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose[d]		
Allergy to beta-lactams			
In patients with NVE due to oral streptococci and *S. gallolyticus* and who are allergic to beta-lactams, vancomycin for 4 weeks is recommended using the following doses:		I	C
Adult antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 doses[e]		
Paediatric antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 doses[e]		
In patients with PVE due to oral streptococci and *S. gallolyticus* and who are allergic to beta-lactams, vancomycin for 6 weeks combined with gentamicin for 2 weeks is recommended using the following doses:		I	C
Adult antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 doses[e]		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose[d]		
Paediatric antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 doses[e]		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose[d]		

IE, infective endocarditis; i.m., intramuscular; i.v., intravenous; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis; U, units.
[a]Class of recommendation.
[b]Level of evidence.
[c]The starting recommended doses are the lower doses which can be scalable to the highest doses.
[d]Maximum doses 240 mg/day. High doses are associated with increased risk of nephrotoxicity. 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 h after injection) serum concentrations should be ~10–12 mg/L.
[e]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/day unless serum levels are monitored and can be adjusted to obtain a peak plasma concentration of 30–45 μg/mL 1 h after completion of the i.v. infusion of the antibiotic.

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

Infective endocarditis due to *Streptococcus pneumoniae* has become rare. It is associated with meningitis and pneumonia in up to 30% of cases,[293–296] which requires special consideration in cases with penicillin resistance. Treatment of penicillin-susceptible strains is similar to that of oral streptococci (see Recommendation Table 7), except for the use of short-term 2-week therapy, which has not been thoroughly investigated. The same holds true for penicillin-susceptible increased exposure or resistant strains without meningitis, although for resistant strains some authors recommend high doses of cephalosporins (e.g. cefotaxime or ceftriaxone) or vancomycin.[295] In cases with meningitis, penicillin must be avoided because of its poor penetration into the cerebrospinal fluid, and should be replaced with ceftriaxone or cefotaxime alone, or in association with vancomycin according to the antibiotic susceptibility pattern.[297,298] After 10–14 days of therapy and when meningitis is not associated, OPAT or outpatient oral antibiotic therapy should be considered if clinically stable (see *Section 7.13*).

Infective endocarditis due to group A, B, C, or G streptococci, including the *Streptococcus anginosus* group (*S. constellatus*, *S. anginosus*, and *S. intermedius*) is relatively rare.[299,300] Group A streptococci are uniformly susceptible to beta-lactams, whereas other serogroups may display some degree of resistance. Infective endocarditis due to group B streptococci was once associated with the peripartum period, but it now occurs in all adults, especially the elderly. Groups B, C, and G streptococci and *S. anginosus* induce abscesses that require adjunctive surgery.[300] Mortality from group B PVE is very high and cardiac surgery is recommended.[301] Antibiotic treatment is similar to that of oral streptococci (see Recommendation Table 7), except that short-term (2 weeks) therapy is not recommended and gentamicin should be given for 2 weeks.

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

Granulicatella and *Abiotrophia* induce IE with a prolonged course and are associated with large vegetations (>10 mm), and consequently with high rates of complications and valve replacement (around 50%).[302,303] This is 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 in case of PVE (for doses, please see Recommendation Table 7).[302–304]

7.6. *Staphylococcus aureus* and coagulase-negative staphylococci

Staphylococcus aureus is usually responsible for acute and destructive IE,[305] whereas CoNS can induce more protracted valve infections.[306,307] Of note, the addition of an aminoglycoside in staphylococcal NVE is no longer recommended because it increases renal toxicity.[264,308] 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 or cefazolin can be used since vancomycin is inferior to beta-lactams.[309] If beta-lactams cannot be given, where available, daptomycin should be chosen and given in combination with another effective anti-staphylococcal drug to increase activity and avoid the development of resistance.[310] *Staphylococcus lugdunensis* is mostly methicillin-susceptible and can be treated with cloxacillin.

Staphylococcus aureus PVE carries a very high risk of mortality (>45%),[305,312,313] 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.[264,314–318] The rationale supporting this recommendation is based on the antagonistic effect of the antibiotic combinations with rifampin against planktonic/replicating bacteria as has been demonstrated in foreign body infection models and clinically in prosthetic orthopaedic and vascular infections.[319] However, a recent study has shown that the addition of aminoglycosides to a regimen containing vancomycin or cloxacillin plus rifampicin in *S. aureus* PVE was not associated with a better outcome.[320] In addition, the risk of nephrotoxicity associated with the use of aminoglycosides should be taken into consideration. Adding rifampin to the treatment of staphylococcal PVE is standard practice despite the weak evidence.[261,321] The potential side effects and drug interactions of rifampin should also be considered. In patients with PVE who are allergic to penicillin, daptomycin can be given combined with ceftaroline or fosfomycin or with gentamicin (for 2 weeks) plus rifampin for at least 6 weeks. After 10–14 days of therapy, OPAT or outpatient oral antibiotic therapy should be considered if clinically stable (see *Section 7.13*).

7.7. Methicillin-resistant staphylococci

Methicillin-resistant *S. aureus* (MRSA) produces low-affinity penicillin-binding proteins (PBPs), which confer cross-resistance to most beta-lactams. Methicillin-resistant *S. aureus* is usually resistant to multiple antibiotics, leaving vancomycin, daptomycin, ceftaroline, and dalbavancin to treat severe infections.[322–324] However, it should be noted that subpopulations susceptible with increased exposure and resistant to vancomycin have emerged worldwide and are associated with IE treatment failures.[325–328] The prevalence of MRSA causing IE that is susceptible with increased exposure or resistant to vancomycin ranges between 19% and 34%. In addition, among patients with IE caused by MRSA, those isolates with a population analysis profile MIC ≥4 mg/L were associated with treatment failure defined by persistent bacteriaemia for ≥7 days or MRSA-attributable mortality.[325] Nephrotoxicity is of concern when using trough monitoring of levels of vancomycin as a surrogate marker of the area under the curve relative to the MIC (AUC/MIC). Therefore, it is recommended to use a target of AUC/MIC between 400 and 600 mg*h/L (assuming an MIC of 1 mg/L) that should be achieved with 48 h of therapy.[329] When the MIC is >1 mg/L, the probability of achieving an AUC/MIC ≥400 is unlikely. In that clinical scenario, changing therapy should be considered due to the high risk of nephrotoxicity with higher doses of vancomycin. Daptomycin is a lipopeptide antibiotic approved for *S. aureus* bacteraemia and right-sided IE.[330] Cohort studies of *S. aureus* and CoNS IE have shown that daptomycin is at least as effective as vancomycin,[327,328] and, in two cohort studies of MRSA bacteraemia with high vancomycin MICs (>1 mg/L),[331,332] 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.[330,333] Therefore, daptomycin should be given at high doses (10 mg/kg), and most experts recommend its combination with beta-lactams[334] or fosfomycin[335] (beta-lactams [and probably fosfomycin] increase membrane

daptomycin binding by decreasing the positive surface charge) for NVE, and with gentamicin and rifampin for PVE.[326–328] However, in a randomized trial including 352 patients with MRSA bacteraemia, daptomycin or vancomycin combined with i.v. flucloxacillin, cloxacillin, or cefazolin did not result in a significant reduction of the primary composite endpoint of mortality, persistent bacteraemia, relapse, or treatment failure as compared with daptomycin or vancomycin alone.[328] The study was stopped prematurely before recruiting the target number of patients ($n = 440$) due to increased incidence of acute kidney injury in the combination therapy arm and, therefore, the results should be interpreted with caution.

Other alternatives include fosfomycin plus imipenem,[336] ceftaroline,[337] quinupristin–dalfopristin with or without beta-lactams,[338,339] beta-lactams plus oxazolidinones (linezolid),[340] beta-lactams plus vancomycin,[341] and high doses of trimethoprim/sulfamethoxazole and clindamycin.[342,343] These clinical and therapeutic scenarios warrant collaborative management with the Endocarditis Team including an infectious disease specialist, since the evidence is based on very small populations.

Recommendation Table 8 — Recommendations for antibiotic treatment of infective endocarditis due to *Staphylococcus* spp.

Recommendations		Class[a]	Level[b]
IE caused by methicillin-susceptible staphylococci			
In patients with NVE due to methicillin-susceptible staphylococci, (flu)cloxacillin or cefazolin is recommended for 4–6 weeks using the following doses:[264,314,316–318]		I	B
Adult antibiotic dosage and route			
(Flu)cloxacillin[c]	12 g/day i.v. in 4–6 doses		
Cefazolin[e]	6 g/day i.v. in 3 doses		
Paediatric antibiotic dosage and route			
(Flu)cloxacillin[c]	200–300 mg/kg/day i.v. in 4–6 equally divided doses		
Cefazolin[e]	6 g/day i.v. in 3 doses		
In patients with PVE due to methicillin-susceptible staphylococci, (flu)cloxacillin or cefazolin with rifampin for at least 6 weeks and gentamicin for 2 weeks is recommended using the following doses:[264,314,316–318,320]		I	B
Adult antibiotic dosage and route			
(Flu)cloxacillin[c]	12 g/day i.v. in 4–6 doses		
Cefazolin	6 g/day i.v. in 3 doses		
Rifampin	900 mg/day i.v. or orally in 3 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Paediatric antibiotic dosage and route			
(Flu)cloxacillin[c]	200–300 mg/kg/day i.v. in 4–6 equally divided doses		
Cefazolin	6 g/day i.v. in 3 doses		
Rifampin	20 mg/kg/day i.v. or orally in 3 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Allergy to beta-lactams			
In patients with NVE due to methicillin-susceptible staphylococci who are allergic to penicillin, cefazolin for 4–6 weeks is recommended using the following doses:[322–327]		I	B
Adult antibiotic dosage and route			
Cefazolin[e]	6 g/day i.v. in 3 doses		
Paediatric antibiotic dosage and route			
Cefazolin[e]	6 g/day i.v. in 3 doses		
In patients with PVE due to methicillin-susceptible staphylococci who are allergic to penicillin, cefazolin combined with rifampin for at least 6 weeks and gentamicin for 2 weeks is recommended using the following doses:[344]		I	B
Adult antibiotic dosage and route			
Cefazolin[e]	6 g/day i.v. in 3 doses		
Rifampin	900 mg/day i.v. or orally in 3 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Paediatric antibiotic dosage and route			
Cefazolin[e]	6 g/day i.v. in 3 doses		
Rifampin	20 mg/kg/day i.v. or orally in 3 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		

Continued

In patients with NVE due to methicillin-susceptible staphylococci who are allergic to penicillin, daptomycin combined with ceftaroline or fosfomycin may be considered.[322–327]		IIb	C
Adult antibiotic dosage and route			
Daptomycin	10 mg/kg/day i.v. in 1 dose		
Ceftaroline[f]	1800 mg/day i.v. in 3 doses		
OR	OR		
Fosfomycin[g]	8–12 g/day i.v. in 4 doses		
In patients with PVE due to methicillin-susceptible staphylococci who are allergic to penicillin, daptomycin combined with ceftaroline or fosfomycin or gentamicin with rifampin for at least 6 weeks and gentamicin for 2 weeks may be considered using the following doses:[344]		IIb	C
Adult antibiotic dosage and route			
Daptomycin	10 mg/kg/day i.v. in 1 dose		
Ceftaroline[f]	1800 mg/day i.v. in 3 doses		
OR	OR		
Fosfomycin[g]	8–12 g/day i.v. in 4 doses		
Rifampin	900 mg/day i.v. or orally in 3 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
IE caused by methicillin-resistant staphylococci			
In patients with NVE due to methicillin-resistant staphylococci, vancomycin is recommended for 4–6 weeks using the following doses:[345]		I	B
Adult antibiotic dosage and route			
Vancomycin[h]	30–60 mg/kg/day i.v. in 2–3 doses		
Paediatric antibiotic dosage and route			
Vancomycin[h]	30 mg/kg/day i.v. in 2–3 equally divided doses		
In patients with PVE due to methicillin-resistant staphylococci, vancomycin with rifampin for at least 6 weeks and gentamicin for 2 weeks is recommended using the following doses:		I	B
Adult antibiotic dosage and route			
Vancomycin[h]	30–60 mg/kg/day i.v. in 2–3 doses		
Rifampin	900–1200 mg/day i.v. or orally in 2 or 3 divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Paediatric antibiotic dosage and route			
Vancomycin[h]	30 mg/kg/day i.v. in 2–3 equally divided doses		
Rifampin	20 mg/kg/day i.v. or orally in 2 or 3 divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
In patients with NVE due to methicillin-resistant staphylococci, daptomycin combined with cloxacillin, ceftaroline or fosfomycin may be considered using the following doses:[335,345–349]		IIb	C
Adult antibiotic dosage and route			
Daptomycin	10 mg/kg/day i.v. in 1 dose		
Cloxacillin[c]	12 g/day i.v. in 6 doses		
OR	OR		
Ceftaroline[f]	1800 mg/day i.v. in 3 doses		
OR	OR		
Fosfomycin[g]	8–12 g/day i.v. in 4 doses		

IE, infective endocarditis; i.m., intramuscular; i.v., intravenous; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis; U, units.
[a]Class of recommendation.
[b]Level of evidence.
[c]Cloxacillin is not recommended if the patient has penicillin allergy.
[d]Maximum doses 240 mg/day. High doses are associated with increased risk of nephrotoxicity. 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 h after injection) serum concentrations should be ~10–12 mg/L.
[e]Cefazolin can replace cloxacillin only in patients with non–immediate-type hypersensitivity reactions to penicillin.
[f]High doses of ceftaroline may be associated with risk of leucopaenia after 2 weeks. Ceftaroline can replace cloxacillin only in patients with non–immediate-type hypersensitivity reactions to penicillin.
[g]In patients with heart failure, the high load of sodium associated with the use of fosfomycin can lead to acute heart failure.
[h]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 (Cmin) 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 h after completion of the i.v. infusion of the antibiotic.

7.8. *Enterococcus* spp.

Enterococcal IE is primarily caused by *E. faecalis* (90% of cases) and less often by *Enterococcus faecium* (5% of cases), or other species.[350] Enterococcal IE poses 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.[351–353] Second, they may be resistant to multiple drugs, including aminoglycosides (HLAR), beta-lactams (via PBP 5 modification and sometimes beta-lactamases), and vancomycin.[351–357]

Penicillin-susceptible strains are treated with penicillin G or ampicillin (or amoxicillin) combined with gentamicin. However, ampicillin (or amoxicillin) is preferred since the MIC is two to four times lower than that of penicillin G. Gentamicin resistance is frequent in both *E. faecalis* and *E. faecium* (up to 75%).[358,359] An aminoglycoside MIC >128 mg/L (HLAR) is associated with the loss of bactericidal synergism with cell wall inhibitors, and aminoglycosides should not be used in such conditions.

There have been two important advances in recent years. First, in several cohort studies of *E. faecalis* IE including hundreds of cases, it was observed that ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin for non-HLAR *E. faecalis* IE. The combination of ampicillin plus ceftriaxone was also associated with a beneficial safety profile, due to the lack of nephrotoxicity.[355,360,361] Therefore, this is the combination of choice for treating NVE and PVE caused by HLAR *E. faecalis*. This double beta-lactam therapy is not effective against *E. faecium* and the experience in the treatment of other enterococcal species is very limited. Second, the total daily dose of gentamicin can be given in a single daily dose instead of the 2 or 3 divided doses previously recommended, and the length of the treatment with gentamicin 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.[266,362,363] After 10–14 days of therapy, OPAT or outpatient oral antibiotic therapy should be considered if the patient is clinically stable (see *Section 7.13*).[364–367]

Beta-lactam or vancomycin resistance is 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, teicoplanin, and tigecycline.[353,365,368] Daptomycin 10–12 mg/kg/24 h, always combined with beta-lactams (ampicillin, ertapenem, or ceftaroline) or fosfomycin in order to prevent the development of daptomycin resistance, is the best option for treating multidrug- and vancomycin-resistant enterococcal IE.[369]

Recommendation Table 9 — Recommendations for antibiotic treatment of infective endocarditis due to *Enterococcus* spp.

Recommendations		Class[a]	Level[b]
Beta-lactam and gentamicin-susceptible strains			
In patients with NVE due to non-HLAR *Enterococcus* spp., the combination of ampicillin or amoxicillin with ceftriaxone for 6 weeks or with gentamicin for 2 weeks is recommended using the following doses:[355,360,361]		I	B
Adult antibiotic dosage and route			
Amoxicillin	200 mg/kg/day i.v. in 4–6 doses		
Ampicillin	12 g/day i.v. in 4–6 doses		
Ceftriaxone	4 g/day i.v. in 2 doses		
Gentamicin[c]	3 mg/kg/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Ceftriaxone	100 mg/kg i.v. in 2 doses		
Gentamicin[c]	3 mg/kg/day i.v. or i.m. in 3 equally divided doses		
In patients with PVE and patients with complicated NVE or >3 months of symptoms due to non-HLAR *Enterococcus* spp., the combination of ampicillin or amoxicillin with ceftriaxone for 6 weeks or with gentamicin for 2 weeks is recommended using the following doses:[355,360,361]		I	B
Adult antibiotic dosage and route			
Amoxicillin	200 mg/kg/day i.v. in 4–6 doses		
Ampicillin	12 g/day i.v. in 4–6 doses		
Ceftriaxone	4 g/day i.v. in 2 doses		
Gentamicin[c]	3 mg/kg/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg/day i.v. in 2 doses		
Gentamicin[c]	3 mg/kg/day i.v. or i.m. in 3 equally divided doses		

Continued

High-level aminoglycoside resistance[d]			
In patients with NVE or PVE due to HLAR *Enterococcus* spp., the combination of ampicillin or amoxicillin and ceftriaxone for 6 weeks is recommended using the following doses:[355,360,361]		I	B
Adult antibiotic dosage and route			
Ampicillin	12 g/day i.v. in 4–6 doses		
Amoxicillin	200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	4 g/day i.v. or i.m. in 2 doses		
Paediatric antibiotic dosage and route			
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg i.v. or i.m. in 2 doses		
Beta-lactam resistant *Enterococcus* spp. (*E. faecium*)[e]			
In patients with IE due to beta-lactam resistant *Enterococcus* spp. (*E. faecium*), vancomycin for 6 weeks combined with gentamicin for 2 weeks is recommended using the following doses:[358,359,369]		I	C
Adult antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2 doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2–3 equally divided doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		
Vancomycin-resistant *Enterococcus* spp.[f]			
In patients with IE due to vancomycin-resistant *Enterococcus* spp., daptomycin combined with beta-lactams (ampicillin, ertapenem, or ceftaroline) or fosfomycin is recommended using the following doses:[369]		I	C
Adult antibiotic dosage and route			
Daptomycin	10–12 mg/kg/day i.v. in 1 dose		
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Fosfomycin	12 g/day i.v. in 4 doses		
Ceftaroline	1800 mg/day i.v. in 3 doses		
Ertapenem[g]	2 g/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Daptomycin	10–12 mg/kg/day i.v. in 1 dose (age-adjusted)		
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Fosfomycin	2–3 g/day i.v. in 1 dose		
Ceftaroline	24–36 mg/kg/day in 3 doses		
Ertapenem[g]	1 g/day i.v. or i.m. in 1 dose [if younger than 12 years, 15 mg/kg/dose (to a maximum of 500 mg) twice daily]		

HLAR, high-level aminoglycoside resistance; IE, Infective endocarditis; i.m., intramuscular; i.v., intravenous; NVE, native valve endocarditis; PBP, Penicillin-binding protein; PVE, prosthetic valve endocarditis.
[a]Class of recommendation.
[b]Level of evidence.
[c]Maximum doses 240 mg/day. High doses are associated with increased risk of nephrotoxicity. 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 h after injection) serum concentrations should be ~10–12 mg/L.
[d]High-level resistance to gentamicin: if susceptible to streptomycin, replace gentamicin with streptomycin 15 mg/kg/day in two equally divided doses.
[e]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.
[f]Multiresistance to aminoglycosides, beta-lactams and vancomycin: suggested alternatives are (i) daptomycin 10 mg/kg/day plus either ampicillin 200 mg/kg/day i.v. in four to six doses, ertapenem (2 g/day i.v.), ceftaroline (600 mg/8 h i.v.), or fosfomycin (3 g/6 h i.v.); (ii) linezolid 2 × 600 mg/day i.v. or orally for ≥8 weeks (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 or fosfomycin), consult infectious disease specialists.
[g]High doses of ertapenem are associated with seizures.

7.9. Gram-negative bacteria

7.9.1. *Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, and Kingella*-related species

Haemophilus, *Aggregatibacter* (previously *Actinobacillus*), *Cardiobacterium*, *Eikenella*, and *Kingella* (HACEK) Gram-negative bacilli are fastidious organisms that require special investigations when they are the suspected cause of IE (see also *Section 5*). Because they grow slowly, standard MIC tests may be difficult to interpret. Some HACEK group bacilli produce beta-lactamases, and therefore ampicillin is no longer the first-line option. Conversely, they are susceptible to ceftriaxone, other third-generation cephalosporins, and fluoroquinolones. The standard treatment is ceftriaxone 2 g/day for 4 weeks in NVE and for 6 weeks in PVE. If they do not produce beta-lactamase, ampicillin (12 g/day i.v. in 4 or 6 doses) for 4–6 weeks plus gentamicin (3 mg/kg/day divided into 2 or 3 doses) for 2 weeks is an

option.[370] Ciprofloxacin (400 mg every 8–12 h i.v. or 750 mg every 12 h orally) is a less well-validated alternative.[370–373]

7.9.2. *Non-Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, and Kingella* species

The ICE cohort reported non-HACEK Gram-negative bacteria in 49 of 2761 (1.8%) IE cases.[279,374] Recommended treatment is early surgery plus prolonged (6 weeks) therapy with bactericidal combinations of beta-lactams and aminoglycosides, sometimes with additional quinolones or cotrimoxazole.[375,376] *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.

Table 11 Antibiotic treatment of blood culture-negative infective endocarditis

Pathogens	Proposed therapy[a]	Treatment outcome
Brucella spp.	Doxycycline (200 mg/24 h) plus cotrimoxazole (960 mg/12 h) plus rifampin (300–600 mg/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 (Q fever agent)	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 <1:400, 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 (Whipple's disease agent)[f]	Doxycycline (200 mg/24 h) plus hydroxychloroquine (200–600 mg/24 h)[c] orally for ≥18 months	Long-term treatment, optimal duration unknown

IE, infective endocarditis; Ig, immunoglobulin; i.v., intravenous.
Adapted from Brouqui *et al.*[383]
[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 infectious disease 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.[385]
[d]Several therapeutic regimens have been reported, including ampicillin or amoxicillin, (12 g/24 h i.v.) or cephalosporins (ceftriaxone 2 g/24 h i.v.) combined with aminoglycosides (gentamicin or netilmicin).[381] Dosages are as for streptococcal and enterococcal IE.[379,380]
[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).

7.10. Blood culture-negative infective endocarditis

The main causes of BCNIE are summarized in *Section 5.3.2*.[377,378] Treatment options are summarized in *Table 11*.[379–383] Treatment of Whipple's IE remains highly empirical. Successes have been reported with long-term therapy (>1 year).[384] In cases of CNS 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*. Consultation with the Endocarditis Team, including an infectious disease specialist, is recommended.

7.11. Fungi

Fungi are most frequently observed in PVE and in IE affecting PWID or immunocompromised patients.[386] *Candida* and *Aspergillus* spp. predominate, the latter resulting in BCNIE.[387,388] Mortality is very high (>50%), and treatment necessitates combined antifungal administration and with a low threshold for surgery.[278,387,388] Antifungal therapy for *Candida* IE includes an echinocandin at high doses or liposomal amphotericin B (or other lipid formulations) with or without flucytosine. for *Aspergillus* IE, voriconazole is the drug of choice. Some experts recommend the addition of an echinocandin or amphotericin B.[278,387–390] Suppressive long-term treatment with oral azoles (fluconazole and voriconazole) is recommended, sometimes lifelong.[278,388,389] Consultation with the Endocarditis Team including an infectious disease specialist is recommended.

7.12. Empirical therapy

Treatment of IE should be started promptly. Three sets of blood cultures should be drawn at 30-minute intervals before initiation of antibiotics.[391]

The initial choice of empirical treatment depends on several considerations:

(i) Previous antibiotic therapy.
(ii) IE in a native valve or a prosthesis (and if so, when surgery was performed [early vs. late PVE]).
(iii) 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.
(iv) Cloxacillin/cefazolin administration is associated with lower mortality rates than other beta-lactams, including amoxicillin/clavulanic acid or ampicillin/sulbactam,[392] and vancomycin for empirically treating MSSA bacteraemia/endocarditis.[309,393] However, recently amoxicillin/clavulanic acid or ampicillin/sulbactam might be an effective empirical treatment for MSSA bacteraemia when de-escalated to cloxacillin or cefazolin within 96 h from the index blood culture.[394]

Native valve endocarditis and late PVE regimens should cover staphylococci, streptococci, and enterococci. If the patient was receiving antibiotic therapy, the empirical therapy should include different antibiotics. CoNS should be empirically covered in PVE but not in NVE. 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 within 24 h), the antibiotic treatment must be adapted to its antimicrobial susceptibility pattern. It should be emphasized that the empirical treatment should be changed to targeted therapy once the organism is identified within 24–48 h.

Recommendation Table 10 — Recommendations for antibiotic regimens for initial empirical treatment of infective endocarditis (before pathogen identification)[a]

Recommendations		Class[b]	Level[c]
In patients with community-acquired NVE or late PVE (≥12 months post-surgery), ampicillin in combination with ceftriaxone or with (flu)cloxacillin and gentamicin should be considered using the following doses:[255]		IIa	C
Adult antibiotic dosage and route			
Ampicillin	12 g/day i.v. in 4–6 doses		
Ceftriaxone	4 g/day i.v. or i.m. in 2 doses		
(Flu)cloxacillin	12 g/day i.v. in 4–6 doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Ceftriaxone	100 mg/kg i.v. or i.m. in 1 dose		
(Flu)cloxacillin	200–300 mg/kg/day i.v. in 4–6 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 3 equally divided doses		
In patients with early PVE (<12 months post-surgery) or nosocomial and non-nosocomial healthcare-associated IE, vancomycin or daptomycin combined with gentamicin and rifampin may be considered using the following doses:[395]		IIb	C
Adult antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 doses		
Daptomycin	10 mg/kg/day i.v. in 1 dose		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose		
Rifampin	900–1200 mg i.v. or orally in 2 or 3 doses		
Paediatric antibiotic dosage and route			
Vancomycin[e]	40 mg/kg/day i.v. in 2–3 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 3 equally divided doses		
Rifampin	20 mg/kg/day i.v. or orally in 3 equally divided doses		
Allergy to beta-lactams			
In patients with community-acquired NVE or late PVE (≥12 months post-surgery) who are allergic to penicillin, cefazolin, or vancomycin in combination with gentamicin may be considered using the following doses:		IIb	C
Adult antibiotic dosage and route			
Cefazolin	6 g/day i.v. in 3 doses		
Vancomycin[e]	30 mg/kg/day i.v. in 2 doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Cefazolin	6 g/day i.v. in 3 doses		
Vancomycin[e]	40 mg/kg/day i.v. in 2–3 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 3 equally divided doses		

Continued

BCNIE, blood culture-negative infective endocarditis; IE, infective endocarditis; i.m., intramuscular; i.v., intravenous; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis.

[a]If initial blood cultures are negative and there is no clinical response, BCNIE aetiology (see *Section 7.10*) and the extension of the antibiotic spectrum to blood culture-negative pathogens should be considered. If cardiac surgery is indicated, molecular diagnosis can be performed.

[b]Class of recommendation.

[c]Level of evidence.

[d]Maximum doses 240 mg/day. High doses are associated with increased risk of nephrotoxicity. 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 h after injection) serum concentrations should be ~10–12 mg/L.

[e]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 h after completion of the i.v. infusion of the antibiotic.

7.13. Outpatient parenteral or oral antibiotic therapy for infective endocarditis

Outpatient parenteral antibiotic treatment or step-down outpatient oral antibiotic treatment is used to consolidate antimicrobial therapy once critical infection-related complications are under control (e.g. perivalvular abscesses, acute HF, septic emboli, and stroke) and the patient is clinically stable.[43,396–399] When feasible, early hospital discharge and OPAT helps to alleviate the effects of infection and prolonged hospitalization especially in the elderly.[400] In the initial phase of IE treatment, standard i.v. treatment is administered according to recommendations for specific microorganisms. Once the clinical condition of the patient is stable, OPAT or step-down outpatient oral antibiotic treatment is a safe alternative to in-hospital i.v. treatment in selected patients.[43,399] Patients may reach such stability at various points in their disease course but, when criteria for stability are reached, the patient may then be switched to OPAT or alternatively to an oral therapy at hospital discharge. The OPAT regime consists of the same antibiotic combinations administered in the acute phase if possible. The 5-year outcomes from the POET trial showed continued effectiveness of oral antibiotic therapy as compared with i.v. antibiotic therapy for IE in selected patients.[401] Hence, clinical stability will then differentiate IE courses into two phases:

(i) Critical phase where at least 10 days of i.v. treatment is required: at this time point, OPAT has a restricted indication.
(ii) Continuation phase (beyond 10 days of therapy and 7 days post-surgery), where OPAT/step-down oral therapy may be feasible.

Supplementary data online, Table S8 summarizes the salient questions to address when considering OPAT/step-down oral therapy for IE.

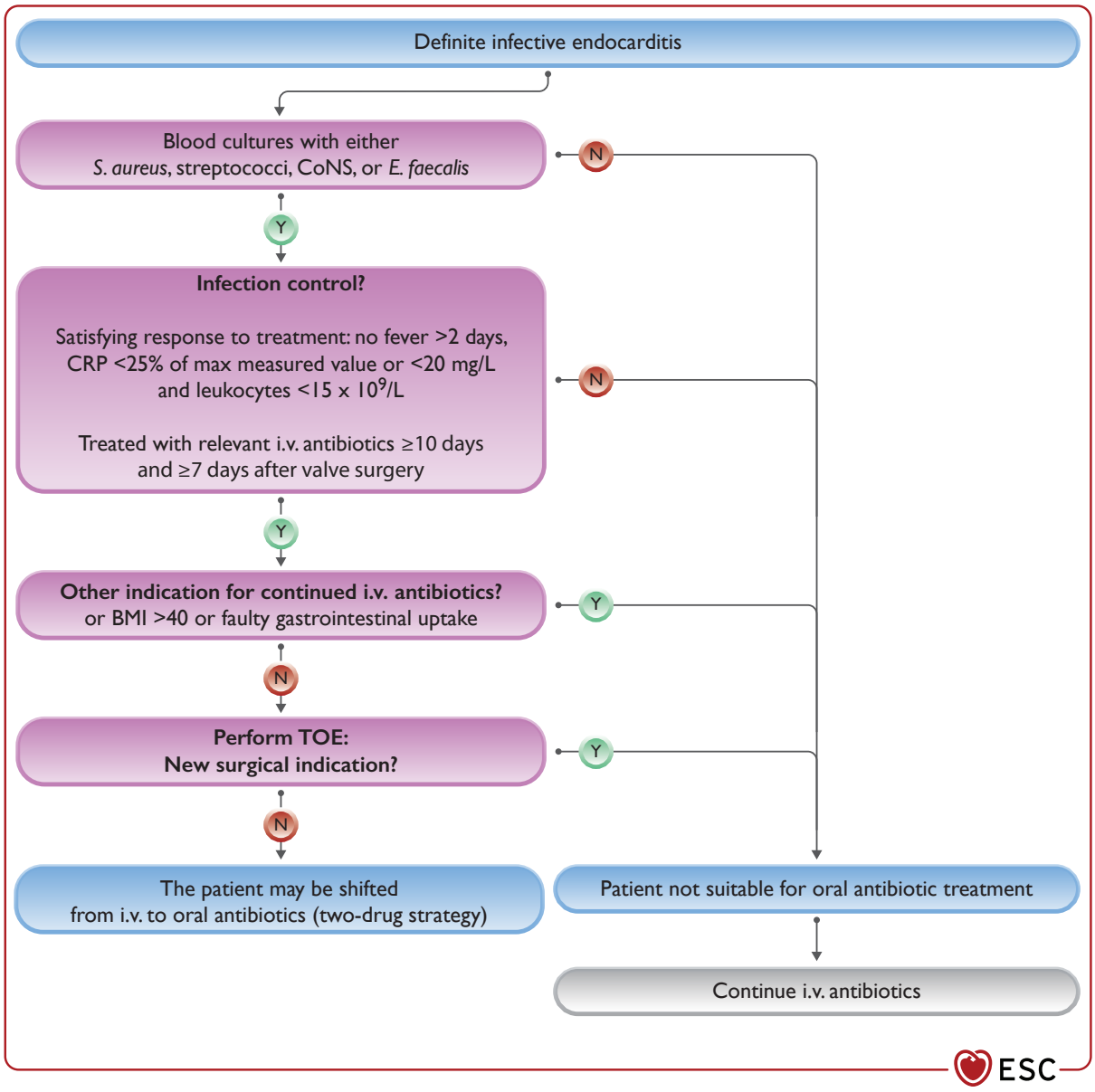

Figure 9 Flowchart to assess clinical stability based on the Partial Oral Treatment of Endocarditis trial. BMI, body mass index; CoNS, coagulase-negative staphylococci; CRP, C-reactive protein; i.v., intravenous; TOE, transoesophageal echocardiography. Adapted with permission from Iversen *et al.*[43]

In addition to the patient being medically stable, general considerations for suitability for OPAT include assessment of the patient's home environment and self-care capabilities. Adherence to treatment and follow-up visits are also crucial for a beneficial outcome of outpatient treatment and the healthcare provider–patient relationship is important for ensuring proper and continued treatment and maintenance of infection control.

7.13.1. Parenteral and oral step-down antibiotic treatment

Stability criteria are essential and timing in the clinical planning the patient's course, especially TOE, becomes key (*Figure 9*). Stability criteria include blood samples, clinical parameters, and TOE.[43]

OPAT has been shown to be a safe treatment in IE for stable patients who are suitable for home treatment.

The patient, and preferably also a caregiver, should be educated carefully in the disease and how to monitor/observe for signs of infection, including daily temperature and other signs of disease progression or complications. In addition, regular post-discharge evaluation is required (nurse once per day, responsible physician 1–3 times per week). For patients receiving OPAT, regular i.v. catheter inspection and care by a healthcare professional should be provided. If the patient is not sufficiently able to self-monitor, and has no close caregivers, added surveillance is required by involved staff and home treatment should generally be carefully considered in such cases.

Certain combinations of two oral antibiotics should be used for oral step-down treatment (see Supplementary data online, *Table S9*).

7.13.2. Other considerations for outpatient oral or parenteral antimicrobial therapy

In the OPAT programme, patients continue with the same antibiotics that are administered in the acute phase in once-daily regimens, or with infusion pumps if antibiotics should be administered intermittently,

or in continuous infusion. Dalbavancin is a glycopeptide antibiotic with a very long half-life that can be administered weekly. There is previous positive experience in sensitive Gram-positive IE, although the most effective administration schedule is not clear.[274,402] The recommended prescription is 1.5 g as a loading dose followed by 0.5–1 g weekly until completing 6 weeks of antibiotic treatment.

Although the evidence is weak, another option (in addition to the combinations listed in the Supplementary data online, *Table S9*) for staphylococcal IE is the combination of i.v. cotrimoxazole (sulfamethoxazole 4800 mg/day and trimethoprim 960 mg/day in 4–6 doses) plus i.v. clindamycin (1800 mg/day in 3 doses) during the first week followed by only oral cotrimoxazole for 5 weeks.[343]

Recommendation Table 11 — Recommendations for outpatient antibiotic treatment of infective endocarditis

Recommendations	Class[a]	Level[b]
Outpatient parenteral or oral antibiotic treatment should be considered in patients with left-sided IE caused by *Streptococcus* spp., *E. faecalis*, *S. aureus*, or CoNS who were receiving appropriate i.v. antibiotic treatment for at least 10 days (or at least 7 days after cardiac surgery), are clinically stable, and who do not show signs of abscess formation or valve abnormalities requiring surgery on TOE.[43,401]	IIa	A
Outpatient parenteral antibiotic treatment is not recommended in patients with IE caused by highly difficult-to-treat microorganisms,[c] liver cirrhosis (Child-Pugh B or C), severe cerebral nervous system emboli, untreated large extracardiac abscesses, heart valve complications, or other severe conditions requiring surgery, severe post-surgical complications, and PWID-related IE.	III	C

CoNS, coagulase-negative staphylococci; IE, infective endocarditis; i.v., intravenous; TOE, transoesophageal echocardiography; PWID, people who inject drugs.
[a]Class of recommendation.
[b]Level of evidence.
[c]Highly difficult-to-treat microorganism: microorganisms requiring i.v. antibiotic combinations that cannot be administered by means of outpatient parenteral antibiotic treatment or that require strict monitoring of drug levels either in blood or in other fluids owing to their potential toxicity or narrow therapeutic index (e.g. MRSA or vancomycin-resistant enterococci also resistant to alternative drugs such as daptomycin and linezolid, multidrug- or extensively drug-resistant Gram-negative rods, highly penicillin-resistant oral streptococci, fungi other than Candida).

8. Indications for surgery and management of main infective endocarditis complications

Infective endocarditis is associated with certain risks and complications that can only be controlled with surgical intervention. Despite the risks of surgery in these patients, current evidence suggests that surgical treatment may generate a survival advantage of up to 20% in the first year.[403,404] There are three main reasons to undergo surgery in the setting of acute IE: HF, uncontrolled infection, and prevention of septic embolization (in particular, to the CNS) (*Figure 10*).

A significant proportion of surgical procedures for IE are performed on an urgent basis. The Task Force has defined urgent surgery as that requiring intervention within 3–5 days, although unnecessary delays should be avoided once the indication for urgent surgery is established. Some cases require emergency surgery (within 24 h), irrespective of the pre-operative duration of antibiotic treatment. A third group requires surgery non-urgently, i.e. within the same hospital admission. In cases where the infective component can be completely healed with antibiotic treatment alone, both timing and indications for treatment of residual valve dysfunction follow the conventional guidelines for valve treatment.[128]

8.1. Pre-operative risk assessment

The risk of surgical therapy during the active phase of IE can be significant. It is heavily influenced by pre-existing co-morbidities and current organ function, but should not be limited by one risk factor alone (e.g. age or liver function).[405,406] The decision to operate should therefore be made by the Endocarditis Team (see *Section 4*),[167] considering urgency of the patient's clinical condition, peri-operative risk, the potential to recover from the infection, and the patient's associated long-term prognosis.[403,404]

There are several scoring systems that predict mortality after general (i.e. non-IE) cardiac surgery and which are in routine clinical use.[407,408] Other scoring systems were designed specifically for the setting of IE including the AEPEI (Association for the Study and Prevention of Infective Endocarditis Study) score, the STS (Society of Thoracic Surgeons) IE score, the PALSUSE (prosthetic valve, age ≥70, large intracardiac destruction, *Staphylococcus* spp., urgent surgery, sex [female], EuroSCORE ≥10) score, the de Feo score, and the ANCLA (anaemia, NYHA [New York Heart Association] class IV, critical state, large intracardiac destruction, surgery of thoracic aorta) score, among others.[256,409–414] Some of these scoring systems are web-based and free of charge (e.g. the AEPEI risk calculator https://www.endocardite.org/index.php/calculateurs/score-de-mortalite-post-chirurgie-aepei). Such scoring systems have been developed based on retrospective data and their performance is variable.[250,256,415–417] In addition, none of these scoring systems are used in daily clinical routine. Therefore, prospective surgical scoring systems with better precision need to be developed, particularly for determining operative futility in prohibitively high-risk patients.

A significant proportion of patients with clear indications for surgery for IE may have multiple risk factors or other reasons that lead to surgery not being performed, and these patients have the worst prognosis.[184,403] Conversely, high-risk but salvageable patients may not be offered life-saving operations on the basis of perceived unacceptable risk, and this is especially true in the elderly (see *Section 12.2*). The complex decision of not offering surgery when indicated should therefore be made in the setting of an Endocarditis Team with experienced surgical input.[418] Determining when operative management for a specific patient is futile requires compassionate multidisciplinary insight along with consideration of the patient's and family's wills (see *Section 13.2*).

8.2. Heart failure

8.2.1. Heart failure in infective endocarditis

Heart failure is the most frequent complication of IE and the main indication for urgent and emergency surgery for IE.[419] The prevalence of HF with left-sided IE is variable and inconsistently defined between reported series, ranging between 19% and 73%.[420–425] Clinical symptoms

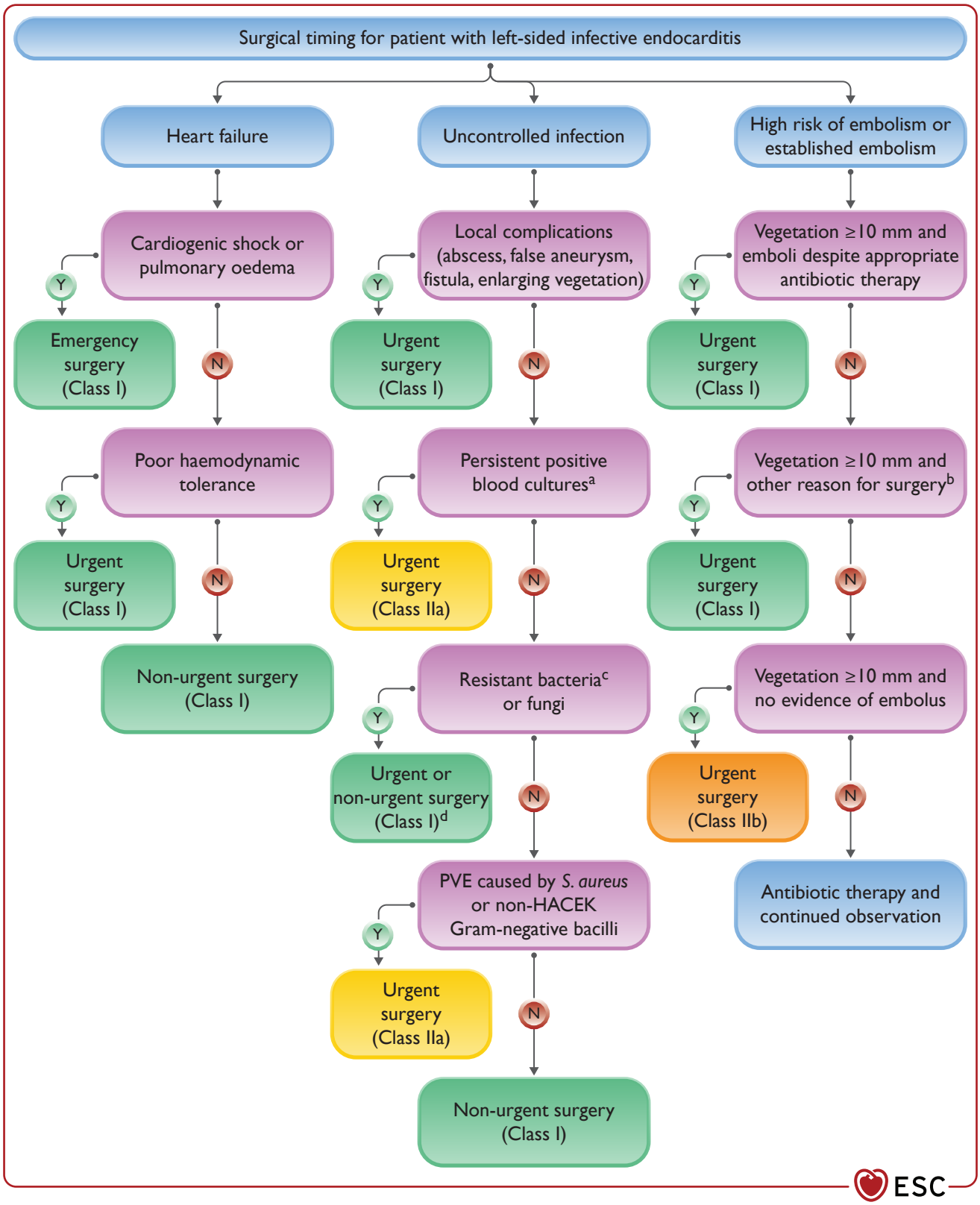

Figure 10 Proposed surgical timing for infective endocarditis. HACEK, *Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, and *Kingella*; PVE, prosthetic valve endocarditis. Surgery timing: emergency, within 24 h. Urgent, within 3–5 days. Non-urgent, within same hospital admission. [a]Despite appropriate antibiotic therapy for >1 week and control of septic embolic foci. [b]E.g. patients with significant valvular dysfunction that is, or is not, a direct result of endocarditis process. [c]*S. aureus* (methicillin resistant and non-methicillin resistant), vancomycin-resistant enterococci, non-HACEK Gram-negative bacteria and fungi. [d]Urgent for *S. aureus*, non-urgent for others.

are mainly caused by congestion and may vary from mild dyspnoea to severe and rapidly worsening dyspnoea, orthopnoea, pulmonary oedema, and cardiogenic shock. Factors associated with increased risk of HF complicating the course of IE include older age, presence of NVE with aortic valve involvement, and high comorbidity.[420–425]

Leaflet perforation and rupture, as well as mitral chordal rupture, lead to new severe valvular regurgitation or worsening of pre-existent valvular regurgitation and subsequent acute HF. Other less common causes of HF include intracardiac fistulae, interference of the vegetation mass with leaflet opening and closure, or myocardial infarction from vegetations embolizing into the coronary arteries. Patients with right-sided IE complicated by HF present with symptoms of right heart congestion, as discussed in *Section 12.6*.

New-onset HF is the predominant clinical presentation in IE patients, whereas worsening of pre-existing HF is less frequent. Cardiogenic shock can be the first presentation in up to 5% of cases, of which half of such patients develop cardiogenic shock within 72 h of admission for IE.[424] On imaging tests, patients with IE complicated by HF present more frequently with lower left ventricular ejection fraction, larger vegetation size, perivalvular abscesses, pseudoaneurysms, and valvular regurgitation secondary to leaflet perforation or rupture.[420–425]

Heart failure complicating IE is independently associated with poor in-hospital and 1-year survival, and surgical treatment is the only effective treatment that is associated with improved survival.[420,421,424,426–430] Even though in-hospital mortality rates increase with the severity of HF presentation, the survival benefit of surgical treatment vs. medical therapy is more pronounced among patients with NYHA functional class III–IV symptoms.[420] TTE provides important information on the severity of the haemodynamic consequences of valve dysfunction. New onset of elevated filling pressures, pulmonary hypertension, and/or pericardial effusion may lead to urgent or emergency recommendation for surgery.[163] Biomarkers such as B-type natriuretic peptide and troponin have been associated with poor prognosis in IE.[431,432]

Patients who are discharged after treatment of IE require subsequent follow-up (see *Section 11*). Heart failure is more likely to develop during follow-up in IE patients who are discharged with valvular regurgitation than in those without regurgitation, particularly if mitral regurgitation is present.[433]

8.2.2. Indications and timing of surgery in the presence of heart failure in infective endocarditis

Timing of surgical intervention in patients with IE (*Figure 10*) complicated by HF should be decided by the Endocarditis Team, although surgery should not be delayed by Endocarditis Team discussions in patients requiring emergency operations. The presence of HF leads to recommendation for surgery in the majority of patients and is the principal indication for urgent surgery in IE patients.[429,434] Emergency surgery should be performed in patients with new-onset NYHA class IV HF symptoms, pulmonary oedema, and/or cardiogenic shock, irrespective of the status of infection or length of antibiotic treatment and when considered non-futile intervention. Urgent surgery is indicated in patients with milder forms of HF (NYHA class II–III) and severe valve regurgitation or echocardiographic signs of haemodynamic compromise (elevated end-diastolic left ventricular pressure, high left atrial pressure, or moderate and severe pulmonary hypertension), or large vegetations. In patients without haemodynamic compromise, i.v. antibiotic therapy and strict clinical and echocardiographic observation are first indicated, and surgery can be temporarily delayed. However, it should be emphasized that early surgery is a good option for patients with surgical indications and low risk of surgery.[403,404]

8.3. Uncontrolled infection

Uncontrolled infection is one of the most common complications of IE and is the second most frequent indication for surgery.[5] Uncontrolled infection is considered to be present when there is: (i) persistent infection or sepsis despite antibiotic therapy; (ii) signs of local infection that do not respond to antibiotic therapy; or (iii) infection with resistant or very virulent organisms.

8.3.1. Septic shock and persistent infection

Septic shock, defined as vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate level greater than 2 mmol/L in the absence of hypovolaemia,[435] is a highly lethal complication of IE and occurs in ~5–10% of patients.[425,436] Risk factors for septic shock include *S. aureus* and Gram-negative bacteria, persistent bacteraemia, nosocomial acquisition, acute renal failure, diabetes mellitus, CNS emboli, and large vegetations.[147,436] Surgery is associated with a significant reduction in early and 1-year mortality for patients with IE and septic shock.[425,436] Urgent surgery is therefore recommended in patients with IE and persistent sepsis or septic shock despite adequate antibiotic therapy, in which surgery is non-futile.

The definition of persistent infection is somewhat arbitrary and consists of fever and persistent positive cultures after 7 days of appropriate antibiotic treatment. It has been demonstrated that persistent blood cultures 48–72 h after initiation of antibiotics are an independent risk factor for hospital mortality.[437] In many cases of persistent infection, antibiotics alone are insufficient to eradicate the infection. Surgery is therefore indicated for persistent infection when extracardiac abscesses (splenic, vertebral, cerebral, or renal) and other potential causes of positive cultures and fever (infected lines and embolic complications) have been excluded. Persistent fever may also be caused as an adverse reaction to antibiotics.[438]

8.3.2. Locally uncontrolled infection

Signs of locally uncontrolled infection include increasing vegetation size, abscess formation, the creation of pseudoaneurysms and/or fistulae, and new atrioventricular block (AVB). The incidence of perivalvular extension ranges from 10% to 30% in NVE with higher incidences found in patients with PVE.[5,439] Perivalvular complications and abscess formation are more frequent in aortic valve than mitral valve IE, and may be higher in patients with bicuspid vs. tricuspid aortic valves.[440] In aortic valve IE, perivalvular extension occurs most frequently in the mitral-aortic intervalvular fibrosa,[441] whereas perivalvular abscesses are usually located posteriorly or laterally in mitral valve IE.[442] Persistent fever and infection, new AVB, chest pain, new heart murmur, recurrent embolism, or HF may indicate perivalvular extension. The diagnosis should be confirmed by TOE, which is more sensitive and specific than TTE.[443] However, mitral annular calcification may obscure small regions of mitral perivalvular extension, particularly in the posterior aspects of the mitral annulus. Cardiac CT has been shown to be an accurate alternative imaging procedure for the evaluation of perivalvular extension of infection, and PET/CT imaging may be particularly helpful in cases of PVE (see *Section 5.4.4*.

8.3.3 Indications and timing of surgery in the presence of uncontrolled infection

Surgery should be considered for uncontrolled infection when antibiotic therapy is ineffective and extracardiac sources are ruled out. Reports in the literature demonstrate that surgery for uncontrolled infection in IE has the potential to improve 1-year survival by 15–20%.[403,429,444]

8.3.3.1. Persistent infection

Uncontrolled infection is present in the form of persistent infection when blood cultures remain positive for >1 week or persistent sepsis despite appropriate antimicrobial therapy and when other causes of bacteraemia have been excluded. Not performing surgery for uncontrolled infection is associated with significantly increased mortality.[444]

8.3.3.2. Locally uncontrolled infection

Uncontrolled infection is also present if signs of local progression, i.e. increasing vegetation size or perivalvular involvement, are observed during follow-up imaging.[5,420,421,445,446] Surgery should be performed urgently (within 3–5 days) in such cases. Rarely, when there are no other reasons for surgery and fever is easily controlled with antibiotics, small abscesses or pseudoaneurysms can be treated conservatively under close clinical and echocardiographic follow-up.[429,444]

8.3.3.3. Infection with resistant or virulent organisms

Microorganisms causing endocarditis that are unlikely to be controlled with current antimicrobial therapy include fungi,[447,448] multiresistant bacteria (e.g. MRSA or vancomycin-resistant enterococci) and, in rare cases, non-HACEK Gram-negative bacteria. *S. aureus* should also be included in this group due to its fast progression and ability to cause local tissue destruction and abscess formation,[5,449] specifically, if a favourable early response to antibiotics is not achieved.[305,312,449] The presence of these organisms should lead to discussions within the Endocarditis Team and urgent surgery.[385,450]

8.4. Prevention of systemic embolism

8.4.1. Incidence of embolic events in infective endocarditis

Embolic events are frequent and potentially life-threatening complications of IE related to the migration of cardiac vegetations.[451,452] The brain and spleen are the most frequent sites of embolism for left-sided IE, while pulmonary embolism is frequent in right-sided and pacemaker lead IE (see *Section 12*). Stroke may be the first clinical manifestation of IE, and is a severe complication that is associated with increased morbidity and mortality.[451,453,454] Embolic events may be clinically silent in up to 50% of patients with IE.[198] Emboli affecting the splenic or cerebral circulation are frequently asymptomatic, and are diagnosed by non-invasive imaging.[197,200] Although whole-body CT imaging (i.e. chest, abdomen, and pelvis) is frequently performed during the work-up for surgery, diagnosis and management of patients is infrequently altered as a result of these investigations.[194] However, cerebral CT may affect clinical decision-making and outcomes when surgery is considered.[452]

Embolic risk in IE is high, with 20–50% of patients being affected.[452,455] The highest incidence of embolic strokes can be observed in the days around the initial diagnosis of IE,[456] and embolic events are often what leads to the initial diagnosis of IE. Embolic risk is highest the day after therapy initiation, and is 10–20 times higher on the day before and after the start of antibiotic treatment compared with 2 weeks before and after.[456] Thus, embolic events occurring after the initiation of antibiotic therapy continuously drop in incidence within the first 2 weeks of antibiotic treatment.[429,455–457] The benefits of surgery to prevent embolism may therefore be greatest during the early stages of therapy, when embolic risk is at its highest.

8.4.2. Predicting the risk of embolism

Predicting the risks of embolization is important for decision-making in IE. Echocardiography plays a key role in identifying potentially embolic structures in the heart,[429,455,456,458] although predicting the time point of embolization remains difficult. Several factors are associated with increased risk of embolism including the size and mobility of vegetations,[455,456,458–460] the location of the vegetation on the mitral valve,[455] the increasing or decreasing size of the vegetation under antibiotic therapy,[455] particular microorganisms (especially *S. aureus*,[455] *S. gallolyticus*,[461] and *Candida* spp.[450]), previous embolism,[455] multivalvular involvement,[458] and biological markers.[462] Among these, the size and mobility of the vegetations are the most important independent predictors of new embolic events.[459,460,463] A recent study, however, demonstrated that vegetation size was predictive of worse outcomes only when present with other indications for surgery (i.e. HF or uncontrolled infection).[464] Staphylococcal endocarditis is also a risk factor for embolization,[465–468] which is particularly important because the incidence of *S. aureus* IE is increasing.[78,469] Risk of neurological complications is particularly high in patients with very large vegetations (>30 mm in length).[451]

Additional factors may need to be taken into account and it may be helpful to use an embolic risk calculator.[470] *S. aureus* infection, previous embolism, vegetation length, age, diabetes, and the presence of atrial fibrillation have been identified as specific risk factors for embolism.[470]

8.4.3. Indications and timing of surgery to prevent embolism in infective endocarditis

Surgical removal of potentially embolic material from the heart may prevent new or additional embolic events. Given the imminent risk and high rates of embolization in patients with mobile and large vegetations,[5,451,455–457,460,471] surgery should be considered urgently (within 3–5 days) in such patients. A prospective randomized trial in young, low-risk patients assessed the effects of early surgery in patients with large vegetations and streptococcal IE.[471] Although there was no difference in all-cause mortality at 6 months between the early surgery and conventional treatment groups, the risk of embolization was significantly reduced with early surgery. Non-randomized observational analyses including patients at higher risk also suggest that early surgery may be beneficial in patients with a high likelihood of embolization,[428,459,472,473] and that initial conservative treatment is associated with increased mortality.[474,475] However, prosthetic dehiscence has also been associated with early surgery in patients with *S. aureus* IE.[429] Individualized decision-making is required to balance the risk of surgery, which is also influenced by pre-operative neurological events or other co-morbidities.[5,453]

The main indications and the timing of surgery to prevent embolism based on the currently available literature are given in Recommendation Table 12 and *Figure 10*.

Recommendation Table 12 — Recommendations for the main indications of surgery in infective endocarditis (native valve endocarditis and prosthetic valve endocarditis)[a]

Recommendations	Class[b]	Level[c]
(i) Heart failure		
Emergency[d] surgery is recommended in aortic or mitral NVE or PVE with severe acute regurgitation, obstruction, or fistula causing refractory pulmonary oedema or cardiogenic shock.[420,423,424,429,476,477]	I	B
Urgent[d] surgery is recommended in aortic or mitral NVE or PVE with severe acute regurgitation or obstruction causing symptoms of HF or echocardiographic signs of poor haemodynamic tolerance.[5,420–422,429]	I	B
(ii) Uncontrolled infection		
Urgent[d] surgery is recommended in locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation, prosthetic dehiscence, new AVB).[5,420,421,429,445]	I	B
Urgent[d] or non-urgent surgery is recommended in IE caused by fungi or multiresistant organisms according to the haemodynamic condition of the patient.[420]	I	C
Urgent[d] surgery should be considered in IE with persistently positive blood cultures >1 week or persistent sepsis despite appropriate antibiotic therapy and adequate control of metastatic foci.[436,437]	IIa	B
Urgent[d] surgery should be considered in PVE caused by *S. aureus* or non-HACEK Gram-negative bacteria[5,385,449]	IIa	C
(iii) Prevention of embolism		
Urgent[d] surgery is recommended in aortic or mitral NVE or PVE with persistent vegetations ≥10 mm after one or more embolic episodes despite appropriate antibiotic therapy.[451,455,457,471,478]	I	B
Urgent[d] surgery is recommended in IE with vegetation ≥10 mm and other indications for surgery.[5,460,465,466,471,478]	I	C
Urgent[d] surgery may be considered in aortic or mitral IE with vegetation ≥10 mm and without severe valve dysfunction or without clinical evidence of embolism and low surgical risk.[460,463,465,473,478]	IIb	B

AVB, atrioventricular block; HACEK, *Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, *Kingella*; HF, heart failure; IE, infective endocarditis; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis.
[a]For right-sided endocarditis, please refer to *Section 12*.
[b]Class of recommendation.
[c]Level of evidence.
[d]Emergency, within 24 h. Urgent, within 3–5 days. Non-urgent, within same hospital admission.

9. Other complications of infective endocarditis

9.1. Neurological complications

Neurological manifestations may occur before or after the diagnosis of IE is established and recurrent events can also take place later in the course of IE.[451] The possibility of IE should be considered in patients who present with stroke, meningitis, or brain abscess. Unexplained fever accompanying a stroke in a patient with valvular disease should trigger the suspicion of IE with blood cultures taken prior to empirical antibiotic therapy.

Symptomatic cerebrovascular complications occur in up to 35% of patients with IE,[145,198,451,452] whereas silent cerebrovascular complications (including ischaemia and microhaemorrhage) occur in up to 80% of patients.[200,204,403] Clinical presentation is variable, but ischaemic stroke and transient ischaemic attack are the most common presentations.[479] Other manifestations include haemorrhage (intracerebral, subarachnoid), meningitis, brain abscess, encephalopathy, and infectious aneurysms. Focal neurological symptoms are present in ∼40% of affected patients, and non-focal presentations occur in approximately one-third.

S. aureus IE is more frequently associated with neurological complications compared with IE caused by other microorganisms. Vegetation size and mobility also correlate with embolic risk.

Neurological complications are associated with excess mortality, as well as long-term morbidity, particularly in the case of stroke.[480] Prompt diagnosis of IE and early initiation of the antibiotic therapy are pivotal to preventing neurological complications. Early cardiac surgery in high-risk patients is key to preventing embolization of vegetations.[471,481] In contrast, antithrombotic/thrombolytic medical therapies are not beneficial.[481–483]

Mechanical thrombectomy may be considered within time limits in selected cases.[484] If mechanical thrombectomy is performed, the retrieved embolic material must be sent off for pathological and microbiological analyses. Neurosurgery or endovascular therapy is recommended for large infective aneurysms, especially when a continuous growth, despite optimal antibiotic therapy or ruptured intracranial infective aneurysms, is observed.[485]

The use of anticoagulation in patients with left-sided IE does not seem to have an effect on the risk of stroke, cerebrovascular haemorrhage, or mortality at 10 weeks and, therefore, continuation of anticoagulation in patients with left-sided IE and with a pre-existing indication for the use of anticoagulants is recommended in the absence of other contraindications.[486] Substitution from oral anticoagulation to heparin in such patients is generally preferred in case of cerebral bleeding or indication for early surgery.

Following a neurological event, the indication for cardiac surgery must be balanced against the peri-operative risk and post-operative prognosis of the patient. Randomized studies are impractical and cohort studies suffer from bias that can only be partially compensated for by statistical methods. The majority of publications demonstrate lower risk of secondary haemorrhagic conversion of uncomplicated ischaemic lesions than the risk of recurrent embolism under antibiotic treatment. Therefore, the available evidence supports early surgery in such patients (see *Section 10.4*).

Recommendation Table 13 summarizes the recommended management of neurological complications in IE; considerations for cardiac surgery after neurological complications are discussed in *Section 10.4*.

9.1.1. The role of cerebral imaging in infective endocarditis

Cerebral imaging is mandatory when neurological complications of IE are suspected. Evaluation should include MRI with and without gadolinium, or CT with and without contrast if MRI is not possible.[487] Vascular imaging should not be performed routinely, and CTA or magnetic resonance angiography (MRA) is probably sufficient for screening when infective aneurysm is suspected. Catheter angiography should be performed in patients in whom an infective aneurysm was diagnosed on CTA or MRA, in patients with an acute brain haemorrhage, or if the suspicion of aneurysm remains despite negative non-invasive techniques, and if mechanical thrombectomy is considered.[488]

In patients without neurological symptoms, cerebral MRI often detects 'silent' lesions such as microbleeds.[204] The lack of association with parenchymal haemorrhage and the absence of post-operative neurological complications in patients with microbleeds suggest that microbleeds should not postpone surgery when indicated.[489]

Recommendation Table 13 — Recommendations for the treatment of neurological complications of infective endocarditis

Recommendations	Class[a]	Level[b]
Brain CT or MRA is recommended in patients with IE and suspected infective cerebral aneurysms.[490]	I	B
Neurosurgery or endovascular therapy is recommended for large aneurysms, those with continuous growth despite optimal antibiotic therapy, and ruptured intracranial infective cerebral aneurysms.[485]	I	C
If non-invasive techniques are negative and the suspicion of infective aneurysm remains, invasive angiography should be considered.[488]	IIa	B
In embolic stroke, mechanical thrombectomy may be considered if the expertise is available in a timely manner.[484]	IIb	C
Thrombolytic therapy is not recommended in embolic stroke due to IE.[481,491]	III	C

CT, computed tomography; IE, infective endocarditis; MRA, magnetic resonance angiography.
[a]Class of recommendation.
[b]Level of evidence.

9.2. Infective aneurysms

An infective (mycotic) aneurysm is a rare but potentially devastating complication of IE. Infective cerebral aneurysms may be asymptomatic, cause headaches, seizures, or focal symptoms, and may progress to a potentially lethal rupture. They are associated with subarachnoid, intracerebral, and intracranial haemorrhage,[201] particularly when the patient is anticoagulated. The true incidence of infective cerebral aneurysms may be underdiagnosed as vascular imaging modalities are not systematically performed in asymptomatic patients. In 168 patients who underwent cerebral angiography with a diagnosis of IE or infected left ventricular assist device were retrospectively reviewed and infective aneurysms were present in 9% of patients.[488] Another series using CTA identified infective aneurysms in up to 32% of patients with left-sided IE.[492]

Digital subtraction angiography (DSA) remains the gold standard diagnostic test for the detection of infective aneurysms.[487] The sensitivity of CTA and MRA progressively increases with the size of the aneurysm. In a large study including 142 patients, the sensitivity for detection of infective aneurysms smaller than 5 mm was 57% for CTA and 35% for MRA, compared with respective 94% and 86% sensitivities for the detection of aneurysms of 5 mm or larger.[493] Compared with the sensitivity of DSA, the sensitivities of CTA and MRA for detecting infective aneurysms are inferior.[488,490] Therefore, in patients with IE and high suspicion of infective aneurysms in whom CTA or MRA are negative, DSA may be considered.[490,494]

Treatment options of infective cerebral aneurysms consist of antibiotic treatment with or without endovascular or surgical therapy, although evidence is limited to case reports and retrospective studies.[495–498] Therefore, management should be discussed among the members of the Endocarditis Team and tailored to individual clinical situations. Shi *et al.*[496] reported that in patients with unruptured infective cerebral aneurysms, antibiotic treatment may have similar outcomes to invasive treatment. However, interventional treatment should be considered in cases of ruptured infective aneurysms or unruptured infective aneurysms that do not respond to antibiotic therapy.[485,495]

Endovascular therapy is highly successful and associated with low morbidity compared with microsurgical and medical management.[487,499] A systematic review including 499 patients with infective cerebral aneurysms reported a 36% rate of aneurysm rupture.[495] Endovascular surgical and conservative therapies were performed in an approximately equal number of patients. Among patients undergoing valve surgery in this series, only 15% underwent cardiac surgery before aneurysm treatment whereas 85% underwent cardiac surgery after aneurysm treatment.[495]

Urgency of cardiac surgery plays a pivotal role in decision-making regarding the type of invasive treatment. Compared with neurosurgical clipping that requires a craniotomy and often at least 2-week delay prior to procedure, cardiovascular surgery can be performed on the same day as endovascular treatment.[485,487,496,499] Finally, endovascular treatment of infective cerebral aneurysms prior to heart valve surgery may be considered, even if no rupture is documented.[499]

9.3. Splenic complications

Splenic complications associated with IE range from asymptomatic infarction[500] and abscess formation[501] through to splenic rupture and cardiovascular collapse.[502] Splenic infarcts are common (~20% of patients in the EURO-ENDO registry) and very often asymptomatic.[5] Up to 5% of splenic infarcts can progress to abscess formation.[503] Persistent or recurrent fever, abdominal pain, and persistent bacteraemia are suggestive for the presence of such complications. Patients with suspected splenic complications should be evaluated with ultrasound, abdominal CT, MRI, or PET/CT.[504]

Treatment of splenic complications includes conservative medical therapy with appropriate antibiotics for splenic infarction or for antibiotic-responsive abscesses, although antibiotic penetration may be poor in these circumstances. When an abscess is large, splenectomy may be considered, but the timing of splenectomy in relation to heart valve surgery needs careful assessment.[505] Splenectomy and heart valve surgery are seldom performed in the same operative episode.[506] Splenectomy is usually performed prior to valve surgery due to concerns of dissemination and reinfection of the heart valve.

Nevertheless, one case series reported that it is safe to address the splenic abscess with splenectomy after valve repair.[502] Alternatives to open splenectomy, i.e. percutaneous drainage[507] and/or laparoscopic surgery,[508] may be considered in patients with high surgical risk. After splenectomy, vaccination against encapsulated microorganisms (*S. pneumoniae*, *N. meningitis*, and *Haemophilus* spp.) is recommended.

9.4. Myocarditis and pericarditis

The actual prevalence of acute myocarditis in the setting of IE is unknown. Myocarditis will usually present in the form of acute HF and/or ventricular arrhythmias indicating myocardial involvement in the inflammatory process most likely mediated by an immune mechanism. Differential diagnosis and exclusion of other potential complications are best assessed using echocardiography and cardiac MRI.[509–511]

Pericarditis is an infrequent complication of IE. In one retrospective series of 95 patients with aortic valve IE, 19% developed pericarditis usually related to ring abscess formation. The same authors also described a 12% rate of pericarditis associated with mitral valve IE.[512,513] The pathophysiological mechanisms most commonly involved in IE-related pericarditis are the extension of inflammation from an infective aneurysm of the aortic root or valve ring abscess, an embolus in an extramural coronary artery, or the rupture of an infective aneurysm. In a recent large series of NVE, pericardial effusion was observed in 7.8% of patients and was associated with a higher risk of HF during admission. After adjusting for possible confounders, patients did not have a higher rate of surgery, and the presence of pericardial effusion was not associated with a higher in-hospital or 1-year mortality.[513]

9.5. Heart rhythm and conduction disturbances

Due to the critical anatomical relationship between heart valves and the conduction system, AVB may complicate the clinical presentation of IE. The atrioventricular node (AVN) and His bundle lie in close proximity to the insertion of the septal leaflet of the tricuspid valve, the aortic root (below the non-coronary and right coronary cusps), and the mitral annulus.[514] A paravalvular abscess of these valves, especially of the aortic valve, may lead to AVB, and new electrocardiographic AVN conduction abnormalities are indicative of a paravalvular extension of the infection. In the EURO-ENDO registry, conduction abnormalities were observed at diagnosis in 11.5% of patients, including first-degree AVB in 8.1%, second-degree AVB in 0.6%, and third-degree AVB in 2.8% of cases.[5] New-onset AVB caused by local extension of IE (i.e. abscess) is an indication for urgent cardiac surgery.

Atrioventricular block may not only occur as a complication of paravalvular extension of the infection, but it may also develop as a consequence of valve surgery. In a series of 444 patients who survived cardiac surgery for IE,[515] 12.8% of patients required pacemaker implantation for AVB. Multivariable analysis identified that prolonged pre-operative PR and QRS intervals, *S. aureus* infection, presence of aortic root abscess, tricuspid valve involvement, and prior valvular surgery were independently associated with the need for post-operative pacemaker implantation.

Pacemaker implantation should be considered in patients with surgery for valvular endocarditis and complete AVB if one or more of these risk factors is present.[515]

Recommendation Table 14 — Recommendations for pacemaker implantation in patients with complete atrioventricular block and infective endocarditis

Recommendations	Class[a]	Level[b]
Immediate epicardial pacemaker implantation should be considered in patients undergoing surgery for valvular IE and complete AVB if one of the following predictors of persistent AVB is present: pre-operative conduction abnormality, *S. aureus* infection, aortic root abscess, tricuspid valve involvement, or previous valvular surgery.[515]	IIa	C

AVB, atrioventricular block; IE, infective endocarditis.
[a]Class of recommendation.
[b]Level of evidence.

9.6. Musculoskeletal manifestations

9.6.1. Osteoarticular infective endocarditis-related infections

Metastatic bone or joint IE-related lesions are relatively frequent due to the spread of the pathogen through the bloodstream and its subsequent tissue implantation. Although these lesions are considered an IE-related distal lesion or complication because infected valves are a continuous source of bacteraemia, it is often impossible to determine whether the primary infection is the valve or the osteoarticular infection. Overall, the incidence of osteoarticular infection among patients with IE is 6–8%, including bones, joints, and vertebral discs.[5,145,247,516]

The prevalence of spondylodiscitis ranges from 2% to 10% in patients with IE, including symptomatic and asymptomatic cases,[248,517] while series of spontaneous spondylodiscitis have reported co-existing IE in up to 20–30% of patients.[518–520] In general, the rate of IE is 10 times higher in patients with known spondylodiscitis. Therefore, in patients with a definite diagnosis of pyogenic spondylodiscitis and positive blood cultures, TTE/TOE is recommended to rule out IE.[521]

The most frequent microorganisms associated with spondylodiscitis are *S. aureus*, followed by *Streptococcus* spp., CoNS, and *Enterococcus* spp.[247,248,305,517–523]

The most common symptom of spondylodiscitis is back pain, although only 4% of patients with IE and back pain have spondylodiscitis.[32,522] An MRI should be performed to accurately diagnose spondylodiscitis. Computed tomography can detect indirect signs of spondylodiscitis: loss of disc height, erosion/destruction of the endplates and vertebral bodies, and paravertebral soft tissue phlegmonous changes or abscess.[206] Whole-body [18F]FDG-PET/CT can also identify spondylodiscitis.[30,32,524] Indeed, spondylodiscitis is frequently detected as an incidental finding when PET/CT is performed for the diagnosis of PVE. Imaging techniques can also be helpful in guiding biopsies to obtain material for cultures in cases of suspected IE with negative blood cultures.[206]

Antibiotic treatment adapted to the antimicrobial susceptibility pattern is appropriate for most cases of spondylodiscitis. The outcome is usually favourable with the 4- to 6-week IE treatment course. Prolonged therapy is necessary in patients with IE caused by difficult-to-treat microorganisms, such as *S. aureus* or *Candida* spp., or in those with epidural or perivertebral abscesses.[523,525] In patients with neurological deficits or severe spinal instability, the indication for

surgical spinal treatment should be considered.[526] In patients with urgent indication for cardiac surgery, the presence of these lesions does not contraindicate the cardiac intervention. Spondylodiscitis does not appear to worsen the prognosis of patients with IE but delaying the diagnosis of IE in patients with spondylodiscitis is associated with poor prognosis.[248,517–520]

9.6.2. Rheumatological manifestations

The pathogenesis of rheumatological manifestations and musculoskeletal symptoms in IE is not well established. The probable immunological-inflammatory aetiology of this clinical presentation is supported by a variety of antibodies and laboratory markers, the sterility of the synovial fluid, and the rapid resolution without sequelae.[527] Myalgia and back pain are reported in 12–15% of cases. Arthralgia occurs in ~10% of patients, sometimes sequentially affecting several joints. Slightly less often are symptoms of peripheral arthritis preferentially involving the major and proximal joints at the lower extremities.[5,145,182,516]

Sacroiliitis is less frequently observed (1% of cases) as well as polymyalgia rheumatic-like syndrome with pain and morning stiffness of the shoulders and hips, proximal muscle weakness (0.9% of cases), and cutaneous leucocytoclastic vasculitis (purpuric skin lesions, 3.6% of cases).[182,527,528] Rheumatological manifestations and musculoskeletal symptoms show rapid and complete resolution with antibiotics and their presence does not impact on the prognosis of IE.[182,529]

Recommendation Table 15 — Recommendations for patients with musculoskeletal manifestations of infective endocarditis

Recommendations	Class[a]	Level[b]
MRI or PET/CT is recommended in patients with suspected spondylodiscitis and vertebral osteomyelitis complicating IE.[30,32,206,524]	I	C
TTE/TOE is recommended to rule out IE in patients with spondylodiscitis and/or septic arthritis with positive blood cultures for typical IE microorganisms.[247,248,517–521,523]	I	C
More than 6-week antibiotic therapy should be considered in patients with osteoarticular IE-related lesions caused by difficult-to-treat microorganisms, such as *S. aureus* or *Candida* spp., and/or complicated with severe vertebral destruction or abscesses.[523,525,530]	IIa	C

IE, infective endocarditis; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/computed tomography, TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography.
[a]Class of recommendation.
[b]Level of evidence.

9.7. Acute renal failure

Acute renal failure is a common complication of IE and is associated with increased morbidity and mortality as well as significant increase in length and cost of hospitalization.[5,531–534] Additionally, renal failure is an independent predictor of poor outcome after cardiac surgery.[417] However, acute renal failure should not be a reason to delay cardiac surgery. The EURO-ENDO registry reported that in patients with IE, acute renal failure was the second most common complication with an incidence of almost 18%.[5] Some single-centre studies that specifically reported on the incidence of acute renal failure (using standardized criteria) in patients with IE reported that any degree of acute renal failure from mild to severe might be observed in 40–69% of cases.[532,535,536] Severe renal failure requiring haemodialysis has been reported in 6% of patients with IE and it is associated with a very high risk of mortality (40%).[537]

Several factors may be responsible for the onset or worsening of renal dysfunction: (i) immune complex and vasculitic glomerulonephritis; (ii) renal infarction due to septic emboli;[538,539] (iii) haemodynamic impairment in patients with HF; (iv) antibiotic and other drug toxicity (notably related to aminoglycosides, vancomycin, nafcillin, amoxicillin, oxacillin, concomitant use of non-steroidal anti-inflammatories, and/or high dose loop diuretics); and (v) nephrotoxicity of contrast agents used for diagnostic imaging techniques.[417,531,534,535,537,540]

To reduce the incidence of acute renal failure, nephrotoxic antibiotics should be avoided if possible or, if not possible, serum levels (aminoglycosides and vancomycin) as well as creatinine should be closely monitored, and the optimal dose of medication should be periodically re-evaluated and discussed with the Endocarditis Team and a pharmacologist.[536] Loop diuretics should also be used cautiously and other potentially nephrotoxic drugs, such as non-steroidal anti-inflammatories, should be avoided.[536] Similarly, the use of nephrotoxic contrast agents for diagnostic imaging techniques should be carefully evaluated and avoided when possible.

In patients with IE and a reduced glomerular filtration rate, contrast enhanced abdominal ultrasound or MRI are reasonable tests to diagnose embolization as cause of renal function impairment.[541]

10. Surgical therapy: principles and methods

Surgery has been demonstrated to be an independent predictor of survival in many retrospective studies of IE patients under various clinical conditions and offers a potential curative therapy to select patient groups.[5,250,403,404,421,436] Optimal management of such patients may lead to lower peri-operative complication rates and further potential benefits of surgical therapy.

10.1. Pre-operative and peri-operative management

10.1.1. Coronary angiography

When cardiac surgery becomes necessary in IE, assessment of coronary anatomy is recommended (see Recommendation Table 16). Classically, pre-operative coronary angiography is recommended for men >40 years, post-menopausal women, and in those with one or more cardiovascular risk factors or history of CAD.[128] The presence of aortic valve vegetations may preclude invasive coronary angiography due to the risk of iatrogenic embolization.[542,543] However, some studies have demonstrated the safety of performing invasive coronary angiography in the presence of aortic valve vegetations, particularly in patients without very large and mobile vegetations.[193,544] Alternatively, coronary CTA can be used to rule out significant coronary obstructions. Furthermore, surgery may need to be conducted without detailed information on coronary anatomy in certain clinical conditions, particularly emergencies. Of note, a recent study questioned the need for coronary artery bypass grafting of non-critical lesions at the time of surgery for IE and suggested that such concomitant intervention may have a negative impact on peri-operative outcomes.[545]

Recommendation Table 16 — Recommendations for pre-operative coronary anatomy assessment in patients requiring surgery for infective endocarditis

Recommendations	Class[a]	Level[b]
In haemodynamically stable patients with aortic valve vegetations who require cardiac surgery and are high risk for CAD, a high-resolution multislice coronary CTA is recommended.[185,546]	I	B
Invasive coronary angiography is recommended in patients requiring heart surgery who are high risk for CAD, in the absence of aortic valve vegetations.	I	C
In emergency situations, valvular surgery without pre-operative coronary anatomy assessment regardless of CAD risk should be considered.[543,545]	IIa	C
Invasive coronary angiography may be considered despite the presence of aortic valve vegetations in selected patients with known CAD or at high risk of significant obstructive CAD.[193,543,544]	IIb	C

CAD, coronary artery disease, CTA, computed tomography angiography.
[a]Class of recommendation.
[b]Level of evidence.

10.1.2. Extracardiac infection

Extracardiac foci may be treated prior to valve surgery, during the valve operation, or post-operatively, dependent on the urgency of cardiac surgery. Regardless of the timing of intervention, infective foci need to be eradicated before completion of antibiotic therapy in order to avoid cardiac valve reinfection.

10.1.3. Intra-operative echocardiography

Intra-operative TOE provides contemporaneous assessment of the extent of infection prior to valve repair/replacement. Extent of infection, stability of known vegetations, re-assessment of previously uninvolved heart valves, and biventricular function are routinely performed with intra-operative TOE. Intra-operative TOE post-surgical repair is mandatory to determine the immediate result and establish a baseline for follow-up comparisons.[547]

10.2. Other intra-operative considerations

Specific peri-operative management considerations are necessary in all IE patients undergoing valve surgery, particularly in those following stroke (see *Section 10.3*). Pre-operative antibiotic therapy must be continued intra-operatively, and doses may need to be repeated in case of prolonged operations or major bleeding. Although the pharmacokinetics of antibiotic therapy is altered during cardio-pulmonary bypass (CPB), adjustment of doses is rarely required.[548] In general, ongoing IE antibiotic treatment offers appropriate surgical site infection prophylaxis. However, when the antibiotic treatment for IE does not fully cover normal surgical prophylactic treatment, conventional prophylaxis should be added. Intra-operative bleeding management is often complicated by marked coagulopathy in patients with IE, particularly those undergoing surgery during persistent sepsis. The management of hypotension and vasoplaegia is particularly challenging in patients presenting with septic shock, and accompanying vasoplaegia tends to worsen significantly during CPB. Norepinephrine is frequently used as first-line therapy for septic shock, followed by vasopressin or terlipressin in cases of resistant vasoplaegia.[549] Methylene blue may be used as a rescue agent in patients who are unresponsive to these measures, but mortality rates are high for such patients.[550]

Retrospective studies have suggested that the use of haemoadsorbent filters during CPB may decrease the negative effects associated with cytokine cascade activation.[551] A recent RCT of haemoadsorption during cardiac surgery in IE patients, however, failed to demonstrate any beneficial effects with regards to adverse events or end-organ function.[552]

10.3. Surgical approach and techniques

Surgery for IE aims to remove infected structures followed by re-establishment of anatomy and haemodynamic function. With regards to the involved heart valve(s), repair or replacement is carried out based on the extent of destruction, acuity of disease, and patient characteristics.[553] Appropriate collection and labelling of tissue samples for pathological, microbiological, and molecular biological analyses are necessary to help guide antibiotic treatment.

Aortic valve replacement is usually required for aortic IE. Aortic valve repair is very uncommon in the acute situation but may be performed for isolated aortic regurgitation after healed endocarditis. In mitral IE, leaflet perforations with preserved free margin and chordae tendinae may be treated with patch repair, particularly in the setting of subacute or healed IE. Although mitral valve repair is feasible in more complex mitral IE involving the annuli, the leaflet free edge, and/or chordae, evidence showing the feasibility and durability of such repair techniques is scarce.[554,555] A large registry on mitral repair vs. replacement in IE was limited by the lack of information on severity of IE, different patient group profiles, and significantly higher incidence of staphylococcal endocarditis in the mitral valve replacement group.[556] Therefore, it cannot be concluded that mitral valve repair is superior to replacement due to the high probability of selection bias. Valve preservation in acute IE should only be attempted if a durable repair is anticipated and complete eradication of infected tissue can be achieved. However, valve repair may be necessary in children, where valve replacement options are more limited.

Invasion of the aortic annuli may create shallow defects (very limited abscess or small pseudoaneurysms) that are still amenable to conventional valve replacement surgery. When disease progresses into an extensive aortic root abscess or periannular destruction, aortic root replacement is usually required. In experienced centres, the use of allografts has been preferred as they have the advantage of adapting to irregular surfaces and provide haemostatic advantages with very good haemodynamic function and low thrombo-embolic risk, and can be used to repair concomitant lesions of the anterior mitral valve leaflet.[557,558] Additionally, allografts and stentless bioprostheses can be beneficial in small aortic roots and are associated with low reinfection rates. However, experience is generally limited to single-centre case series and there is no clear evidence of superiority of one valve substitute over the other.[559] In very selected patients and children in particular, the Ross operation (pulmonary valve autotransplantation) may be considered for aortic root IE.[128]

The use of patches to cover abscess cavities and prevent extensive resection and reconstruction is discouraged in aortic root IE as it may be associated with recurrences, periprosthetic leaks, and pseudoaneurysm formation. After exclusion from the circulation, abscess and pseudoaneurysm cavities are left to drain into the pericardial cavity.

When periannular infection of the aortic root extends into the intervalvular fibrosa body, complex surgical reconstructions are required and are frequently the only option to achieve patient survival. The reported

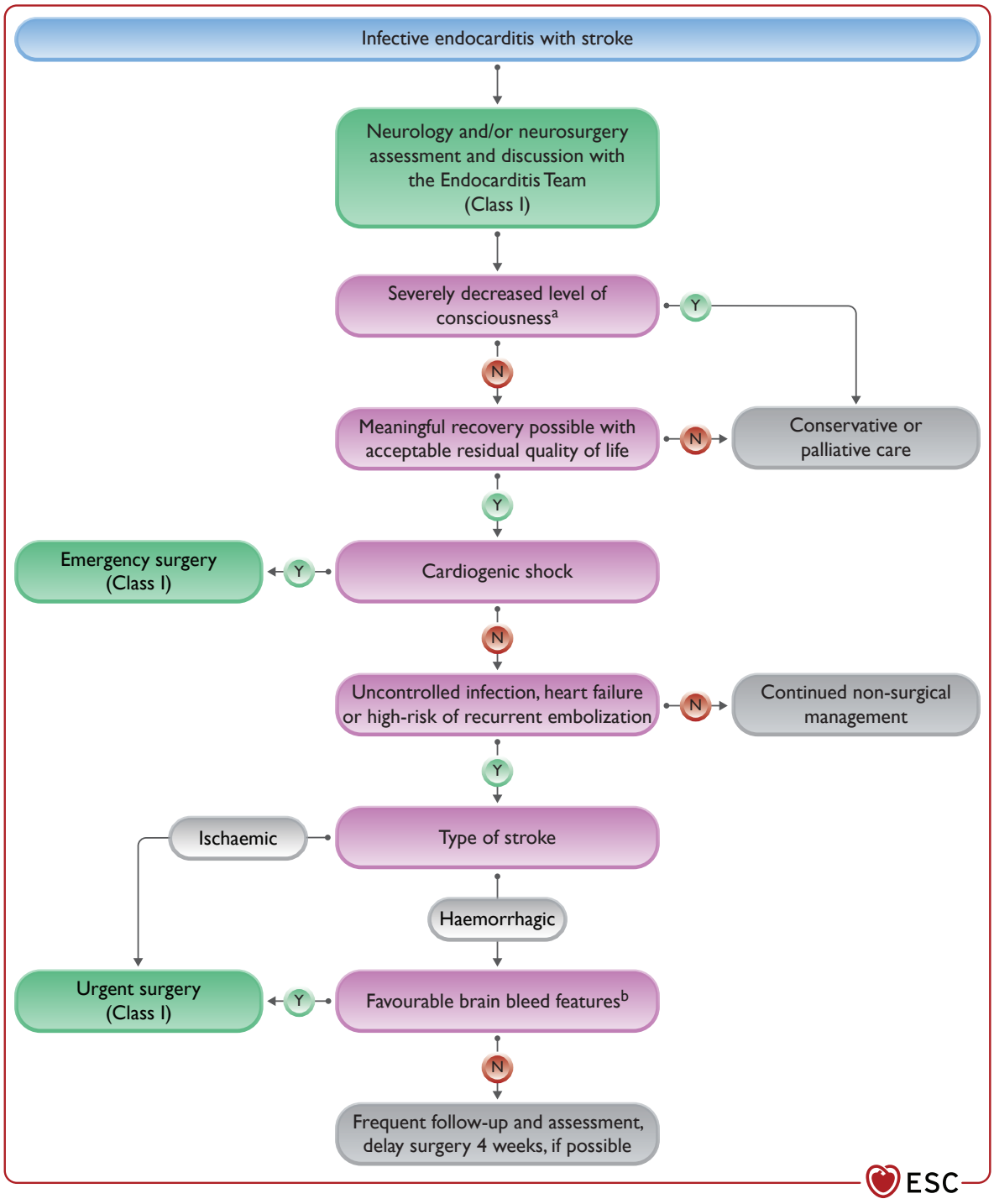

Figure 11 Surgery for infective endocarditis following stroke. NIHSS, National Institutes of Health Stroke Scale Score. Surgery timing: emergency, within 24 h. Urgent, within 48–72 h. Non-urgent, within same hospital admission. [a]Glasgow Coma Scale ≤4 or NIHSS >18. [b]Intracranial haemorrhage volume <30 mL or NIHSS <12.

pooled peri-operative survival rate of such surgical technique is 84%.[560] Even more extensive repairs may be required for cases involving the intervalvular fibrosa, central fibrous body, and mitral valve, with or without fistulation to the right-side chambers. These operations are technically complex and require a surgeon who is very experienced in IE, which may not be available in every cardiovascular surgery department.

Exceptionally, heart transplantation has been utilized for carefully selected patients without other surgical options.[561]

10.3.1. Choice of valve prosthesis

Many patient characteristics are taken into account when deciding the type of valve prosthesis to implant in a given patient with IE. The studies published to date evaluating various valve prostheses in the setting of IE, however, suffer from numerous biases.[90,559,562–566]

Beyond the patient characteristics that apply in the non-IE setting,[128] valve selection in IE is influenced by the presence of recent stroke, risk of new-onset bleeding, complexity of expected post-operative course,

Table 12 Features favouring a non-mechanical valve substitute in the setting of surgery for acute infective endocarditis

Early surgery after a recent ischaemic stroke
Evidence of intracranial bleeding
Woman of childbearing age
High likelihood of prolonged mechanical circulatory support
Advanced age or frailty
Poor or unknown medical compliance
Expected complicated and prolonged post-operative course
Patient preference

and the ability of the patient to participate in decision-making, especially for emergency surgery (*Table 12*). In the absence of specific contraindications for a particular valve substitute, patient preferences should determine the final decision.

10.4. Timing of surgery after ischaemic and haemorrhagic stroke

There is a general trend of offering early surgery in IE in light of the improved operative outcomes and survival benefits observed with operative management.[451,567] For patients who have suffered a neurological injury, however, the optimal timing of surgery remains to be defined.[568] There are no RCTs specifically assessing this clinically relevant issue and contemporary evidence arises from observational studies.[415,454,473,569,570]

Neurological exacerbation may occur during surgery or early post-operatively due to the altered physiology conditions during and immediately after cardiac repair.[571] Several peri-operative variables should be addressed in order to lower the risk of neurological deterioration and haemorrhagic transformation post-stroke (see Supplementary data online, *Table S10*).

The risk of neurological exacerbation during surgery needs to be balanced against that of delaying a cardiac operation. When haemodynamic disturbances are present, surgery should be pursued without delay (see *Figure 11* and Recommendation Table 17).[451,468,473,567,568,570–578] A more common situation occurs when surgery is considered for the prevention of recurrent embolism after stroke, due to the presence of large vegetations (>10 mm). In patients that have suffered a transient ischaemic attack, the risk of surgery is usually low and surgery should be performed without delay. For patients with ischaemic stroke, multiple observational data exist supporting a non-delayed (urgent) intervention, unless the neurological status is poor (i.e. coma or extensive damage leading to poor functional prognosis).[573,578] Involvement of an expert neurology/neurosurgical specialist will help in risk assessment discussions.

The risk of post-operative haemorrhagic conversion after pre-operative stroke is reported in the range of 2–7%.[453,579] Remarkably, bleeding transformation after cardiac surgery can also occur in patients with silent pre-operative cerebral embolisms, with similar frequency as in patients with overt neurological deficits. Unfortunately, these events cannot currently be accurately predicted prior to surgery. When haemorrhagic transformation occurs, it is associated with high mortality (40%) and may require rescue neurointerventional or neurosurgical treatment to control bleeding or allow cerebral decompression by means of craniectomy.[577,580]

Several retrospective studies report benefits of early surgery (within 2 weeks) after haemorrhagic stroke without further compromising neurological outcomes.[574,581,582] Decisions should be taken on a case-by-case basis by the Endocarditis Team, including a neurologist, and should be adapted to the mechanism of intracranial haemorrhage and its severity including intracranial haemorrhage volume measurement and National Institutes of Health Stroke Scale Score (NIHSS) score (see *Figure 11*).[495] In patients in whom surgery is delayed, repeat CT or MRI imaging should be performed 1–2 weeks following intracranial haemorrhage (or earlier in the case of clinical deterioration) in order to assess stability of the cerebral finding and potentially re-assess timing of surgery. The timing of surgery after intracranial haemorrhage is controversial and an area where further evidence is urgently required.

Recommendation Table 17 — Indications and timing of cardiac surgery after neurological complications in active infective endocarditis

Recommendations	Class[a]	Level[b]
After a transient ischaemic attack, cardiac surgery, if indicated, is recommended without delay.[454,468]	I	B
After a stroke, surgery is recommended without any delay in the presence of HF, uncontrolled infection, abscess, or persistent high embolic risk, as long as coma is absent and the presence of cerebral haemorrhage has been excluded by cranial CT or MRI.[451,468,473,567,568,570–578]	I	B
Following intracranial haemorrhage, delaying cardiac surgery >1 month, if possible, with frequent re-assessment of the patient's clinical condition and imaging should be considered.[571]	IIa	C
In patients with intracranial haemorrhage and unstable clinical status due to HF, uncontrolled infection or persistent high embolic risk, urgent or emergency surgery should be considered weighing the likelihood of a meaningful neurological outcome.[199,581–584]	IIa	C

CT, computed tomography; HF, heart failure; MRI, magnetic resonance imaging.
[a]Class of recommendation.
[b]Level of evidence.

10.5. Post-operative complications

Post-operative management of patients with IE may be challenging due to pre-operative multiorgan involvement and often complex surgical procedures. The risk of in-hospital mortality associated with IE surgery remains high (10–20%), particularly in patients >75 years of age, usually due to co-morbidities and complications of IE. Further research should focus on methods to lower surgical mortality.

The most frequent serious post-operative complications are coagulopathy requiring extensive use of blood products and clotting factors, re-exploration of the thorax due to bleeding/tamponade, haemodialysis, stroke, or cerebral haemorrhagic transformation of prior cerebrovascular lesions, low cardiac output syndrome, respiratory complications and tracheostomy, prolonged hospital stay, and need for a permanent pacemaker.[515,585,586] When mortality occurs, the cause of death is often multifactorial. Post-mortem examination is helpful for determining the cause of death, further understanding of disease process, teaching purposes at academic environments, and quality control.

10.6. Management of antithrombotic therapy after surgery

The management of antithrombotic therapy early after surgery for IE may need to be altered when compared with non-IE clinical scenarios (see also *Section 12.10*).[128] This is mainly due to known increased risk of intracranial haemorrhage after cerebral embolism. Restrictive or tailored use of antiplatelet and antithrombotic agents after surgery are key to avoid further complications,[203,587] which is more feasible in patients who received bioprosthetic valve prostheses or valve repair operations than after mechanical valve replacement surgery.

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

Following in-hospital treatment, patients should be followed-up for the occurrence of main post-discharge complications, including recurrence of infection, HF, need for valve surgery or additional intervention, stroke, need for renal replacement therapy, psychological complications, and death.[86,588,589]

11.1. Recurrences: relapses and reinfections

The risk of recurrence (which includes relapses and reinfections) among survivors of IE varies significantly between studies, ranging from 2% to 9% in more contemporary analyses.[86,589–595] However, it has been shown that reinfections have worse outcomes as compared with relapses.[592]

Figure 12 illustrates the diagnostic paths to differentiate relapse from reinfection.[596]

Conceptually, relapse refers to a repeat episode of IE caused by the same microorganism and represents a failure of treatment due to insufficient duration of initial treatment, sub-optimal choice of initial antibiotics, or a persistent focus of infection.[592] Conversely, reinfection is related to patients' clinical and immunological profiles, describes an infection caused by a different microorganism usually more than 6 months after the initial episode,[4,596] and is associated with worse outcome.[592] The differentiation between relapse and reinfection needs to be interpreted with caution, however, as a long time period from initial infection suggests reinfection even in the presence of the same strain. Contemporary data report low rates of relapse,[86] most probably reflecting improved management of these patients. Relapse should be treated with i.v. antibiotics for an additional 4–6 weeks, depending on the causative microorganism and its antibiotic susceptibility, and cardiac surgery should be considered. It is also important to consider that antibiotic resistance may develop over time. Factors associated with an increased rate of relapse are listed in *Table 13*.[588,595,597]

In surgically managed NVE, the risk of IE recurrence is no different when comparing valve replacement and valve repair.[84,598] Several previous studies have also reported no difference regarding the risk of recurrent IE between types of valve implanted.[599–601] However, the most recent Danish registry study reports increased risk of IE recurrence associated with biological vs. mechanical prostheses.[84]

Partial oral vs. i.v. antibiotic treatment of IE, as well as OPAT vs. hospital-based antibiotic treatment in select stable patients, is not associated with an increased risk of recurrent IE.[43,396,399,602] Notably, residual vegetation after treatment for IE also did not show increased association with recurrence of IE,[602] although this result should be interpreted with caution. Patients with relapse or reinfection IE should be managed as indicated in *Sections 7* and *8* (if complicated IE).

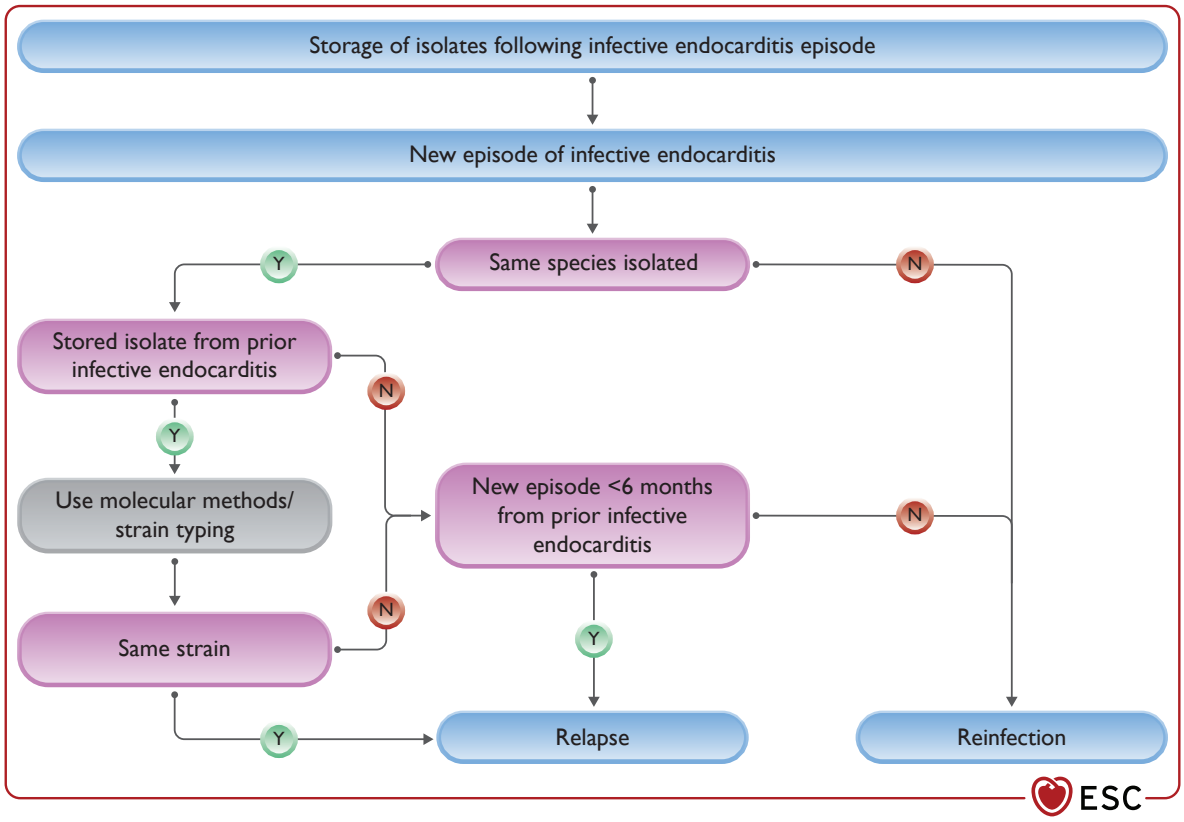

Figure 12 Algorithm differentiating relapse from reinfection. Reproduced with permission from Chu *et al.*[596]

Table 13 Factors associated with an increased rate of relapse of infective endocarditis

Inadequate antibiotic treatment (i.e. agent, dose, duration)
Resistant microorganisms (i.e. *Brucella* spp., *Legionella* spp., *Chlamydia* spp., *Mycoplasma* spp., *Mycobacterium* spp., *Bartonella* spp., *C. Burnetii*, fungi)
Infective endocarditis caused by *S. aureus* and *Enterococcus* spp.
Polymicrobial infection in people who inject drugs
Periannular extension
Prosthetic valve endocarditis
Persistent metastatic foci of infection (abscesses)
Resistance to conventional antibiotic regimens
Positive valve culture
Persistence of fever at the 7th post-operative day
Chronic kidney disease, especially on dialysis
High-risk behaviour, inability to adhere to medical treatment
Poor oral hygiene

11.2. First year follow-up

Patients discharged after the first episode of IE should remain under close surveillance for potential long-term complications. A partnership between cardiologists, infectious disease specialists, cardiac surgeons, general practitioners, and dentists is encouraged to improve patient care and reinforce prophylaxis measures. In medically treated patients, residual valve dysfunction may worsen, or structural valve deterioration may progress, despite bacteriological cure. To monitor the risk of development of secondary HF, an initial clinical evaluation and baseline TTE should be performed at the completion of antimicrobial therapy and repeated if a change in the clinical condition occurs.

Clinical re-assessment should be performed one or more times in the first year and yearly thereafter depending on the individual risk profile. The need for late valve surgery is relatively low, ranging from 3% to 11%.[27,588,592] Blood testing for inflammatory markers (i.e. WBC, C-reactive protein, procalcitonin) should be performed early after finishing antimicrobial treatment and repeated thereafter when clinically indicated.[592] Due to the increased risk of relapse for virulent microorganisms, blood cultures are encouraged within the first week after finishing treatment.

The early period after discharge might be challenged by slow physical and mental recovery.[603,604] Patients' and families' concerns should be addressed during follow-up. Supporting the family may indirectly support the patient during recovery and reduce the psychological burden. Cardiac rehabilitation, including physical exercise training and patient education, may be beneficial, and has been shown to be safe and feasible in stable patients at a minimum of 2 weeks after surgery for left-sided IE.[605] Physical training should start as early as possible and can be adapted post-sternotomy with isolated lower-limb training. Adherence is improved if the delay to training is minimized, and rebuilding muscle mass and reducing frailty should be a priority.

Patients, and their caregivers, should be informed of their risk of IE recurrence and be educated on preventive measures and self-monitoring. In particular, patients should be educated that new onset of fever, chills, or other signs of infection mandate immediate evaluation, including procurement of blood cultures before empirical use of antibiotics, and that contact with the Heart Valve Centre is mandatory in case of suspected recurrent IE. Good oral health maintenance, preventive dentistry, and advice about skin hygiene, including advice on tattoos and skin piercing, are mandatory. Deficiencies in dental surveillance contribute to the continuous gradual increase in the incidence of IE, which underlines the need for repeating the principles of IE prevention at each follow-up visit. In PWID patients, follow-up care should include a strategy for addiction treatment, involve relevant addiction specialists before hospital discharge, and possibly including medication for opioid-use disorder.[606,607]

Recommendation Table 18 — Recommendations for post-discharge follow-up

Recommendations	Class[a]	Level[b]
Patient education on the risk of recurrence and preventive measures, with emphasis on dental health, and based on the individual risk profile, is recommended during follow-up.[608]	I	C
Addiction treatment for patients following PWID-related IE is recommended.[606,607]	I	C
Cardiac rehabilitation including physical exercise training should be considered in clinically stable patients based on an individual assessment.[605,609]	IIa	C
Psychosocial support may be considered to be integrated in follow-up care, including screening for anxiety and depression, and referral to relevant psychological treatment.[605,609]	IIb	C

IE, infective endocarditis; PWID, persons who inject drugs.
[a]Class of recommendation.
[b]Level of evidence.

11.3. Long-term prognosis

Contemporary long-term survival rates after the completion of IE treatment are estimated to be ~85–90% and 70–80% at 1 and 5 years, respectively.[589,592–594,610,611] Impact of referral bias, however, should be taken into consideration.[612] The main predictors of long-term mortality are age, co-morbidities, PWID, double valve infection, recurrences of IE, and HF, especially when cardiac surgery cannot be performed.[588,589,592,593,613] Compared with an age- and sex-matched general population, patients that survived a first episode of IE have significantly worse survival when suffering relapses or reinfections.[589,614] This excess mortality is especially high within the first few years after hospital discharge and can be explained by late complications such as HF, risk of recurrences, and higher patient vulnerability.[589,611] In fact, most recurrences of IE and late cardiac surgeries occurred during this period of time.[589,592,611]

12. Management of specific situations

12.1. Prosthetic valve endocarditis

Prosthetic valve endocarditis is the most severe form of IE and occurs in 1–6% of patients with valve prostheses,[615] with an incidence of 0.3–1.2% per patient-year.[5,420,616,617] PVE accounts for 20–30% of all cases of IE,[618] and may be more common after biological than after mechanical valve replacement surgery.[619,620] PVE was observed in 21% of cases of IE in a French survey,[618] in 26% of cases in the Euro Heart Survey,[419] and in 20% of cases in the ICE-PCS.[621] Real-world

observational studies demonstrated stable rates of IE, but a remarkable increase in PVE between 1998 and 2013.[80] Recently, a further increase in PVE cases (31%) was observed in the EURO-ENDO registry.[5] PVE is still associated with difficulties in diagnosis, determination of the optimal therapeutic strategy, and poor prognosis.

12.1.1. Definition and pathophysiology

A distinction is commonly made between early PVE and late PVE based on the time since valve surgery, because of significant differences in the microbiological profiles between these two groups.[622] However, the time to IE onset is prognostically less important than the connection of IE to the peri-operative period or to specific pathogens. Prosthetic valve endocarditis with an onset in the peri-operative period involves mainly *S. aureus*, *Staphylococcus epidermidis*, or nosocomial microorganisms, such as Gram-negative pathogens or fungi. Late PVE more commonly mimics the pattern of NVE, which is mostly represented by streptococcal and staphylococcal infections.[623] *S. aureus* is more commonly observed in patients with mechanical valves, while alpha-haemolytic streptococci, enterococci, and CoNS are more common in patients with bioprosthetic valves.[624] PVE due to *Mycobacterium chimaera* is an uncommon form of nosocomial infection that can result from contaminated CPB heater-cooler systems. Such infections present many months after the index operation and can therefore be challenging to identify, and are associated with high mortality.[625]

The pathogenesis of PVE differs according to both the type of contamination and the type of prosthetic valve (see Supplementary data online, *Section S6.1*).

12.1.2. Diagnosis

Diagnosis is more difficult in PVE than in NVE. Clinical presentation is frequently atypical, particularly in the early post-operative period, in which fever and inflammatory syndromes are common in the absence of macroscopic alterations of the prosthesis on cardiac imaging. 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 associated with a sensitivity of only 60% for the definite diagnosis of endocarditis.[212]

Although TOE is mandatory in suspected PVE (*Figure 6*), its diagnostic value is lower than in NVE. Identification of a new periprosthetic leak is a major criterion of IE and urges additional imaging modality to confirm the diagnosis (see *Section 5*).[533,626] Recently, nuclear techniques, particularly [18F]FDG-PET/CT, have been shown to improve the diagnostic accuracy of the Duke criteria and increase sensitivity.[34,209] Combinations of different imaging techniques such as cardiac CT, nuclear imaging, and TOE, improve diagnostic accuracy and provide relevant information in terms of prognosis.[33,627] In select cases of suspected PVE, and non-diagnostic results for the above-listed exams, intracardiac echocardiography may be considered.

12.1.3. Prognosis and treatment

A high in-hospital mortality rate of 20–40% has been reported in PVE.[628,629] Compared with NVE, PVE is associated with increased in-hospital mortality and morbidity as well as reduced long-term survival.[88,630] Several factors have been associated with poor prognosis in PVE, including older age, diabetes mellitus, healthcare-associated infections, and early PVE.[312] Among the different causative organisms, staphylococcal or fungal infection seem to be more aggressive, whereas enterococcal infections are associated with similar mortality but higher recurrence rates.[628] Haemodynamic instability, multivalvular involvement as well as involvement of the aortomitral fibrosa have been associated with worse outcomes. It is noteworthy that the most important risk factor for recurrent IE and mortality is withholding surgery despite an obvious indication.[5]

The best therapeutic option in PVE is still debated. Although surgery is generally considered the best option when PVE causes severe prosthetic dysfunction or HF, in the EURO-ENDO registry it was performed in only 73% of patients with PVE despite a clear indication for surgical treatment.[5] In a single-series study of 523 PVE patients, early surgery was a large independent predictor of early and 1-year survival.[631] 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.[421] In this series, however, surgery was beneficial in the subgroup of patients with the strongest indications for surgery including valve regurgitation, vegetation, and dehiscence or paravalvular abscess/fistula formation.[421] Therefore, a surgical strategy is recommended for PVE in high-risk subgroups identified by prognostic assessment, i.e. PVE complicated with HF, severe prosthetic dysfunction, abscess, or persistent fever. Conversely, patients with uncomplicated non-staphylococcal late PVE can be managed conservatively.[632–634] However, patients who are initially treated medically require close follow-up because of the risk of late events and the higher risk of relapse or valvular dysfunction.

Surgery for PVE follows the general principles outlined for NVE. However, the reoperation setting and the higher incidence of periprosthetic tissue destruction increase the complexity of the procedure. Meticulous and radical debridement of the infected material, including the original prosthesis, suture, and pledgets, is recommended. The type of valve substitute used for PVE follows the same recommendations as for NVE (see also *Section 10.3.1*).

Early PVE following valve replacement surgery is a separate entity associated with a high mortality rate, where conservative treatment with antibiotics is unlikely to lead to a cure and repeat surgery should be performed.[621,635] Staphylococci, Cutibacteria, or similar species are the usual causative organisms.[622,636]

Recommendation Table 19 — Recommendations for prosthetic valve endocarditis

Recommendations	Class[a]	Level[b]
Surgery is recommended for early PVE (within 6 months of valve surgery) with new valve replacement and complete debridement. [621,635]	I	C

PVE, prosthetic valve endocarditis.
[a]Class of recommendation.
[b]Level of evidence.

12.2. Endocarditis in the elderly

Characteristics of patients with IE have dramatically changed over recent decades, with an increasing prevalence and specific features of IE in the elderly population.[25,145,637,638] In this population, enterococci and *S. aureus* are reported to be the most frequent aetiological agents. In addition, the higher presence of intracardiac prosthetic devices (CIED and valvular prosthesis/repair including TAVI devices) and increased incidence of healthcare-associated IE episodes are observed.[25,637] Finally, a lower risk of embolic episodes has been observed in this subgroup.[462,639–641]

A number of studies have shown that cardiac surgery positively affects the clinical outcome of IE patients. Nevertheless, old age, co-morbidities, and previous non-cardiac and cardiac procedures lead to surgical hesitancy by referring physicians, surgeons, and patients themselves.[642] Moreover, these characteristics also influence the outcome of this fragile cohort.[400,433] As a result, less frequent performance of curative surgery and increased mortality are typical hallmarks of IE episodes in elderly as compared with the younger population.[640] In a recently published Swedish propensity analysis of IE patients from 2006 to 2017, the authors found that surgery was underused in the elderly and that 1-year mortality was significantly higher in elderly patients who did not undergo surgery.[641] In a sub-analysis of the ESC EORP EURO-ENDO registry, the indication for surgery was less often recognized (51% vs. 57%) and surgery was far less frequently performed when indicated (35% vs. 68%) in patients >80 vs. <80 years. However, mortality of surgically treated patients was remarkably similar in patients <80 and >80 years after propensity matching (19.7% vs. 20.0%). Age was also not demonstrated to be an independent predictor of mortality in this large prospective study.[640,643] These findings suggest that performance of surgery in well-selected elderly patients is underutilized and may increase their chance of survival.

In elderly IE patients, functional and nutritional status are important predictors of outcomes.[400] When considering cardiac surgery in elderly patients, functional and nutritional status, and their associated risks, should be accurately explored through a comprehensive assessment by geriatricians. In addition, the earliest possible discharge home to facilitate the patient's functional recovery should be considered in this subgroup of patients.

12.3. Transcatheter prosthetic valve endocarditis

12.3.1. Endocarditis following transcatheter aortic valve implantation

The incidence of IE post-TAVI ranges from 0.3 to 1.9 per 100 patient-years,[94,623,644–648] which is similar to that reported following surgical aortic valve replacement in both observational studies and RCTs.[94,623,646,647] One recent study, however, reported a lower incidence of PVE after TAVI compared with surgical prostheses.[649] The risk of IE is higher within the first year following the procedure, and particularly within the initial 3 months.[644,645,648,650–652] A modest decrease in the incidence of IE post-TAVI has been observed in recent years, particularly in the early period following the procedure, presumably related to multiple technical improvements, more streamlined procedures, and a reduction of periprocedural complications.[650,652] A similar IE rate has been reported irrespective of transcatheter valve type,[653] and predisposing factors, including younger age, male gender, renal dysfunction, and significant residual aortic regurgitation, have been identified.[94,644–646,648,651,652]

12.3.1.1. Diagnosis

The diagnosis of IE post-TAVI is challenging. The stent frame of transcatheter valves, with a much higher amount of metal surrounding the valve leaflets compared with surgical prostheses, and the characteristics of TAVI patients (frequently elderly with multiple co-morbidities) may increase the diagnostic challenges in this population. The clinical presentation is frequently atypical, with fever lacking in 13–20% of patients.[623,645,650] Enterococci and *S. aureus* are the two most common microorganisms involved in IE post-TAVI, followed by streptococci and CoNS.[644–646,650]

Some important aspects should be considered regarding TOE in patients with suspected IE post-TAVI: (i) no vegetations are detected in 38–60% of cases;[623,645,650,651] (ii) vegetations are located in the stent frame of the transcatheter valve (and not on the valve leaflets) in 12% of cases, and this rate increases up to 19% in the presence of some self-expanding valve systems with a longer stent frame occupying the ascending aorta;[653] and (iii) the vegetations are located outside the transcatheter valve in about one-third of cases, mainly at the level of the mitral valve.[645,650,651] Nuclear imaging or CT have been useful to diagnose IE post-TAVI.[654,655] The addition of [18F]FDG-PET/CT and/or CTA to the diagnostic work-up of IE in TAVI changed the final clinical diagnosis in 33% of patients.[655] Intracardiac echocardiography may also be useful for detecting vegetations in patients with suspected IE after TAVI and negative TOE.[165]

12.3.1.2. Prognosis and treatment

Prognosis and treatment of post-TAVI PVE is complicated by the fact that patients are older and have more co-morbidities than post-surgical PVE patients. About two-thirds of patients with IE post-TAVI exhibit at least one complication, with acute kidney injury and HF being the most frequent adverse events.[645,646,656] The in-hospital and 30-day mortality rates are very high, ranging from 16% to 36%,[623,644–647,657] and increase up to 41–59% at 1-year follow-up.[644,645,652,657] A higher patient risk profile, *S. aureus*, and the occurrence of IE complications have been identified as risk factors for increased mortality.[645,652,657]

Antimicrobial therapy for IE post-TAVI is similar to that of PVE (see *Section 7*). Similar to surgical PVE, cardiac surgery is considered the best option in the presence of IE complications, particularly severe prosthetic failure or HF, but is infrequently performed. Surgery is performed in ~20% of cases (ranging from 3.8% to 31.3%),[645,652,656] a much lower rate compared with NVE and surgical PVE. The characteristics of the TAVI population, with often advanced age and high or prohibitive surgical risk, along with the potential difficulties associated with the removal of some transcatheter valve systems (particularly those with a large amount of stent frame, frequently adherent to the ascending aorta after a few months following the TAVI procedure) may play a role in the low rate of surgical interventions.

To date, all studies but one failed to demonstrate the potential benefit of surgery in IE post-TAVI patients,[442,645,652,656,658] but the relatively small sample size of the studies and the multiplicity of potential confounders when comparing to those patients not receiving surgical treatment precludes definite conclusions. The only study showing a beneficial effect of surgical intervention focused on those patients who had a local extension of the infection (i.e. abscess or fistula).[442]

The decision to proceed with surgery in IE post-TAVI patients should be individualized, balancing the surgical risks and the prognosis of medical treatment alone. In cases with local extension of the infection, surgery may be recommended in the absence of a prohibitive surgical risk. In cases with healed IE and valve prosthesis dysfunction, repeat transcatheter therapy (valve-in-valve procedure) can be performed in select patients.[659] Such interventions should be performed at least 1–3 months after the healed endocarditis episode and following a negative follow-up TOE.

12.3.2. Endocarditis following transcatheter pulmonary valve implantation

The incidence of IE post-transcatheter pulmonary valve implantation (TPVI) ranges from 1.6 to 4.0 per 100 patient-years,[93,660–667] which seems to be higher than that reported following surgical pulmonary valve interventions (observational studies, no randomized data).[662,663,667,668] While some studies suggest a higher risk associated with the use of bovine jugular vein valves,[662,667,669] a recent large multicentre study including different transcatheter valve systems did not

observe differences between valve types.[665] The most consistent factors associated with an increased risk of IE following TPVI have been younger age, a previous history of IE, and a higher transvalvular residual gradient.[93,663,665]

12.3.2.1. Diagnosis

The diagnosis of IE in TPVI recipients may be challenging, and the use of intracardiac echocardiography and [18F]FDG-PET/CT has been shown to be useful in cases with a clinical suspicion and negative TTE/TOE.[34,93,210,660,665,670] *S. aureus* and oral group streptococci species are the most common microorganisms causing IE post-TPVI.[660,664–666]

12.3.2.2. Prognosis and treatment

New moderate or severe prosthetic valve stenosis occurs much more frequently (one-third to one-half of patients) in post-TPVI PVE than in aortic PVE, and the rate of surgical valve replacement therapy ranges from 26% to 56%.[93,660,661,664,665] The possibility of a transcatheter therapy (valve-in-valve intervention) for treating severe prosthesis dysfunction in cases with healed endocarditis or as an urgent treatment (balloon dilatation) in severe valve stenosis cases has also been reported.[660,665] A valve-in-valve intervention should be delayed at least 1–3 months following antibiotic treatment of the endocarditis episode. The mortality rate related to the IE episode ranges from 0% to 11%.[93,660,661,664,665] This rate is much lower compared with TAVI patients, which is likely to be related to the younger and less co-morbid characteristics of the TPVI population.

12.4. Infective endocarditis affecting cardiac implantable electronic devices

Device-related infection is one of the most serious complications of CIED therapy and is associated with significant mortality and morbidity.[671]

12.4.1. Definitions of cardiac device infections

A recent EHRA consensus document has published criteria for CIED infection.[130] Localized infections may be either superficial incisional infections (acute infection without involvement of the pocket or hardware) or isolated pocket infections (limited to the hardware in the pocket), and can be either acute or chronic. Systemic CIED infections may occur with or without pocket infection, and with or without visible vegetations on the tricuspid or pulmonary valves or pacing leads. Cardiovascular implanted electronic device-related IE is defined as evidence of CIED infection with clinical signs of pocket infection and/or imaging findings (lead vegetations, positive FDG-PET on the generator/leads etc.) which fulfil the criteria for valvular IE (see *Section 5*).

12.4.2. Pathophysiology and microbiology

Cardiovascular implanted electronic device-related IE occurs by two mechanisms. Local infection usually results from bacterial flora from the patient's skin that is introduced into the pocket at the time of incision despite surgical preparation.[672] Seeding via bacteraemia from a distant focus is less frequent.[673–676]

Whereas CoNS are most frequently the cause of chronic pocket infection, the most frequent agents identified with bacteraemia in CIED infection are *S. aureus* and CoNS.[677,678] Other causative organisms are *Enterococcus* spp., β-haemolytic streptococci, oral streptococci group, *Cutibacterium acnes*, and *Corynebacterium* spp.[674,678,679] More rarely, systemic infection is caused by Gram-negative (mainly *P. aeruginosa* or *Serratia marcescens*)[680] or polymicrobial agents, whereas systemic fungal infections (*Candida* spp. and *Aspergillus* spp.)[681] are exceptional.

12.4.3. Risk factors

Risk factors may be divided into patient-related, procedure-related, and device-related factors.[118] The PADIT (Previous procedure on same pocket; Age; Depressed renal function; Immunocompromised; Type of procedure) study randomized 19 603 patients undergoing CIED implantation to conventional treatment (pre-procedural cefazolin infusion) vs. different regimens of incremental treatment.[682] The primary outcome was 1-year hospitalization for device infection which was not significantly different between groups. A risk score for infection has been derived from the study (see Supplementary data online, *Table S11*)[683] and has been validated externally.[684] A web-based calculator is available (https://padit-calculator.ca).[683]

12.4.4. Prophylaxis

Antibiotic prophylaxis to prevent CIED-related IE before interventions, such as dental, respiratory, gastrointestinal, or genitourinary procedures, is not warranted as the risk is very low.

Prevention of CIED infection at implantation hinges upon careful planning, pre-operative antibiotic prophylaxis, correction of modifiable risk factors, hygienic surgical environment and technique, ancillary measures in case of increased risk (e.g. use of an antibacterial envelope), and proper post-operative care.

Correction of modifiable risk factors includes general measures such as postponing the procedure in cases of fever or signs of infection and avoiding temporary pacing. Routine administration of prophylactic systemic antibiotics within 1 h of incision is the standard of care.[118] RCTs have used flucloxacillin (1–2 g i.v.)[117] and first-generation cephalosporins, such as cefazolin (1–2 g i.v.).[116] Vancomycin (1–2 g over 60–90 min) may be used in case of allergy to cephalosporins with other alternatives, including teicoplanin and clindamycin.[117] Coverage of MRSA should be guided by the prevalence in the implanting institution.

Haematoma is a major contributor to risk of infection, and all possible measures should be taken to avoid this complication.[685,686] Another major risk factor is a revision with re-opening of the pocket (e.g. for lead repositioning). Technical aspects have recently been covered in detail in an EHRA consensus document on CIED implantation.[687]

It is generally not recommended to wash the pocket with antibiotics, nor to administer antibiotic treatment post-operatively, as shown by the PADIT trial.[682] An antibiotic mesh envelope, which locally releases minocycline and rifampin for a minimum of 7 days and is fully absorbed in ~9 weeks, may, however, be useful to reduce risk of infection in selected patients. The Worldwide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT) showed that the mesh envelope significantly reduces the incidence of CIED infection in patients at increased risk (i.e. undergoing a pocket revision, generator replacement, system upgrade, or implantation of a cardiac resynchronization therapy [CRT]-implantable cardioverter defibrillator [ICD]).[688] The number needed to treat was, however, high at 200, but is ~50 in patients undergoing CRT reoperations (replacement/upgrade/revision) in a recent observational study.[689]

12.4.5. Diagnosis

Clinical presentation of CIED-associated IE is similar to valvular IE with patients frequently presenting with fever, chills, and embolic events. Signs of pocket infection (swelling, tenderness, erythema, purulent discharge etc.) may or may not be present.

The probability that a positive blood culture in a CIED recipient represents underlying device infection depends on the organism type and duration of bacteraemia. Suspicion of CIED-associated IE should be particularly high in the event of *S. aureus* bacteraemia.[675] CIED infection is less likely with Gram-negative bacteraemia, and in these instances, the pocket usually shows signs of infection.[680,690,691]

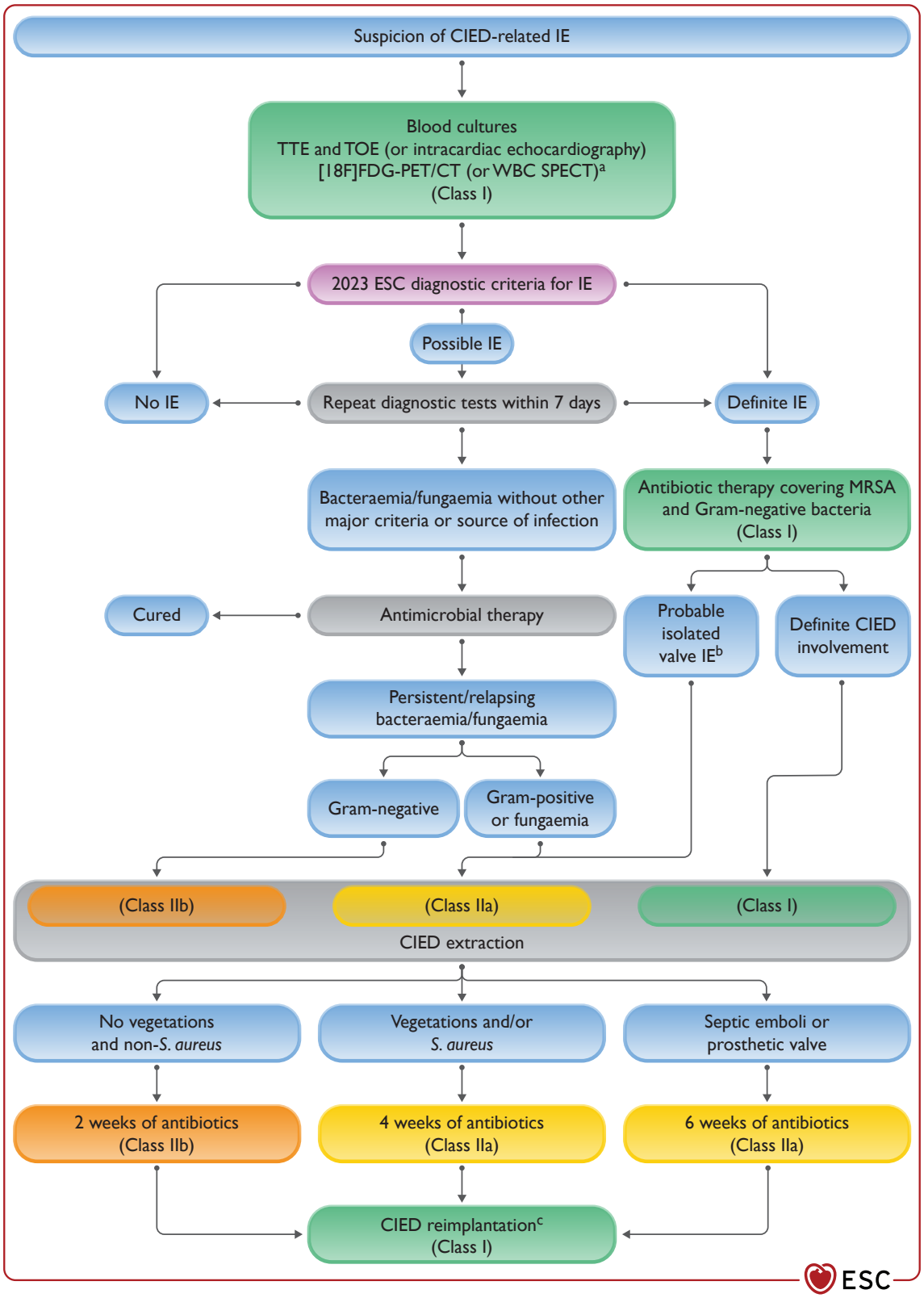

Figure 13 Management of cardiovascular implanted electronic device-related infective endocarditis. [18F]FDG-PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; CIED, cardiovascular implanted electronic device; ESC, European Society of Cardiology; IE, infective endocarditis; MRSA, methicillin-resistant *S. aureus*; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography; WBC SPECT/CT, white blood cell single photon emission tomography/computed tomography. [a]If no signs of pocket infection and negative TOE. [b]Taking into account the identified pathogen, procedural risk, and requirement for valve surgery. [c]At a distant site and postponed as long as possible (until signs and symptoms of infection have resolved and blood cultures are negative for >72 h in the absence of vegetations and /or 'ghosts', or otherwise after >2 weeks of negative blood cultures).

Transthoracic echocardiography and TOE are both recommended in the case of suspected CIED-related IE.[692–694] Intracardiac echocardiography may also be used to visualize vegetations,[695] and may be useful in patients in whom TOE is not possible. However, the absence of vegetations does not rule out IE, as these may be present on extracardiac segments of the lead which cannot be visualized. Repeating TTE and/or TOE within 5–7 days is recommended in case of initially negative examination when clinical suspicion of CIED-related IE remains high. It is important to note that fibrinous lead masses may be observed in asymptomatic CIED patients, and do not predict CIED-related IE over long-term follow-up.[696]

Diagnosis of CIED-related endocarditis by [18]FDG-PET/CT has good sensitivity and specificity,[129] and is particularly useful in the setting of possible CIED-related IE without signs of pocket infection.[238] Results should be interpreted with caution, however, if the CIED is recently implanted (<6 weeks).[130]

White blood cell SPECT/CT has also been used for diagnosing CIED infection but has limited availability.[216,697] A chest X-ray or CT should be performed in all patients to evaluate the presence of pulmonary complications.

12.4.6. Antimicrobial therapy

Treatment of CIED infection involves early[698,699] and complete removal of all parts of the system, combined with initial empirical antibiotic therapy directed at MRSA and Gram-negative bacteria, while awaiting identification of the pathogen.[130,700,701] Antibiotic treatment follows the recommendations indicated in *Section 7*. In exceptional cases where complete device removal is not possible, i.v. antibiotics for 4–6 weeks may be administered followed by close follow-up after interruption of antibiotic therapy or, alternatively, individualized long-term suppressive oral therapy.

12.4.7. Device extraction

When CIED and lead extraction is required, such procedures should be performed in centres with the corresponding expertise. Complete CIED removal is recommended for all patients with confirmed infection of the lead(s), as conservative treatment is associated with increased mortality.[678,699] In patients with left-sided prosthetic heart valves and CIED infection, complete CIED removal combined with prolonged (4–)6 week antibiotic therapy may prevent left-sided valve infection.[130,702] Complete CIED extraction should also be considered in case of valvular IE without definite lead involvement, taking into account the identified pathogens (*Staphylococcus* spp. infections may be more prone to seed the CIED),[673,675,676] procedural risk, and indication for valve surgery.

Complete device extraction should be considered even in the absence of vegetations in the setting of persistent or relapsing Gram-positive bacteraemia or fungaemia after a course of appropriate antibiotic therapy, if there is no other identified source (see *Figure 13*).[681] In all instances of lead extraction, procedural risk should be carefully evaluated taking into account lead dwell time, pacemaker dependency, patient frailty, and other co-morbidities within the process of shared decision-making.[703]

Lead extraction should be performed, without delay (i.e. within the first days of admission), as this has been shown to be associated with improved outcomes.[698,699,704] Percutaneous rather than surgical extraction is the preferred procedure, but requires specialized tools and should be performed in centres with expertise in this technique and with onsite surgical backup, due to the risk of life-threatening tamponade and vein laceration.

Large vegetations may be aspirated percutaneously before lead extraction to reduce risk associated with embolization.[705] Surgical lead extraction should be considered in case of large vegetations (e.g. >20 mm)[679] and if aspiration is not available or is unsuccessful. Surgical removal is also the preferred technique if valve surgery is indicated. Hardware retrieved from extraction, especially the lead tip, should be cultured.[706] Sonication has been shown to increase diagnostic yield.[707,708]

12.4.8. Device reimplantation

The indication for reimplantation should always be carefully evaluated and no part of the removed CIED system should be reimplanted. Quality of evidence regarding timing of reimplantation is poor.[709] Reimplantation should be performed at a site distant from that of the previous generator, and delayed until signs and symptoms of local and systemic infection have resolved and blood cultures are negative for at least 72 h after extraction in the absence of vegetations or 'ghosts' (fibrous remnants after lead extraction, which have been associated with death and reinfection),[710] or after 2 weeks of negative blood cultures if vegetations were visualized.[701,711]

For patients with a high risk of sudden cardiac death, a wearable defibrillator is an option as a bridge to reimplantation. In pacemaker-dependent patients, an active-fixation lead may be introduced via the internal jugular vein and connected to an external pacemaker for up to 4–6 weeks, thereby preserving the contralateral side for definitive device reimplantation.[712] As an alternative to delayed reimplantation in pacemaker-dependent patients, an epicardial pacemaker may be implanted before lead extraction, although this strategy has been associated with a higher risk of device re-intervention.[713] Alternative devices such as leadless pacemakers[714] or subcutaneous ICD[715] may be implanted in selected patients if the risk of new infection is deemed high.

Recommendation Table 20 — Recommendations for cardiovascular implanted electronic device-related infective endocarditis

Recommendations	Class[a]	Level[b]
Antibiotic prophylaxis covering *S. aureus* is recommended for CIED implantation.[118]	I	A
TTE and TOE are both recommended in case of suspected CIED-related IE to identify vegetations.[692–694]	I	B
Complete system extraction without delay is recommended in patients with definite CIED-related IE under initial empirical antibiotic therapy.[698,699]	I	B
Obtaining at least three sets of blood cultures is recommended before prompt initiation of empirical antibiotic therapy for CIED infection,[710] covering methicillin-resistant staphylococci and Gram-negative bacteria.	I	C
If CIED reimplantation is indicated after extraction for CIED-related IE, it is recommended to be performed at a site distant from the previous generator, as late as possible, once signs and symptoms of infection have abated and until blood cultures are negative for at least 72 h in the absence of vegetations, and negative for at least 2 weeks if vegetations were visualized.[701,711]	I	C

Continued

Complete CIED extraction should be considered in case of valvular IE, even without definite lead involvement, taking into account the identified pathogen and requirement for valve surgery.	IIa	C
In cases of possible CIED-related IE with occult Gram-positive bacteraemia or fungaemia, complete system removal should be considered in case bacteraemia/fungaemia persists after a course of antimicrobial therapy.[673–676]	IIa	C
Extension of antibiotic treatment of CIED-related endocarditis to (4–6) weeks following device extraction should be considered in the presence of septic emboli or prosthetic valves.[702]	IIa	C
Use of an antibiotic envelope may be considered in select high-risk patients undergoing CIED reimplantation to reduce risk of infection.[688,689]	IIb	B
In cases of possible CIED-related IE with occult Gram-negative bacteraemia, complete system removal may be considered in case of persistent/relapsing bacteraemia after a course of antimicrobial therapy.[680,690,691]	IIb	C
In non-*S. aureus* CIED-related endocarditis without valve involvement or lead vegetations, and if follow-up blood cultures are negative without septic emboli, 2 weeks of antibiotic treatment may be considered following device extraction.	IIb	C
Removal of CIED after a single positive blood culture, with no other clinical evidence of infection, is not recommended.[675]	III	C

CIED, cardiovascular implanted electronic device; IE, infective endocarditis; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography.
[a]Class of recommendation.
[b]Level of evidence.

12.5. Infective endocarditis in patients admitted to intensive care units

Infective endocarditis is frequently associated with severe life-threatening cardiac and/or systemic complications and the number of patients requiring intensive care unit (ICU) admission has steadily been growing in recent years, as shown in a large retrospective study.[716] The need for ICU admission, advanced monitoring, vasoactive treatment, and organ support is most commonly prompted by the occurrence of septic shock, acute HF, and cardiogenic shock leading to multiorgan failure. Moreover, in recent years, an increase in healthcare-associated IE, usually of staphylococcal origin, predominantly in older patients with an increased number of comorbidities, and more likely to lead to critical illness, has also been reported.[29,717–719] Any IE patient requiring ICU admission should be urgently discussed within the Endocarditis Team.

In the largest multicentre retrospective series, focusing on critically ill IE patients with organ failure requiring ICU admission in France over an 18-year period, overall in-hospital mortality was 32%.[716] Multivariate analysis showed age, Simplified Acute Physiology Score (SAPS) II score, organ failure, stroke, and *Staphylococcus* spp. to be associated with an increased risk of death. In contrast, cardiac surgery, CIED, male gender, and *Streptococcus* spp. as the causative microorganism of IE, were associated with a better survival.[716] In another study that reported an even higher mortality (42%), four independent prognostic factors were identified: high SAPS II (>35 points) and Sequential Organ Failure Assessment (>8 points) scores, MRSA infection, and native valve IE.[718]

Right-sided IE, which is more commonly associated with PWID, accounts for <10% of IE cases but is associated with high mortality in patients needing ICU admission.[717]

12.5.1. Causative microorganisms

The majority of retrospective series in the ICU setting point to *Staphylococcus* spp. as the main causative agent of IE episodes. Indeed, *S. aureus* has emerged as the most feared aetiological agent with the highest rates of complications and mortality, being responsible for up to 56% of IE cases in one observational study.[719] *Streptococcus* spp., *Enterococcus* spp., Gram-negative bacilli, and *Candida* spp. are less frequently reported.[718,719] Identification of the infecting microorganism remains the mainstay of effective therapy in complicated IE cases. Hence, in patients with negative blood cultures, serological or molecular testing by PCR should be considered (see *Section 5.3*).

12.5.2. Diagnosis

The diverse nature, epidemiological profile, and presentation phenotype of IE in the ICU setting may hinder early diagnosis. In particular, pyrexial episodes suggestive of an alternative infective source and neurological manifestations, such as confusion, delirium, or focal symptoms may initially mislead the clinician from a diagnosis of IE.

The diagnosis of IE in ICUs follows the same modified criteria as in non-ICU patients (see *Section 5*). Transoesophageal echocardiography has a prominent role as a tool for diagnosis of IE and its complications in the ICU.[720]

12.5.3. Management

Antimicrobial therapy and indications for surgery in patients with IE are described in *Sections 7* and *10*, respectively. Surgical therapy has been associated with an improved early and late outcome both in the general population and in patients admitted to ICUs. Although surgery is the treatment of choice in about one-half of patients, surgical therapy in ICU patients is characterized by more complex procedures with increased peri-operative mortality, as well as difficult post-operative care due to higher requirements of circulatory and pulmonary support. Five independent predictors of post-operative need for advanced circulatory support were found in one study of patients with IE: male sex, increased surgery duration, renal dysfunction (pre-operative estimated glomerular filtration <60 mL/min/m^2), HF prior to surgery, and lower pre-operative platelet count.[721]

Extracorporeal membrane oxygenation is occasionally required in patients post-surgery but is associated with poor outcomes.[722]

Decision-making in ICU patients with IE should always be a product of consensus of the Endocarditis Team to determine the best management strategy. Pre-operative haemodynamic optimization and goal-directed therapy protocols including vasoactive drugs and mechanical circulatory support may be considered in these complex high-risk patients.[721]

12.6. Right-sided infective endocarditis

Right-sided IE accounts for ~5–10% of patients with IE,[723] but its frequency may be increasing as its risk factors are increasing in some countries.[133,724] Risk factors for right-sided IE include patients with CHD, indwelling catheters, and CIED, as well as immunocompromised and PWID patients. Of these, PWID is an increasingly common risk

factor,[133,723] while patients with indwelling vascular catheters have the worst prognosis.[725] IE of transcatheter pulmonary valves is covered in *Section 12.2*, whereas CIED-related right-sided IE is covered in *Section 12.3*.

The most common microorganism causing right-sided IE is *S. aureus*, accounting for the majority of patients.[723,726] The tricuspid valve is much more commonly infected than the pulmonary valve in patients with right-sided IE.[723,727] Right-sided IE may also involve non-functional embryonic remnants of the right atrium (e.g. Eustachian valve).[723,727] Right-sided IE rarely spreads to involve the left-sided cardiac structures, whereas spread from left- to right-sided structures is not uncommon.[728]

12.6.1. Diagnosis and complications

Right-sided IE patients present with fever, bacteraemia, and pulmonary complaints (i.e. cough, chest pain, or haemoptysis). Right-sided HF may also occur due to tricuspid or pulmonary regurgitation, or to pulmonary hypertension induced by multiple pulmonary septic emboli.[133]

Diagnosis is most frequently confirmed by echocardiographic findings of vegetations on the tricuspid valve or, less frequently, pulmonary valve. Adequate evaluation of the tricuspid valve may be performed with TTE, due to the anterior location of the valve and the large vegetations frequently observed in right-sided IE. Transoesophageal echocardiography is frequently required, however, particularly for evaluation of the pulmonary valve or in patients with indwelling venous catheters or intracardiac devices.[729] Intracardiac echocardiography may also be helpful in select patients. Vegetations may be challenging to identify on the pulmonary valve even with TOE, especially in patients with a prosthetic valve in the pulmonary position. [18]FDG-PET imaging may be very helpful in such patients.[34,730] Perivalvular abscess formation and invasion into surrounding structures is rarely seen in right-sided IE, unless it is a secondary consequence of left-sided IE.[728] CT is useful in order to identify concomitant pulmonary disease, including infarcts and abscess formation.

12.6.2. Endocarditis in people who inject drugs

Infective endocarditis in PWID is an increasing global phenomenon.[10,132,133,141] Repeat i.v. injections result in contaminated particles that reach the tricuspid valve and right-heart chambers and can also lead to infection of left-heart structures, which is associated with worse prognosis.[614] PWID patients also have an increased rate of human immunodeficiency virus (HIV) and hepatitis than other patients with right-sided IE.[731] The majority of right-sided IE in PWID can be treated successfully with antibiotic therapy. Mortality rates of PWID are relatively low, even when surgery is required, probably due to the young patient age.[723] However, PWID have a markedly increased rate of IE recurrence, particularly in the first 6 months post-surgery.[133,614,723,732]

12.6.3. Prognosis and treatment

Right-sided IE is generally a more benign clinical entity than left-sided IE and can be medically managed in ~90% of patients, with surgery reserved for those who fail medical therapy.[733] Patients with CIED-related right-sided IE have a worse prognosis as compared with non-CIED-related right-sided IE (see *Section 12.4*).[723 725] Right-sided IE in immunocompromised patients, particularly fungal infections, carries a very poor prognosis.

12.6.3.1. Antimicrobial therapy

S. aureus and CoNS are the cause of right-sided IE in a large proportion of cases, with *S. aureus* predominating in PWID and CoNS being more common in patients with indwelling devices.[723,726] MRSA rates may be increasing over time, particularly in PWID.[133] Right-sided IE due to *Streptococcus* spp. is unusual but can be observed in alcoholics and diabetics. *P. aeruginosa* and other Gram-negative organisms are rare causes of right-sided IE, while *Candida albicans* is mostly seen in immunocompromised patients.

Empirical antimicrobial therapy depends on the suspected microorganism, the type of drug and solvent used by the PWID, and the infection location,[734] but *S. aureus* must be initially covered in all cases. Initial treatment consists of penicillinase-resistant penicillin, vancomycin, or daptomycin, depending on the local prevalence of MRSA,[735] in combination with gentamicin. If the patient is a pentazocine addict, an anti-*Pseudomonas* agent may also be required, as the use of recreational drugs may also entail infections with Gram-negative bacteria.[735] Very large vegetations and history of brown heroin use dissolved in lemon juice suggest infection for *Candida* spp. (not *C. albicans*), and therefore antifungal treatment should be added.[736] Antifungals may be necessary in selected PWID, particularly if immunocompromised.[737]

Once the causative organisms have been isolated, therapy has to be adjusted. An RCT demonstrated that a 2-week treatment course may be sufficient and that aminoglycosides may be unnecessary.[738 717] Two-week treatment with oxacillin (or cloxacillin) without gentamicin is effective when:

(i) MSSA is the causative organism;
(ii) There is good clinical and microbiological response to treatment (>96 h);[739]
(iii) The vegetation size is ≤20 mm; and
(iv) There is an absence of metastatic sites of infection or empyema and cardiac or extracardiac complications,[739,740] prosthetic valve or left-sided valve infection,[741] and severe immunosuppression.[742]

Glycopeptides (vancomycin) should not be used in a 2-week treatment. The standard 4–6-week regimen should be used in the remaining patients or when therapy with antibiotics other than penicillinase-resistant penicillins are used.[330,739–744] When the conventional i.v. route therapy is not possible, *S. aureus* right-sided IE in PWID may also be treated with oral ciprofloxacin (750 mg twice a day) plus rifampin (300 mg twice a day) if the strain is susceptible to both drugs, the case is uncomplicated, and patient adherence is monitored carefully.[745] Partial oral antibiotic treatment may also be beneficial for PWID with IE.[746]

For organisms other than *S. aureus*, therapy in PWID does not differ from that in other patients.

12.6.3.2. Surgery

The commonly accepted indications for surgical treatment of right-sided IE in patients who are receiving appropriate antibiotic therapy are (see Recommendation Table 19):

- Persistent bacteraemia after at least 1 week of appropriate antibiotic therapy.[10]
- Tight ventricular dysfunction secondary to acute severe tricuspid regurgitation non-responsive to diuretics.[479]
- Respiratory insufficiency requiring ventilatory support after recurrent pulmonary emboli.[747]
- Involvement of left-sided structures;[748,749] and
- Large residual tricuspid vegetations (>20 mm) after recurrent pulmonary emboli.[145,471]

Patients should be individually assessed by the Endocarditis Team. An isolated vegetation is not an indication for surgery. Patients with

residual large vegetations frequently present with right-heart and/or respiratory failure, as well as persistent sepsis.[750]

The common surgical strategies for tricuspid valve IE include valve repair, replacement and, less commonly, surgical valvectomy.[751] Tricuspid valve repair is more frequently performed than valve replacement in right-sided IE, although the extent of valve destruction may make repair impossible.[725,752] Tricuspid valve repair may also be associated with better short- and long-term outcomes than replacement for right-sided IE, particularly with regards to recurrent infection and need for repeat surgery.[479,723]

When valve replacement for right-sided IE is required, bioprostheses are frequently preferred due to concerns with the management and risks of lifelong anticoagulation, especially in PWID, and the risks of thrombo-embolism for mechanical valves in the right heart.[726]

Prophylactic placement of permanent epicardial leads should be performed at the time of tricuspid valve surgery for right-sided IE, particularly if heart block is present in the operating room to prevent damage of a replaced valve during subsequent transvenous lead displacement and to lower the risk of reinfection.[733]

Recently, interest has been generated in the extraction of large vegetations using percutaneous extracorporeal circuitry for aspiration.[753] The main goals have been debulking of septic intracardiac masses, reducing the infectious load, and achieving clinical stability.[754]

Recommendation Table 21 — Recommendations for the surgical treatment of right-sided infective endocarditis

Recommendations	Class[a]	Level[b]
Surgery is recommended in patients with right-sided IE who are receiving appropriate antibiotic therapy for the following scenarios:		
Right ventricular dysfunction secondary to acute severe tricuspid regurgitation non-responsive to diuretics.[479]	I	B
Persistent vegetation with respiratory insufficiency requiring ventilatory support after recurrent pulmonary emboli.[479,755]	I	B
Large residual tricuspid vegetations (>20 mm) after recurrent septic pulmonary emboli.[145,471]	I	C
Patients with simultaneous involvement of left-heart structures.[749]	I	C
Tricuspid valve repair should be considered instead of valve replacement, when possible.[479]	IIa	B
Surgery should be considered in patients with right-sided IE who are receiving appropriate antibiotic therapy and present persistent bacteraemia/sepsis after at least 1 week of appropriate antibiotic therapy.[436,755]	IIa	C
Prophylactic placement of an epicardial pacing lead should be considered at the time of tricuspid valve surgical procedures.[733]	IIa	C
Debulking of right intra-atrial septic masses by aspiration may be considered in selected patients who are high risk for surgery.[753]	IIb	C

IE: infective endocarditis.
[a]Class of recommendation.
[b]Level of evidence.

12.7. Infective endocarditis in congenital heart disease

Although the incidence of CHD is relatively constant, the overall population with CHD is constantly increasing due to increased survival following CHD surgery in childhood and increased longevity of adults with CHD. The presence of CHD, even after repair, is recognized as a lifelong potential substrate for IE. Congenital heart disease predisposes to IE via several mechanisms including turbulent non-laminar blood flow causing shear stress and endothelial damage, the presence of intracardiac foreign material such as prosthetic valves or CIED, cyanosis, and recurrent exposure to cardiac procedures.[98]

There are marked variations in susceptibility to IE between CHD lesions. Some simple conditions, such as secundum atrial septal defect, patent ductus arteriosus, and pulmonary valve stenosis, carry a low risk of IE, while others, such as bicuspid aortic valve carry a somewhat increased risk.[8] However, CHD often presents with multiple cardiac lesions, each adding to the total risk of IE.[8,756] In general terms, IE is more common in CHD with multiple defects and in patients with more complex CHD.[757]

Specific high-risk conditions are prosthetic valves, including transcatheter valves, valve repair using a prosthetic ring, previous IE, any unrepaired cyanotic CHD, and any CHD repaired with prosthetic material for up to 6 months after the procedure, or lifelong if residual shunt or valvar regurgitation remains.[758] Contemporary studies confirm the relatively high risk of IE in CHD patients after valve surgery.[8,47,90,759] Specific awareness is needed after TPVI (see *Section 12.3.2*).[666,759,760]

The distribution of causative microorganisms does not differ from the pattern found in acquired heart disease, with *Streptococcus* spp. and *Staphylococcus* spp. being the most common strains.[98,757,761,762] As in other groups, the diagnosis of IE is often made late,[757] highlighting the need to consider the diagnosis of IE in any CHD patient presenting with persisting fever or other signs of ongoing infection. Multiple blood cultures are essential before starting antibiotic treatment. The principal symptoms, complications, and basis for diagnosis do not differ from IE in general. However, in CHD right-sided IE is more frequent than in non-CHD-acquired cardiac disease.

Transthoracic echocardiography is sufficient in many cases to image the infectious lesions and their complications. However, complex anatomy and the presence of artificial material may reduce the rate of vegetation detection and other features of IE, thus favouring the addition of TOE, particularly in adults and larger children. Despite the improved sensitivity of TOE for the detection of IE, TOE may only perform similarly to TTE for anterior structures of the heart, such as the right ventricular outflow tract, or infected sites at distal structures, such as stents or other prosthetic material within branch pulmonary arteries. Hence, a negative study does not exclude the diagnosis of IE. In patients with prosthetic material advanced imaging such as [18F]FDG-PET/CT and PET/CTA, can increase the diagnostic accuracy.[223]

In addition to the usual Endocarditis Team (see *Section 4*), multidisciplinary care of CHD patients with IE from diagnosis to treatment should be provided in specialized CHD centres with expertise in CHD cardiac imaging, CHD surgery, infectious disease, and intensive care. Surgical indications do not differ from those of acquired heart disease IE. Mortality rates in CHD vary from 6% to 15%.[757,761–764] This better prognosis compared with acquired heart disease IE may reflect the higher proportion of right-heart IE, younger overall patient age, or the comprehensive care in CHD centres.

Primary prevention of IE in CHD patients and corresponding patient education is essential (see *Section 3*).[765]

12.8. Infective endocarditis in rheumatic heart disease

Infective endocarditis is a known complication of RHD,[766] and acute rheumatic fever (the antecedent of RHD) may even present with concomitant IE.[767] Of the 3343 participants enrolled in The Global Rheumatic Heart Disease Registry (REMEDY),[768] 133 (2.4%) had a history of IE at enrolment,[769] and 20 (0.7%; 3.65 per 1000 patient-years) developed IE during the 27-month follow-up.[770] These participants were young with a median age of 28 years (interquartile range 18–40 years), 66.2% were women, and over 30% were children. The majority of the over 40 million patients with RHD[771] live in low- and middle-income countries and face socioeconomic and health-system barriers[772] to adequate prevention, early diagnosis, and advanced care and, therefore, are at particular risk of IE.[773]

Global access to surgery for RHD and RHD-associated complications is extremely limited.[774] RHD patients presenting with fever, changing or new murmurs should be investigated for IE. In studies from RHD-endemic regions, RHD is the most common underlying cardiac condition, with significant mortality and morbidity.[775–784] In those affected with oral bacteria-related IE linked to RHD, oral *Streptococcus* spp. was the main cause of IE associated with poor oral health status.[785] In RHD-endemic countries, IE in children is strongly linked to RHD,[786–788] and when causing HF, carries the highest case fatality rate.[789] IE is associated with enhanced risk of death among patients with RHD undergoing isolated mitral valve replacement (odds ratio 5.22, 95% confidence interval [CI], 1368–19 915; $P = 0.008$).[790] Pregnancy is a particularly high-risk period for women with RHD, with an increased risk of developing IE.[791,792] However, high-income countries or countries with emerging economies are seeing less IE linked to RHD, as the incidence rates of RHD in these regions decrease.[793–796]

12.9. Infective endocarditis during pregnancy

Infective endocarditis in pregnancy is a rare but extremely serious condition with high maternal and foetal morbidity and mortality, and is estimated to complicate ~1 in 100 000 pregnancies.[797–799] Maternal mortality approaches 18%, with most deaths relating to HF or an embolic event, while pre-term birth is reported at 55.7% and foetal mortality at 29%.[800] Recurrent infective complications can occur in up to 27% of women post-partum.[801]

The diagnosis must be considered in pregnant women with unexplained fever and cardiac signs (especially tachycardia), new or changing cardiac murmurs, and peripheral signs of septic emboli.[802] Women with CHD, RHD,[803] and structural heart disease, together with those with prosthetic heart valves and with PWID are at particular risk.[800,804–807]

The gravity of the condition requires the inclusion of gynaecologists, obstetricians, and neonatologists in the Endocarditis Team in any suspected cases, and a diagnosis and treatment plan should be formulated without delay, as this is key to saving the lives of mothers and infants.[799,808,809] Management can be challenging, especially when the pregnant patient warrants a cardiac operation under CPB. Although this poses a considerable risk to the foetus, urgent surgery when indicated should not be delayed.[799,810]

12.10. Infective endocarditis in immunocompromised patients

12.10.1. Solid organ transplant recipients

The incidence of IE in recipients of solid organ transplantation (SOT) ranges between 1% and 2%.[107] SOT recipients with IE are younger and have higher prevalence of co-morbidities (particularly renal and liver disease) compared with non-SOT patients with IE. Among the SOT patients with IE, the most common transplanted organ is the kidney (72%), followed by liver (17%), and pancreas (8%).[811] Similar to non-SOT patients, aortic followed by mitral IE are the most common forms of IE while right-sided IE is uncommon. Interestingly, SOT patients with IE more frequently have atrial or ventricular vegetations without valve involvement (mural IE).[107] In-hospital and healthcare-related IE are the most frequent causes of IE in recipients of SOT and the most frequent microorganism involved is *S. aureus* (34%), followed by *Enterococcus* spp. (17%), and *Streptococcus* spp. (11%).[107,811]

Surgical valve repair/replacement is less frequently performed in SOT patients with IE as compared with non-SOT patients. Interestingly, the outcomes of IE in patients with SOT do not differ from those of non-SOT with IE.[107,811] The reasons for the similar outcomes may rely on the younger age of the SOT patients, the frequent contact with the healthcare system which may lead to early diagnosis and treatment of IE, and the frequent involvement of infectious disease specialists in the care of hospitalized SOT patients. However, compared with SOT patients without IE, those who develop IE during the index transplant hospitalization have worse outcomes.[811] The high levels of immunosuppression probably negatively impact the IE course in these patients.

Heart transplant recipients represent 10% of SOT with IE patients.[811] Among 57 heart transplant recipients who developed IE, the most frequent organism was *S. aureus* (26%), followed by *A. fumigatus* (19%), and *E. faecalis* (12%).[105] The median time to IE presentation after heart transplant was 8 years and the mitral valve was the most frequently affected, followed by mural and tricuspid valve IE. All-cause mortality in this group of patients is high (45%), and fungal aetiology is associated with worse outcomes. Similar to other SOT recipients, heart transplant recipients were not frequently referred to surgery (35%).[105]

12.10.2. Patients with human immunodeficiency virus

The advent of combined antiretroviral treatment has led to a reduction in the risk of developing acquired immune deficiency syndrome (AIDS) but people living with HIV remain a vulnerable population for IE.[812] The incidence of IE in people living with HIV has decreased over the last two decades. A retrospective study from Spain has shown a reduction in the incidence of IE from 18.2 per 100 000 patient-years between 1997 and 1999 to 2.9 events per 100 000 patient-years between 2000 and 2014.[813] Similarly, a registry from the United States of America reported a reduction in the incidence of IE from 148 in 2007 to 112 in 2017.[141] Patients living with HIV and presenting with IE are becoming older, and have a higher percentage of substance abuse and co-morbidities.[141,813] Of importance, the number of patients living with HIV who are admitted with IE have higher frequency of CHD, prior valve surgery, CIED infection, and haemodialysis.[141,813] The most frequent microorganisms causing IE are *Staphylococcus* spp. (the majority of which is *S. aureus*), followed by *Streptococcus* spp., Gram-negative bacilli, and enterococci. It is important to note that over the last two decades, the frequency of CoNS as a cause of IE has decreased whereas the frequency of streptococci, Gram-negative bacilli, enterococci, and fungus has increased.[813] Community-acquired IE has become the most frequent form while healthcare-associated IE rates have significantly decreased over time.

The outcomes of IE in people living with HIV have improved over the years (from 23.9 to 5.5 deaths per 100 000 patient-years) and surgical

treatment should follow the same indications as in patients without HIV.[813]

12.10.3. Patients with neutropaenia

Neutropaenia is common in patients with haematological malignancies and in patients receiving chemotherapy for other malignancies, but is rare in patients presenting with IE.[814] Neutrophils play an important role in the pathogenesis of IE by producing layers of extracellular traps that entrap bacteria-platelet aggregates, leading to expansion of these aggregates, vegetation growth, and the destruction of tissues.[814] The diagnosis of IE can therefore be challenging in patients with neutropaenia, delaying the appropriate treatment, and worsening outcomes. Series reporting the clinical characteristics and outcomes of IE in patients with neutropaenia are anecdotal.[814] As in any other immunocompromised patient with IE, antibiotic and surgical treatment are the same as in patients without neutropaenia. It is important to take into consideration the side effects of some antibiotics which may worsen the neutropaenia, such as cloxacillin and ceftaroline.[815,816]

12.11. Antithrombotic and anticoagulant therapy in infective endocarditis

Infective endocarditis by itself is not an indication for antithrombotics or anticoagulants, and bleeding complications or stroke may in contrast justify discontinuation or interruption of such therapies. Indications for antithrombotic therapy or anticoagulants (e.g. atrial fibrillation, valve prostheses, ischaemic heart disease, prior stroke, etc.) are prevalent in the general population and, as a result, the clinician is often faced with the challenge of these therapies in patients presenting with IE, especially in cases where surgery is part of the treatment course. For patients with IE and stroke, thrombolytic therapy is not recommended (see *Section 9.1*). However, thrombectomy may be considered in selected cases with large vessel occlusion.

The level of evidence underlying the recommendations for antithrombotic and anticoagulant therapy in IE is low and should be discussed within the Endocarditis Team. Bridging with low-molecular-weight heparin/unfractionated heparin instead of oral anticoagulants should be considered early on in the IE course, especially for patients in whom surgery is indicated. To date, no data support initiation of either antithrombotics nor anticoagulants for treatment or prevention of stroke in IE.

Recommendation Table 22 — Recommendations for the use of antithrombotic therapy in infective endocarditis

Recommendation	Class[a]	Level[b]
Interruption of antiplatelet or anticoagulant therapy is recommended in the presence of major bleeding (including intracranial haemorrhage).[482,483]	I	C
In patients with intracranial haemorrhage and a mechanical valve, reinitiating unfractionated heparin should be considered as soon as possible following multidisciplinary discussion.[817]	IIa	C
In the absence of stroke, replacement of oral anticoagulant therapy by unfractionated heparin under close monitoring should be considered in cases where indication for surgery is likely (e.g. *S. aureus* IE).[451,817]	IIa	C
Thrombolytic therapy is not recommended in patients with IE.[481,491]	III	C

Continued

IE, infective endocarditis.
[a]Class of recommendation.
[b]Level of evidence.

12.12. Non-bacterial thrombotic endocarditis

Non-bacterial thrombotic endocarditis (NBTE) is a rare condition with an incidence varying from 1.1% to 1.6% in patient-series from autopsy studies.[818,819] Non-bacterial thrombotic endocarditis occurs in patients with a predisposing factor and/or a hypercoagulable state, such as systemic lupus erythematous (SLE), APLs (Libman–Sacks endocarditis), cancer (marantic endocarditis), disseminated intravascular coagulation (DIC), or various other chronic diseases (tuberculosis or autoimmune disease).[820,821] Increased production of coagulation factors, of cytokines, and high tissue factor expression are potential mechanisms underlying NBTE in cancer patients.[822]

In a recent contemporary registry, 41% of NBTE patients had cancer, 33% SLE, and 36% APLs, with 21% of patients having both SLE and APLs.[823] Among the patients with malignancies, the three most frequent cancers were lung adenocarcinoma, breast, and pancreatic cancer. Stroke was the most frequent clinical presentation at admission (60%), while HF was observed in 21% and acute coronary syndrome in 7% of patients. Transthoracic echocardiography was able to confirm the diagnosis in 45% of patients. The mitral valve was more often affected (62%) than the aortic valve (24%).[823]

The diagnosis of NBTE remains challenging and should be suspected in patients presenting with systemic embolization and a predisposing factor (i.e. cancer, APLs, SLE). Laboratory findings of a hypercoagulable state (eg. lupus anticoagulant, anti-cardiolipin antibodies, and anti-β_2-glycoprotein 1 antibodies or DIC) may be present, but are non-specific and may also be demonstrated in other IE patients with embolic events.[162]

Echocardiography diagnosis should attempt to differentiate non-bacterial thrombotic vegetation from IE, Lambl excrescences, or fibroelastoma, or other benign intracardiac masses/tumours.[824] Libman–Sacks vegetations may present with various shapes (sessile, tubular, or coalescent), various levels of echogenicity (heterogeneously or homogeneously), could be nodular or protuberant, are generally located near the leaflet's edge of coaptation, and frequently have extensions to the mid and basal portions of the leaflet. They are rarely associated with valve dysfunction and never with valve perforation, which is an important method of differentiating from bacterial IE.[824] Compared with TOE, TTE has a lower sensitivity (63%), specificity (58%), negative predictive value (40%), and a moderate positive predictive value (78%) for the detection of NBTE.[823,824] Compared with two-dimensional TOE, three-dimensional TOE provides additional information and allows a better characterization of the vegetation.[823]

The treatment of the underlying cause (i.e. SLE or cancer) is crucial to prevent recurrent NBTE. Anticoagulant treatment should be considered in all patients and should be balanced against the individual

patient's bleeding risk.[821] Patients may be anticoagulated with low-molecular-weight heparin, vitamin K antagonists, or unfractionated heparin. There are no data to support the use of direct oral anticoagulants in NBTE. In a randomized open-label multicentre study comparing rivaroxaban and warfarin in patients with thrombotic APLs, the use of rivaroxaban was associated with an increased rate of thrombo-embolic events and major bleeding.[825] The role of surgery is controversial and remains to be clarified. However, surgery should be considered in patients with severe valve dysfunction or with large vegetations.[823]

12.13. Infective endocarditis and malignancy

There are limited data on the prevalence, clinical presentation, management, and outcome of IE in patients with malignancy. In a retrospective Japanese cohort study including 170 patients, 17.6% had active malignancy.[826] Compared with patients without malignancy, patients with malignancies were older, nosocomial IE was more frequent, and procedures before IE (non-dental, i.v. catheter insertion, invasive endoscopic, or genitourinary procedures) were more frequent.[826] Another recent study from the EURO-ENDO registry of 3085 patients with IE found a history of malignancy in 11.6% of patients.[827] Patients with a history of malignancy had a similar rate of theoretical indications for surgery, but surgery was performed less often in this group. Mortality was higher in the malignancy group with independent predictors for mortality being elevated creatinine >2 mg/dL, congestive HF, and unperformed cardiac surgery when indicated.[827] In IE patients with concomitant cancer, indications for valve surgery should be discussed within the Endocarditis Team, including a cardio-oncologist and the oncologist in charge of the patient, in order to take into account the risks and benefits of surgery and cancer prognosis.

13. Patient-centred care and shared decision-making in infective endocarditis

13.1. What is patient-centred care and shared decision-making and why is it important?

Patient-centred care encourages involvement and collaboration between patients, families, and healthcare providers during all stages of diagnosis, treatment, and recovery.[828–831] Core elements of patient-centred care include: involvement of family and caregivers, respect for patients' preferences and values, care co-ordination and continuity, information and education, as well as physical comfort and emotional support (*Figure 14*).[828–830]

Shared decision-making involves a bidirectional process where patients, family, and healthcare providers share information and discuss care options in the context of the patients' preferences, beliefs and values, and the best available evidence ensuring that the patient understands the risks,[832,833] benefits, and possible consequences of the different options.[834–836] The majority of patients prefer sharing decisions about their own health, if they are sufficiently informed and prepared.[837,838] Patient-centred care and shared decision-making have been shown to contribute to improved concordance between care providers and patients on treatment plans, as well as increased patient satisfaction, quality of life, and health outcomes.[830,839–843]

13.2. Patient-centred care and shared decision-making in infective endocarditis

The severity of IE, the complex and comprehensive diagnostics and treatment, as well as the long illness trajectory, put special emphasis on patient-centred care and shared decision-making in IE (*Figure 14*). Quality of life appears to be impaired in IE survivors, with a significant number of patients developing symptoms of anxiety, depression, or even post-traumatic stress disorder following IE treatment.[604,844]

The time of diagnosis is often emotionally distressing to the patient and family, as they face a life-threatening condition and lengthy treatment.[845]

During the diagnostic and active treatment phase, healthcare providers should make every effort to minimize patient discomfort (e.g. related to symptoms and diagnostic procedures), and alleviate distress in both patient and family by providing support and comprehensive and timely information about the patient's condition, therapeutic options, and prognosis. Independent of the therapeutic strategy (i.e. surgical vs. conservative), patient-centred care is key to ensure a good physical and mental outcome during a lengthy treatment and hospitalization associated with IE. Maintaining continuity of care, when possible, by minimizing the number of providers the patient encounters and minimizing transfers between and within units, is all part of a patient-centred care approach. Allowing family visits at any time and providing the opportunity to uphold personal integrity and autonomy are important issues for patients. National patient organizations and associations may be an option for offering information and support to patients and their families.

The role of outpatient antimicrobial treatment options in IE should be discussed using a shared decision-making approach, involving the patient's partner or family if possible. The outpatient treatment should be in concordance with the patient's and family's preferences, also considering transportation and self-care abilities. To monitor possible complications, it is important to inform and educate patients and caregivers about the signs and symptoms of disease progression or recurrence.

The early period after discharge can be challenging for patients and their families, and patients report slow physical and mental recovery after IE, often extending longer than anticipated.[603,604,846,847] Patient-centred care should therefore extend further than the clinical treatment at the hospital to ensure a good outcome after discharge. Though little research has explored patients' and families' needs for recovery and rehabilitation following IE, patients with heart disease report experiencing new and continuous challenges and a lack of knowledge and understanding after discharge, which should be addressed to optimize recovery.[848]

It is recommended that a recovery plan is developed in collaboration with the patient and their caregivers and that the plan is reviewed and potentially adjusted following a short period after discharge.[849]

Physical exercise should be recommended based on an individual assessment of functional capacity (guided by physicians and physiotherapists), and patient education and psychosocial support should address the main problems and concerns patients and families have. Importantly, patient education should also include information about the risk of recurrence and preventive measures described in *Sections 3* and *11*. Special consideration should be taken for patients with no close relatives. Self-support groups or mentors may be introduced to patients without support networks. Also, follow-up by telephone from the ward staff, until full recovery has been reached, may be an option.

A palliative approach aims to improve the quality of life of patients and their families who are facing problems associated with life-threatening illness, which is relevant for many patients with IE. This approach includes a holistic, needs-based perspective with the aims of

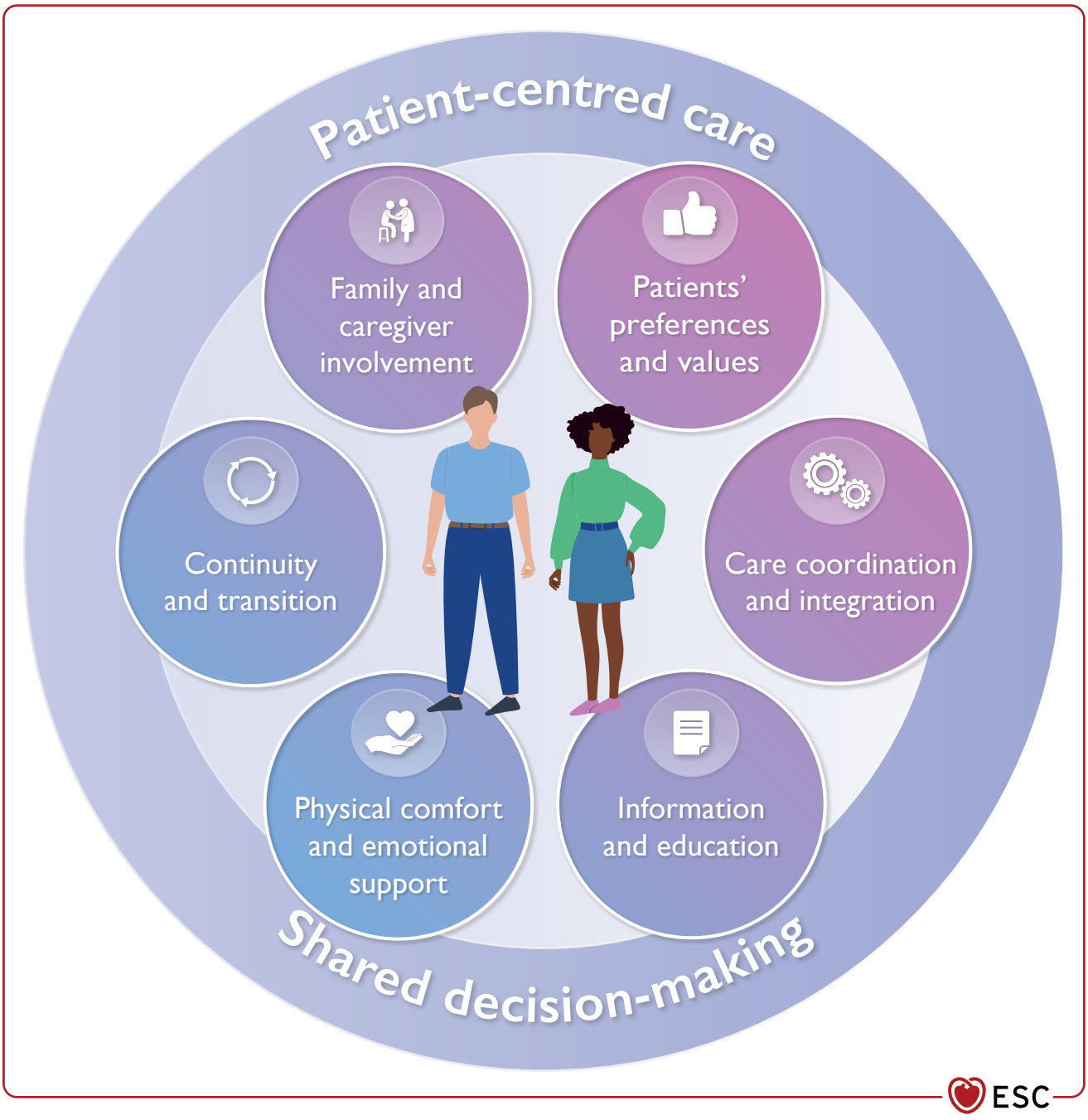

Figure 14 Concept of patient-centred care in infective endocarditis.

assessing and improving symptom management, communication, advanced care planning, as well as psychosocial and spiritual needs.[850]

14. Sex differences

Female sex is less common in patients diagnosed with IE, being present in approximately one-third of cases; a finding that has been demonstrated in multiple IE patient subpopulations and across different regions.[5,59,723,851,852] The reason why female sex is observed less frequently in IE is unknown and deserves further investigation. Possible reasons include underdiagnosis of IE in women, referral bias in published studies, intrinsic protective mechanisms against IE in women, and decreased incidence of risk factors for IE in women (e.g. bicuspid aortic valve disease, previous heart valve replacement surgery), among others. A recent nationwide population study of individual patient-level linkage data of 7513 patients hospitalized for IE in Scotland, however, demonstrated roughly equal proportions of male and female patients throughout the 25-year study period.[27]

Female patients with IE have been demonstrated to have a higher prevalence of several risk factors for IE in comparison to their male counterparts including older age, mitral valve involvement, *S. aureus* infection, neurological symptoms, and haemodialysis.[853–856] However, men have a higher prevalence of other important risk factors including previous prosthetic valve replacement, periannular complications, CAD, and liver cirrhosis.[855]

Some studies have demonstrated higher mortality rates for female patients with IE,[856] while others have demonstrated no differences in

early and 1-year mortality rates between males and females.[853,855,857] The abovementioned population study from Scotland showed lower mortality rates for women during the study period.[27]

Although surgery has been demonstrated to be protective against mortality in several clinical scenarios (see *Section 8*), surgery is performed less frequently in female patients with IE.[855,856] In a study using the National Inpatient Sample of 81 942 patients hospitalized for IE over an 11-year period, women were 43% less likely to undergo valve replacement surgery, a significant difference that remained after adjusting for confounding factors.[855] The reason for decreased surgery in female IE patients is unknown and requires further investigation.

Female sex has also been identified as an independent risk factor for mortality in prediction models for patients with IE undergoing surgery.[416] However, a single-centre study suggested that worse observed surgical outcomes in female patients with IE was related to their increased risk factors and severity of presentation, rather than gender per se.[854] In addition, a large multicentre registry of 4300 patients undergoing surgery for IE failed to identify female gender as an independent predictor of mortality.[852]

15. Key messages

Prevention:

- Populations at high risk of IE include patients with previous IE, patients with surgical or transcatheter prosthetic valves or post-cardiac valve repair, and patients with untreated CHD and surgically corrected CHD.
- Prevention of IE comprise hygienic measures (including oral hygiene) for all individuals and antibiotic prophylaxis for patients at high risk of IE undergoing oro-dental procedures.

The Endocarditis Team:

- The diagnosis and management of patients with IE should be discussed with the Endocarditis Team, which includes healthcare professionals with the expertise to diagnose and treat IE and its complications.
- Uncomplicated IE can be managed in a Referring Centre that remains in early and regular communication with the Endocarditis Team of the Heart Valve Centre.
- Patients with complicated IE should be treated in the Heart Valve Centre, which must offer a wide range of ancillary specialty support including onsite cardiac surgery expertise.

Diagnosis:

- The diagnosis of IE is based on major criteria, which include positive blood cultures and valvular and perivalvular/periprosthetic anatomic and metabolic lesions detected on imaging, and on minor criteria which have been updated to include frequent embolic vascular dissemination including asymptomatic lesions detected by imaging only.
- Clear diagnostic algorithms have been established to diagnose NVE, PVE, and right-sided IE.

Antimicrobial therapy – principles and methods:

- Successful treatment of IE relies on microbial eradication by antimicrobial drugs. Surgery contributes by removing infected material and draining abscesses.
- Antibiotic treatment of PVE should last longer (≥6 weeks) than that of NVE (2–6 weeks).
- 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.
- The initial choice of empirical treatment depends on the use of previous antibiotic therapy, whether IE is NVE or PVE (and if so, when surgery was performed [early vs. late PVE]), the place where the infection took place (community, nosocomial, or non-nosocomial healthcare-associated IE), and knowledge of the local epidemiology.
- The antibiotic treatment of IE has two phases. The first phase consists of 2 weeks of in-hospital i.v. treatment. In this initial phase, cardiac surgery should be performed if indicated, infected foreign bodies should be removed, and cardiac as well as extracardiac abscesses should be drained. In the second phase, in selected patients, the antibiotic treatment can be completed within an outpatient parenteral or oral antibiotic programme for up to 6 weeks.
- Aminoglycosides are not recommended in staphylococcal NVE because their clinical benefits have not been demonstrated. In IE caused by other microorganisms in which aminoglycosides are indicated, they should be prescribed in a single daily dose to reduce nephrotoxicity.
- Rifampin should be used only in IE involving foreign material, such as PVE, after 3–5 days of effective antibiotic therapy.
- When daptomycin is indicated, it must be given at high doses (10 mg/kg once daily) and combined with a second antibiotic (beta-lactams or fosfomycin in beta-lactam allergic patients) to increase activity and avoid the development of resistance.
- OPAT can only start when a TOE shows absence of local progression and complications (e.g. severe valvular dysfunction).
- In the OPAT programme, patients continue with the same antibiotics administered in the acute phase, if possible.

Indications for surgery and management of main infective endocarditis complications:

- There are three main reasons to undergo surgery in the setting of acute IE: HF, uncontrolled infection, and prevention of septic embolization.
- While surgery during the acute phase of IE is usually performed on an urgent basis (i.e. the patient undergoes surgery within 3–5 days), some cases require emergency surgery (i.e. within 24 h), irrespective of the pre-operative duration of antibiotic treatment.

Other complications of infective endocarditis:

- Stroke may be the first presenting symptom in patients with IE. Unexplained fever accompanying a stroke in a patient with risk factors for IE should trigger the suspicion of IE.
- Epicardial pacemaker implantation should be considered in patients undergoing surgery for IE with complete AVB and other risk factors.
- MRI or PET/CT are indicated in patients with suspected spondylodiscitis and vertebral osteomyelitis complicating IE.

Surgical therapy principles and methods:

- The indication to perform invasive coronary angiography or CTA prior to surgery for IE should be based on the presence of cardiovascular risk factors in patients with aortic valve IE.
- Surgery should not be delayed in patients with non-haemorrhagic stroke and clear indications for surgery. In patients with significant

pre-operative haemorrhagic stroke, a delay in operative management (≥4 weeks) is generally recommended.
- The decision of not offering surgery when indicated should be made in the setting of an Endocarditis Team.

Outcome after discharge – follow-up and long-term prognosis:

- Relapse is a repeat episode of IE caused by the same microorganism and represents a failure of treatment, and mandates a search for a persistent focus of infection and an evaluation towards surgical therapy.
- Reinfection is an infection caused by a different microorganism, usually more than 6 months after the initial episode.
- Once antibiotic treatment has been completed, blood cultures should be performed.
- Patients discharged after the first episode of IE should remain under close surveillance for potential long-term complications.

Management of specific situations:

- Antibiotic prophylaxis to prevent CIED-related IE before dental and other non-cardiac interventions is not warranted.
- A single positive blood culture with no other clinical evidence of infection should not result in removal of the CIED. Complete CIED removal is recommended for all patients with confirmed infection of the lead(s).
- The indication for CIED reimplantation should always be re-evaluated and no part of the removed system should be reimplanted. In pacemaker-dependent patients, an active-fixation lead may be introduced and connected to an external pacemaker for up to 6 weeks.
- Surgical treatment of right-sided IE is indicated in patients with persistent bacteraemia, right ventricular dysfunction, recurrent septic pulmonary embolism and respiratory compromise, and involvement of left-sided structures.
- Multidisciplinary care of CHD patients with IE, from diagnosis to treatment, should be provided in specialized CHD centres with expertise in CHD cardiac imaging, CHD surgery, and intensive care.

Patient-centred care and shared decision-making in infective endocarditis:

- In patients with IE, shared decision-making enables the integration of patients' preferences, values, and priorities to achieve a good treatment decision.
- In patients with IE and without support networks or severely impacted by social determinants, a recovery plan developed in collaboration with the patient should be established, highlighting the information about the risk of recurrence and preventive measures.

Sex differences:

- Female sex is less common in patients diagnosed with IE, being present in approximately one-third of cases.

16. Gaps in evidence

- The majority of the recommendations with a level of evidence B are based on observational studies rather than single RCTs or meta-analyses from RCTs.

Prevention:

- In the intermediate or unknown risk condition groups, there is no evidence to recommend antibiotic prophylaxis.
- There is currently no evidence to support the use of antibiotic prophylaxis after the implantation of a left atrial appendage occlusion device.

Diagnosis:

- More data on the accuracy of diagnosis of culture-negative IE using molecular biology techniques, or the determination of bacterial/fungal cell-free DNA in blood samples, is required.
- Standardization of the methodology to assess the size of the vegetations has not been established.
- More data on the diagnostic performance of intracardiac echocardiography in PVE are needed.
- The role of [18F]FDG-PET/CT(A) in NVE needs to be established.
- Routine use of imaging tests to screen the presence of embolic events, especially brain imaging, is not well established.
- In fungal endocarditis, the role of molecular and biochemical indicators to establish the diagnosis is not well studied.

Antimicrobial therapy – principles and methods:

- Clinical trials are needed to assess the efficacy and safety of recommended antimicrobial treatment regimens and new combinations or antimicrobials. Many recommendations come from clinical trials for bacteraemia and not for IE.
- Effective antibiotic treatment in patients with highly penicillin-resistant oral streptococci should be investigated.
- Randomized data to establish the best medical strategy in staphylococcal IE are required.
- Effective antibiotic treatments for patients with HLAR *E. faecalis* IE and hypersensitivity to beta-lactams need further research.
- Effective treatments for vancomycin-resistant enterococcal IE need further research.
- Randomized head-to-head comparisons of different antibiotics to better judge efficacy and toxicity (e.g. for aminoglycosides) are needed.
- The duration of antibiotic treatment has been established empirically and no randomized data have been published.
- The efficacy of combined antifungal therapy has not been studied.
- The empirical use of an aminoglycoside-sparing empirical combination regimen has not been extensively studied.
- More data on implementation of oral treatment in large studies are needed.

Indications for surgery and management of main infective endocarditis complications:

- The indication of surgical treatment in patients with IE rely mainly on expert opinion based on observational studies.
- RCTs are required to establish the indication and timing of surgery in patients with:
  - Increased surgical risk.
  - Large vegetations but without other indications for surgery.
  - Cerebral emboli or bleeding.
  - Patients with uncontrolled infection.
- More data on the need and timing of coronary angiogram before endocarditis surgery.
- There is a lack of information on timing and sequence of interventions in patients with multiple septic sources.
- More data are needed on the efficacy and safety of vegetation extraction systems in right-sided IE.

Other complications of infective endocarditis:

- There is limited information on the safety and efficacy of mechanical thrombectomy in IE-related embolic strokes.
- There are no prospective data on the timing and safety of splenectomy for splenic abscess, complicating IE in relation to surgical valve treatment.

Surgical therapy principles and methods:

- There is a significant need for scores to predict futility of surgical management in very high-risk patients.
- There is a lack of data on the most appropriate anticoagulation regimen in patients with PVE complicated by haemorrhagic stroke.

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

- Clinical trials are required to assess the efficacy of rehabilitation, including optimal timing, duration, methods, and components.
- Data on patient-reported outcomes during short- and long-term follow-up are needed.

Management of specific situations:

- Additional data on the incidence, characteristics, and outcomes of IE in patients treated with transcatheter valve therapies or left atrial appendage occluders are needed.
- There is an unmet clinical question on the efficacy and safety of surgical treatment of IE in patients previously treated with transcatheter valve therapies.
- Randomized data on the timing of CIED reimplantation after device removal after CIED infection are needed.
- There is a lack of evidence on whether or not CIED removal should be routinely performed in patients with left-sided IE.
- Randomized data on surgery in right-sided IE are required.

Patient-centred care and shared decision-making in infective endocarditis:

- As no disease-specific evidence exists, data on patient-centred care and shared decision-making in IE is needed.
- Data on how patient-centred care and shared decision-making in patients with social and mental health vulnerabilities can improve their outcomes are lacking.
- Data on the effect of patient-centred care and shared decision-making interventions are required to implement effective strategies.

Sex differences:

- Further data are required to determine why IE is less frequently observed, and why the outcomes are worse, in female patients.
- The reasons for lower referral to surgery in female patients with IE as compared with male patients need to be determined and addressed.

17. 'What to do' and 'What not to do' messages from the Guidelines

Table 14 'What to do' and 'What not to do'

Recommendations	Class[a]	Level[b]
Recommendations for antibiotic prophylaxis in patients with cardiovascular diseases undergoing oro-dental procedures at increased risk of infective endocarditis		
Antibiotic prophylaxis is recommended in patients with previous IE.	I	B
General prevention measures are recommended in individuals at high and intermediate risk of IE.	I	C
Antibiotic prophylaxis is recommended in patients with surgically implanted prosthetic valves and with any material used for surgical cardiac valve repair.	I	C
Antibiotic prophylaxis is recommended in patients with transcatheter implanted aortic and pulmonary valvular prostheses.	I	C
Antibiotic prophylaxis is recommended in patients with untreated cyanotic CHD, and patients treated with surgery or transcatheter procedures with post-operative palliative shunts, conduits, or other prostheses. After surgical repair, in the absence of residual defects or valve prostheses, antibiotic prophylaxis is recommended only for the first 6 months after the procedure.	I	C
Antibiotic prophylaxis is recommended in patients with ventricular assist devices.	I	C
Antibiotic prophylaxis is not recommended in other patients at low risk of IE.	III	C
Recommendations for infective endocarditis prevention in high-risk patients		
Antibiotic prophylaxis is recommended in dental extractions, oral surgery procedures, and procedures requiring manipulation of the gingival or periapical region of the teeth.	I	B
Recommendations for infective endocarditis prevention in cardiac procedures		
Pre-operative screening for nasal carriage of *S. aureus* is recommended before elective cardiac surgery or transcatheter valve implantation to treat carriers.	I	A
Peri-operative antibiotic prophylaxis is recommended before placement of a CIED.	I	A
Optimal pre-procedural aseptic measures of the site of implantation are recommended to prevent CIED infections.	I	B
Periprocedural antibiotic prophylaxis is recommended in patients undergoing surgical or transcatheter implantation of a prosthetic valve, intravascular prosthetic, or other foreign material.	I	B

Continued

Surgical standard aseptic measures are recommended during the insertion and manipulation of catheters in the catheterization laboratory environment.		I	C
Systematic skin or nasal decolonization without screening for *S. aureus* is not recommended.		III	C
Recommendations for the Endocarditis Team			
Diagnosis and management of patients with complicated IE are recommended to be performed at an early stage in a Heart Valve Centre, with immediate surgical facilities and an 'Endocarditis Team' to improve the outcomes.		I	B
For patients with uncomplicated IE managed in a Referring Centre, early and regular communication between the local and the Heart Valve Centre endocarditis teams is recommended to improve the outcomes of the patients.		I	B
Recommendations for the role of echocardiography in infective endocarditis			
A. 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
TOE is recommended in patients with clinical suspicion of IE, when a prosthetic heart valve or an intracardiac device is present.		I	B
Repeating TTE and/or TOE within 5–7 days is recommended in cases of initially negative or inconclusive examination when clinical suspicion of IE remains high.		I	C
TOE is recommended 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.		I	C
B. Follow-up under medical therapy			
Repeating TTE and/or TOE is recommended as soon as a new complication of IE is suspected (new murmur, embolism, persisting fever and bacteraemia, HF, abscess, AVB).		I	B
TOE is recommended when the patient is stable before switching from intravenous to oral antibiotic therapy.		I	B
C. Intra-operative echocardiography			
Intra-operative echocardiography is recommended in all cases of IE requiring surgery.		I	C
D. Following completion of therapy			
TTE and/or TOE are recommended at completion of antibiotic therapy for evaluation of cardiac and valve morphology and function in patients with IE who did not undergo heart valve surgery.		I	C
Recommendations for the role of computed tomography, nuclear imaging, and magnetic resonance in infective endocarditis			
Cardiac CTA is recommended in patients with possible NVE to detect valvular lesions and confirm the diagnosis of IE.		I	B
[18F]FDG-PET/CT(A) and cardiac CTA are recommended in possible PVE to detect valvular lesions and confirm the diagnosis of IE.		I	B
Cardiac CTA is recommended in NVE and PVE to diagnose paravalvular or periprosthetic complications if echocardiography is inconclusive.		I	B
Brain and whole-body imaging (CT, [18F]FDG-PET/CT, and/or MRI) are recommended in symptomatic patients with NVE and PVE to detect peripheral lesions or add minor diagnostic criteria.		I	B
Recommendations for antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus gallolyticus* group			
Penicillin-susceptible oral streptococci and *Streptococcus gallolyticus* group			
Standard treatment: 4-week duration in NVE or 6-week duration in PVE			
In patients with IE due to oral streptococci and *S. gallolyticus* group, penicillin G, amoxicillin, or ceftriaxone are recommended for 4 (in NVE) or 6 weeks (in PVE), using the following doses:		I	B
Adult antibiotic dosage and route			
Penicillin G	12–18 million U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Paediatric antibiotic dosage and route			
Penicillin G	200 000 U/kg/day i.v. in 4–6 divided doses		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg/day i.v. in 1 dose		
Standard treatment: 2-week duration (not applicable to PVE)			
2-week treatment with penicillin G, amoxicillin, ceftriaxone combined with gentamicin is recommended only for the treatment of non-complicated NVE due to oral streptococci and *S. gallolyticus* in patients with normal renal function using the following doses:		I	B
Adult antibiotic dosage and route			
Penicillin G	12–18 million U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		

Continued

Ceftriaxone	2 g/day i.v. in 1 dose		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Penicillin G	12–18 million U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg i.v. in 1 dose		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose or 3 equally divided doses		
Allergy to beta-lactams			
In patients allergic to beta-lactams and with IE due to oral streptococci and *S. gallolyticus*, vancomycin for 4 weeks in NVE or for 6 weeks in PVE is recommended using the following doses:		I	C
Adult antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2 doses		
Paediatric antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2 or 3 equally divided doses		
Oral streptococci and *Streptococcus gallolyticus* group susceptible, increased exposure or resistant to penicillin			
In patients with NVE due to oral streptococci and *S. gallolyticus*, penicillin G, amoxicillin, or ceftriaxone for 4 weeks in combination with gentamicin for 2 weeks is recommended using the following doses:		I	B
Adult antibiotic dosage and route			
Penicillin G	24 million U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	2 g/day i.v. in 6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		
In patients with PVE due to oral streptococci and *S. gallolyticus*, penicillin G, amoxicillin, or ceftriaxone for 6 weeks combined with gentamicin for 2 weeks is recommended using the following doses:		I	B
Adult antibiotic dosage and route			
Penicillin G	24 million U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	2 g/day i.v. in 6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		
Allergy to beta-lactams			
In patients with NVE due to oral streptococci and *S. gallolyticus* and who are allergic to beta-lactams, vancomycin for 4 weeks is recommended using the following doses:		I	C
Adult antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2 doses		
Paediatric antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2 doses		
In patients with PVE due to oral streptococci and *S. gallolyticus* and who are allergic to beta-lactams, vancomycin for 6 weeks combined with gentamicin for 2 weeks is recommended using the following doses:		I	C
Adult antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2 doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2 doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		
Recommendations for antibiotic treatment of infective endocarditis due to *Staphylococcus* spp.			
IE caused by methicillin-susceptible staphylococci			
In patients with NVE due to methicillin-susceptible staphylococci, (flu)cloxacillin or cefazolin is recommended for 4–6 weeks using the following doses:		I	B
Adult antibiotic dosage and route			
(Flu)cloxacillin	12 g/day i.v. in 4–6 doses		
Cefazolin	6 g/day i.v. in 3 doses		
Paediatric antibiotic dosage and route			
(Flu)cloxacillin	200–300 mg/kg/day i.v. in 4–6 equally divided doses		
Cefazolin	6 g/day i.v. in 3 doses		

Continued

In patients with PVE due to methicillin-susceptible staphylococci, (flu)cloxacillin or cefazolin with rifampin for at least 6 weeks and gentamicin for 2 weeks is recommended using the following doses:		I	B
Adult antibiotic dosage and route			
(Flu)cloxacillin	12 g/day i.v. in 4–6 doses		
Cefazolin	6 g/day i.v. in 3 doses		
Rifampin	900 mg/day i.v. or orally in 3 equally divided doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Paediatric antibiotic dosage and route			
(Flu)cloxacillin	200–300 mg/kg/day i.v. in 4–6 equally divided doses		
Cefazolin	6 g/day i.v. in 3 doses		
Rifampin	20 mg/kg/day i.v. or orally in 3 equally divided doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Allergy to beta-lactams			
In patients with NVE due to methicillin-susceptible staphylococci who are allergic to penicillin, cefazolin for 4–6 weeks is recommended using the following doses:		I	B
Adult antibiotic dosage and route			
Cefazolin	6 g/day i.v. in 3 doses		
Paediatric antibiotic dosage and route			
Cefazolin	6 g/day i.v. in 3 doses		
In patients with PVE due to methicillin-susceptible staphylococci who are allergic to penicillin, cefazolin combined with rifampin for at least 6 weeks and gentamicin for 2 weeks is recommended using the following doses:		I	B
Adult antibiotic dosage and route			
Cefazolin	6 g/day i.v. in 3 doses		
Rifampin	900 mg/day i.v. or orally in 3 equally divided doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Paediatric antibiotic dosage and route			
Cefazolin	6 g/day i.v. in 3 doses		
Rifampin	20 mg/kg/day i.v. or orally in 3 equally divided doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
IE caused by methicillin-resistant staphylococci			
In patients with NVE due to methicillin-resistant staphylococci, vancomycin is recommended for 4–6 weeks using the following doses:		I	B
Adult antibiotic dosage and route			
Vancomycin	30–60 mg/kg/day i.v. in 2–3 doses		
Paediatric antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2–3 equally divided doses		
In patients with PVE due to methicillin-resistant staphylococci, vancomycin with rifampin for at least 6 weeks and gentamicin for 2 weeks is recommended using the following doses:		I	B
Adult antibiotic dosage and route			
Vancomycin	30–60 mg/kg/day i.v. in 2–3 doses		
Rifampin	900–1200 mg/day i.v. or orally in 2 or 3 divided doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Paediatric antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2–3 equally divided doses		
Rifampin	20 mg/kg/day i.v. or orally in 2 or 3 divided doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Recommendations for antibiotic treatment of infective endocarditis due to *Enterococcus* spp.			
Beta-lactam and gentamicin-susceptible strains			
In patients with NVE due to non-HLAR *Enterococcus* spp., the combination of ampicillin or amoxicillin with ceftriaxone for 6 weeks or with gentamicin for 2 weeks is recommended using the following doses:		I	B
Adult antibiotic dosage and route			
Amoxicillin	200 mg/kg/day i.v. in 4–6 doses		
Ampicillin	12 g/day i.v. in 4–6 doses		

Continued

Ceftriaxone	4 g/day i.v. in 2 doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Ceftriaxone	100 mg/kg i.v. in 2 doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 3 equally divided doses		
In patients with PVE and patients with complicated NVE or >3 months of symptoms due to non-HLAR *Enterococcus* spp., the combination of ampicillin or amoxicillin with ceftriaxone for 6 weeks or with gentamicin for 2 weeks is recommended using the following doses:		I	B
Adult antibiotic dosage and route			
Amoxicillin	200 mg/kg/day i.v. in 4–6 doses		
Ampicillin	12 g/day i.v. in 4–6 doses		
Ceftriaxone	4 g/day i.v. in 2 doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg/day i.v. in 2 doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 3 equally divided doses		
High-level aminoglycoside resistance			
In patients with NVE or PVE due to HLAR *Enterococcus* spp., the combination of ampicillin or amoxicillin and ceftriaxone for 6 weeks is recommended using the following doses:		I	B
Adult antibiotic dosage and route			
Ampicillin	12 g/day i.v. in 4–6 doses		
Amoxicillin	200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	4 g/day i.v. or i.m. in 2 doses		
Paediatric antibiotic dosage and route			
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg i.v. or i.m. in 2 doses		
Beta-lactam-resistant *Enterococcus* spp. (*E. faecium*)			
In patients with IE due to beta-lactam-resistant *Enterococcus* spp. (*E. faecium*), vancomycin for 6 weeks combined with gentamicin for 2 weeks is recommended using the following doses:		I	C
Adult antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2 doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2–3 equally divided doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		
Vancomycin-resistant *Enterococcus* spp.			
In patients with IE due to vancomycin-resistant *Enterococcus* spp., daptomycin combined with beta-lactams (ampicillin, ertapenem, or ceftaroline) or fosfomycin is recommended using the following doses:		I	C
Adult antibiotic dosage and route			
Daptomycin	10–12 mg/kg/day i.v. in 1 dose		
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Fosfomycin	12 g/day i.v. in 4 doses		
Ceftaroline	1800 mg/day i.v. in 3 doses		
Ertapenem	2 g/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Daptomycin	10–12 mg/kg/day i.v. in 1 dose (age-adjusted)		
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Fosfomycin	2–3 g/day i.v. in 1 dose		
Ceftaroline	24–36 mg/kg/day in 3 doses		
Ertapenem	1 g/day i.v. or i.m. in 1 dose (if younger than 12 years, 15 mg/kg/dose [to a maximum of 500 mg] twice daily)		

Continued

Recommendations for outpatient antibiotic treatment of infective endocarditis		
Outpatient parenteral antibiotic treatment is not recommended in patients with IE caused by highly difficult-to-treat microorganisms, liver cirrhosis (Child–Pugh B or C), severe cerebral nervous system emboli, untreated large extracardiac abscesses, heart valve complications, or other severe conditions requiring surgery, severe post-surgical complications, and PWID-related IE.	III	C
Recommendations for the main indications of surgery in infective endocarditis (native valve endocarditis and prosthetic valve endocarditis)		
(i) Heart failure		
Emergency surgery is recommended in aortic or mitral NVE or PVE with severe acute regurgitation, obstruction, or fistula causing refractory pulmonary oedema or cardiogenic shock.	I	B
Urgent surgery is recommended in aortic or mitral NVE or PVE with severe acute regurgitation or obstruction causing symptoms of HF or echocardiographic signs of poor haemodynamic tolerance.	I	B
(ii) Uncontrolled infection		
Urgent surgery is recommended in locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation, prosthetic dehiscence, new AVB).	I	B
Urgent or non-urgent surgery is recommended in IE caused by fungi or multiresistant organisms according to the haemodynamic condition of the patient.	I	C
(iii) Prevention of embolism		
Urgent surgery is recommended in aortic or mitral NVE or PVE with persistent vegetations ≥10 mm after one or more embolic episodes despite appropriate antibiotic therapy.	I	B
Urgent surgery is recommended in IE with vegetation ≥10 mm and other indications for surgery.	I	C
Recommendations for the treatment of neurological complications of infective endocarditis		
Brain CT or MRA is recommended in patients with IE and suspected infective cerebral aneurysms.	I	B
Neurosurgery or endovascular therapy is recommended for large aneurysms, those with continuous growth despite optimal antibiotic therapy, and ruptured intracranial infective cerebral aneurysms.	I	C
Thrombolytic therapy is not recommended in embolic stroke due to IE.	III	C
Recommendations for patients with musculoskeletal manifestations of infective endocarditis		
MRI or PET/CT is recommended in patients with suspected spondylodiscitis and vertebral osteomyelitis complicating IE.	I	C
TTE/TOE is recommended to rule out IE in patients with spondylodiscitis and/or septic arthritis with positive blood cultures for typical IE microorganisms.	I	C
Recommendations for pre-operative coronary anatomy assessment in patients requiring surgery for infective endocarditis		
In haemodynamically stable patients with aortic valve vegetations who require cardiac surgery and are high risk of CAD, a high-resolution multislice coronary CTA is recommended.	I	B
Invasive coronary angiography is recommended in patients requiring heart surgery who are high risk of CAD, in the absence of aortic valve vegetations.	I	C
Indications and timing of cardiac surgery after neurological complications in active infective endocarditis		
After a transient ischaemic attack, cardiac surgery, if indicated, is recommended without delay.	I	B
After a stroke, surgery is recommended without any delay in the presence of HF, uncontrolled infection, abscess, or persistent high embolic risk, as long as coma is absent and the presence of cerebral haemorrhage has been excluded by cranial CT or MRI.	I	B
Recommendations for post-discharge follow-up		
Patient education on the risk of recurrence and preventive measures, with emphasis on dental health, and based on the individual risk profile is recommended during follow-up.	I	C
Addiction treatment for patients following PWID-related IE is recommended.	I	C
Recommendations for prosthetic valve endocarditis		
Surgery is recommended for early PVE (within 6 months of valve surgery) with new valve replacement and complete debridement.	I	C
Recommendations for cardiovascular implanted electronic device-related infective endocarditis		
Antibiotic prophylaxis covering *S. aureus* is recommended for CIED implantation.	I	A
TTE and TOE are both recommended in cases of suspected CIED-related IE to identify vegetations.	I	B
Complete system extraction without delay is recommended in patients with definite CIED-related IE under initial empirical antibiotic therapy.	I	B

Continued

Obtaining at least three sets of blood cultures is recommended before prompt initiation of empirical antibiotic therapy for CIED infection, covering methicillin-resistant staphylococci and Gram-negative bacteria.	I	C
If CIED reimplantation is indicated after extraction for CIED-related IE, it is recommended to be performed at a site distant from the previous generator, as late as possible, once signs and symptoms of infection have abated, and until blood cultures are negative for at least 72 h in the absence of vegetations, and negative for at least 2 weeks if vegetations were visualized.	I	C
Removal of CIED after a single positive blood culture, with no other clinical evidence of infection, is not recommended.	III	C
Recommendations for the surgical treatment of right-sided infective endocarditis		
Surgery is recommended in patients with right-sided IE who are receiving appropriate antibiotic therapy for the following scenarios:		
Right ventricular dysfunction secondary to acute severe tricuspid regurgitation non-responsive to diuretics.	I	B
Persistent vegetation with respiratory insufficiency requiring ventilatory support after recurrent pulmonary emboli.	I	B
Large residual tricuspid vegetations (>20 mm) after recurrent septic pulmonary emboli.	I	C
Patients with simultaneous involvement of left-heart structures.	I	C
Recommendations for the use of antithrombotic therapy in infective endocarditis		
Interruption of antiplatelet or anticoagulant therapy is recommended in the presence of major bleeding (including intracranial haemorrhage).	I	C
Thrombolytic therapy is not recommended in patients with IE.	III	C

[18F]FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; AVB, atrioventricular block; CAD, coronary artery disease; CHD, congenital heart disease; CIED, cardiovascular implanted electronic device; CT, computed tomography; CTA, computed tomography angiography; HF, heart failure; HLAR, high-level aminoglycoside resistance; IE, infective endocarditis; i.m., intramuscular; i.v., intravenous; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NVE, native valve endocarditis; PET, positron emission tomography; PVE, prosthetic valve endocarditis; PWID, people who inject drugs; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography.
[a]Class of recommendation.
[b]Level of evidence.

18. Supplementary data

Supplementary data are available at *European Heart Journal* online.

19. Data availability

No new data were generated or analysed in support of this research.

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21. Appendix

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