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2023 ESC Guidelines for the management of endocarditis Supplementary data

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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Abbreviations and acronyms

[18F]FDG	^{18}F-fluorodeoxyglucose
99mTc-HMPAO	^{99m}Technetium-hexamethylpropyleneamine oxime
ACT	Active clotting time
CIED	Cardiovascular implanted electronic device
CoNS	Coagulase-negative staphylococci
CPB	Cardio-pulmonary bypass
CRT	Cardiac resynchronization therapy
CT	Computed tomography
CTA	Computed tomography angiography
ECG	Electrocardiogram
EURO-ENDO	European Infective Endocarditis Registry
GFR	Glomerular filtration rate
HACEK	*Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella,* and *Kingella*
HF	Heart failure
HIV	Human immunodeficiency virus
IABP	Intra-aortic balloon pump
ICD	Implantable cardioverter defibrillator
IE	Infective endocarditis
Ig	Immunoglobulin
i.v.	Intravenous
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
NPV	Negative predictive value
NVE	Native valve endocarditis
OAI	Osteoarticular infection
OPAT	Outpatient parenteral antibiotic therapy
PADIT	Previous procedure on same pocket; Age; Depressed renal function; Immunocompromised; Type of procedure
PET/CT(A)	Positron emission tomography/computed tomography (angiography)
PVE	Prosthetic valve endocarditis
PWID	People who inject drugs
RCT	Randomized clinical trial
RVOT	Right ventricular outflow tract
SUVmax	Maximum standardized uptake value
SUVmean	Mean standardized uptake value
SUVratio	Prosthesis-to-background (hepatic or blood pool) standardized uptake value
TAVI	Transcatheter aortic valve implantation
TOE	Transoesophageal echocardiography
TTE	Transthoracic echocardiography
WBC SPECT	White blood cell single photon emission tomography

1. Prevention

1.1. Cardiac or vascular interventions

Prophylaxis in cardiovascular implanted electronic device (CIED) implantation is recommended. A randomized clinical trial (RCT) has shown the efficacy of 1 g intravenous (i.v.) cefazolin on the prevention of local and systemic infections before pacemaker implantation.[1] In transcatheter valve procedures staphylococcal and enterococcal infections are the more frequent, with enterococcal infection more prevalent periprocedurally.[2] The high prevalence of *Enterococcus faecalis* in patients with infective endocarditis (IE) after transcatheter aortic valve implantation (TAVI) may be related to differences in the flora colonizing the groin when the femoral vascular access is used.[3,4] This underscores the focus on procedural infection prevention as much as prophylaxis in those higher risk patients. That should include aseptic measures during the insertion and manipulation of catheters with surgical standards also used in the catheter laboratory environment.

In terms of antibiotic prophylaxis, the International Society for Cardiovascular Infectious Diseases recommends antibiotic prophylaxis to cover for *Enterococcus* spp.[4] The present Task Force extends this recommendation to all transcatheter valvular procedures:

- Single dose of amoxicillin/clavulanic acid 2.2 g i.v. within 120 min before vascular access (ideally within 60 min). As an alternative to this regimen, a single dose of ampicillin 3 g i.v. can be used.
- In case of beta-lactam allergy, a single dose of vancomycin 15 mg/kg or teicoplanin 9–12 mg/kg i.v. is recommended.[4]

In other structural transcatheter procedures (interatrial or ventricular septal and left atrial appendage occluders, edge-to-edge repair devices), there is a lack of robust data on the incidence of IE. While the reported number of observed IE seem to be low, empirical periprocedural prophylaxis should be considered.[5,6]

2. Diagnosis

2.1. Clinical features

Table S1 Symptoms and signs of infective endocarditis in the EURO-ENDO registry

	PVE (%) (*n* = 939)	NVE (%) (*n* = 1764)	CIED (%) (*n* = 308)
Signs and symptoms			
Fever	77.3	78.9	72.3
Cough	13.1	20.1	12.8
Dizziness	9.9	11.4	8.8
Cerebrovascular accident	7.3	7.2	2.4
Syncope	2.6	2.8	2.4
Cardiac murmur	65.6	70.8	31.5
Congestive heart failure	27.1	27.7	28.9
Cardiogenic shock	1.4	2.7	2.6
Septic shock	6.3	7.1	5.5
Osler nodes	1.1	2.6	0.6
Janeway lesions	1.9	4.9	0.6
Roth spots	0.4	2.1	0.3
Complications			
Paravalvular abscess	13.8	11.5	7.8
Spondylitis	4.5	5.8	4.5
Embolic events	21.4	30.1	11.7
Pulmonary	9.5	27.5	75.0
Cerebral	51.2	43.3	16.7
Splenic	25.9	22.0	5.6
Coronary	2.0	3.2	2.8
Renal	7.5	11.1	2.8
Hepatic	1.5	2.4	0.0
Peripheral	12.4	12.2	2.8
Haemorrhagic stroke	1.7	2.7	0.6

CIED, Cardiac implanted electronic devices; EURO-ENDO, European Infective Endocarditis; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis.
Adapted from the EURO-ENDO registry.[7]

Continued

2.2. Imaging techniques

Table S2 Imaging techniques for the diagnosis of infective endocarditis

Imaging technique	Infective endocarditis	
	Strengths	Weaknesses
Echocardiography TTE – TOE	• Good diagnostic accuracy in NVE (vegetations, leaflet perforation, leaks). • Acceptable diagnostic accuracy in PVE (TOE > TTE) • Acceptable diagnostic accuracy in CIED IE (TOE > TTE), including assessment of tricuspid valve involvement. • Evaluation of valvular function and haemodynamic consequences of valve damage. • Prognostic value. • Embolic risk assessment. • Broad availability, including bedside. • Suitable for unstable patients. • Useful for follow-up (response to antibiotic therapy, baseline study after surgery). • No radiation.	• Difficulties evaluating anterior structures and RVOT tract (limitations in right-sided IE). • Limited sensitivity for perivalvular complications, especially in PVE. • Limited sensitivity in CIED-related IE: difficulties in differentiating lead vegetations from non-infected thrombi or residual fibrous sheaths of leads after device extraction. • No detection of peripheral complications or distant lesions. • Potential procedural complications for TOE.
ECG-gated cardiac CTA	• Very good accuracy to detect perivalvular complications (abscess/pseudoaneurysm) in NVE and PVE. • Acceptable diagnostic ability for detecting severe leaflet thickening, vegetations, perforations, and fistulas. • CIED-related IE: assessment of venous accesses patency (relevant for implantation of a new device). • Coronary artery pre-operative assessment: relevant information for surgical planning (local extension of the infection, aortic calcification). • Can be performed in patients with haemodynamic instability.	• Limited sensitivity for vegetations <10 mm in both NVE and PVE. • No valvular function assessment. • Limited in assessment of generator/pocket infection (difficult to differentiate from reactive changes after recent implantation) • Limited diagnostic ability for CIED-related IE (small vegetations and lead artefacts). • Variable image quality depending on scanner specifications. • Radiation exposure/potential risk of nephrotoxicity[a].

Continued

[18F]FDG-PET/CT(A) cardiac images	• High sensitivity for PVE. • Good accuracy to detect perivalvular/periprosthetic complications in NVE and PVE. • Evaluation of the local extension of the infection. • Evaluation of other prosthetic materials beyond prosthetic valves (e.g. in congenital heart disease patients). • CIED-related IE: very high sensitivity and specificity for generator/pocket and extracardiac or intravascular lead infection. • Assessment of venous accesses patency (if CTA). • Contemporary assessment of metabolic imaging and anatomy (if CTA).	• Low sensitivity in NVE • Limited sensitivity for very small vegetations (<5 mm) • No valvular function assessment. • Radiation exposure/potential risk of nephrotoxicity if CTA used[a]. • Limited in patients with haemodynamic instability. • Need to be aware of the length of the antibiotic treatment that can affect metabolism. • Specific expertise to acquire and analyse images.
WBC SPECT	• High specificity for IE. • CIED IE: good sensitivity and specificity for generator/pocket and extracardiac or extravascular lead infection.	• Limited use to pyogenic infections. • Limited sensitivity for small vegetations and NVE (low spatial resolution). • Several time point acquisitions needed. • Radiation exposure. • Specific expertise to acquire and analyse images.
Whole-body images	• Detection of distant lesions (embolic). • Alternative diagnosis in rejected IE. • Detection of the original source of infection (especially in some IE-related microorganisms, occasionally unknown neoplastic lesions).	

CT(A) and MRI	• Detection of distant lesions and systemic complications:
	  • Intra-abdominal emboli.
	  • Pulmonary emboli (right-sided CIED IE).
	  • Central nervous system infarction, embolism, bleeding, and aneurysms
	• Spondylodiscitis/other OAIs.
	• Mycotic/infectious arterial aneurysms/pseudoaneurysms.
		• Radiation exposure/risk of nephrotoxicity[a] (CT[A])
		• Restricted use in patients with CIED (MRI).

[18F]FDG-PET/CT(A), ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (angiography); CIED, cardiac implantable electronic device; CT(A), computed tomography (angiography); ECG, electrocardiogram; IE, infective endocarditis; MRI, magnetic resonance imaging; NVE, native valve endocarditis; OAI, osteoarticular infection; PVE, prosthetic valve endocarditis; RVOT, right ventricular outflow tract; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography; WBC SPECT, white blood cell single photon emission tomography.
[a]In patients with renal impairment (CTA, iodinated contrast; MRI, gadolinium contrast).

Table S3 Definition of cardiac lesions characteristic of infective endocarditis as detected by imaging techniques and surgery

	Echocardiography	ECG-gated cardiac CT	[18F]FDG-PET/CT(A) and WBC SPECT/CT	Surgery
Valvular lesions				
Leaflet thickening	Diffuse increase in thickness, more or less regular, of one or more leaflets, without vegetations	Diffuse increase in thickness, more or less regular, of one or more leaflets, without vegetations	No visually detectable uptake or mild uptake at the valve leaflets	Diffuse or nodular increase in leaflet thickness
Vegetation	Oscillating or non-oscillating intracardiac echogenic mass attached to a valve or other endocardial structures (chordae, chamber walls), or attached to implanted intracardiac material	Low/intermediate-attenuation mobile soft tissue lesions of variable size attached to valves, endocardium, or prosthetic material	Usually not detectable or sometimes seen as focal uptake at the valve (intravalvular in the leaflets) or at the valvular/prosthetic ring (following the supporting structure of the valve)	Infected mass attached to an endocardial structure or on implanted intracardiac material

Continued

Leaflet perforation	Leaflet tissue defect through which flow is observed with colour Doppler images	Leaflet tissue defect observed in more than one-dimensional view	Usually not detectable	Leaflet tissue defect
Perivalvular or periprosthetic complications				
Abscess	Non-homogeneous echogenic or echolucent perivalvular thickening	Soft tissue thickening around a valve/prosthesis or a graft	Increased perivalvular uptake (focal or heterogeneous pattern) at the valvular/prosthetic ring (following the supporting structure of the valve)	Perivalvular cavity with necrosis and purulent material (or without purulent material if direct contact with the cardiovascular lumen)
Pseudoaneurysm	Pulsatile perivalvular echo-free space, with colour Doppler flow detected	Contrast-filled sacculation arising from a cardiac/vascular structure (valve/prosthesis, aortic root, graft sutures, etc.) Pulsatility may be seen in multiphasic cardiac CT (cine images)	Increased perivalvular/periprosthetic uptake (focal or heterogeneous pattern) at the pseudoaneurysm	Perivalvular cavity communicating with the cardiovascular lumen
Infected collection	Well-defined accumulation of liquid, with an echolucent appearance and an organized wall (often around aortic grafts)	Well-defined lesion with hypodense content (liquid and corpuscular material) surrounded by an iso/hyperdense wall (frequently visualized around aortic grafts)	Increased perivalvular/periprosthetic uptake (focal or multifocal pattern) at an anatomical lesion with hypodense content, normally at the wall	Peritubular accumulation of liquid
Fistula	Colour Doppler communication between two neighbouring cavities through a perforation	Abnormal contrast-filled tract or focal communication between vascular structures/cardiac chambers	No visually detectable uptake or increased perivalvular/periprosthetic uptake (linear pattern, following the supporting structure of the valve)	Communication between two neighbouring cavities through a perforation and/or tract
Prosthetic valve dehiscence	Paravalvular regurgitation identified in colour Doppler, with or without rocking motion of the prosthesis	Extensive periprosthetic tissue defect or extensive continuity solution in the sewing ring suture causing misalignment of the prosthesis. Rocking motion of the prosthesis may be seen in multiphasic cardiac CT (cine images)	Increased periprosthetic uptake (focal, multifocal, heterogeneous pattern)	Separation of sewing ring from the surrounding annular tissue

[18F]FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; CT, computed tomography; CTA, computed tomography angiography; ECG, electrocardiogram; WBC SPECT, white blood cell single photon emission tomography.

2.2.1. Echocardiography

2.2.1.1. Risk scores to identify patients at high risk of infective endocarditis

In patients with *Staphylococcus aureus* bacteraemia, the incidence of IE varies from 6–32%.[8,9] 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. The sensitivities of the POSITIVE, PREDICT, and VIRSTA scores were 78% (95% CI, 66–87%), 85% (95% CI, 76–92%), and 99% (95% CI, 96–100%), respectively, while the negative predictive values (NPVs) were 93% (95% CI, 83–96%), 95% (95% CI, 91–97%), and 99% (95% CI, 95–100%), respectively.[10,11] In patients with *S. aureus* bacteraemia and without any high-risk criteria (defined as community-acquired *S. aureus* bacteraemia, high-risk cardiac conditions [prosthetic heart valve, prosthetic material, congenital heart disease, cardiac transplantation, prior IE, CIED], and people who inject drugs [PWID]), a normal transthoracic echocardiography (TTE) could rule out IE with high sensitivity (97%, 95% CI, 87–100%) and high NPV (99%, 95% CI, 96–100%).[12] To identify the patients with bacteriaemia due to *E. faecalis* who do not need transoesophageal echocardiography (TOE), the DENOVA score has shown better discrimination as compared with the NOVA score.[13] Therefore, these scores could be useful to guide the use of echocardiography in patients with *S. aureus* and *E. faecalis* bacteriaemia. In streptococcal bloodstream bacteraemia, the HANDCOC score has been proposed to indicate an echocardiogram.[14] The cut-off values of the various scores are provided in *Supplementary Table S4*.

Table S4 Indications for screening echocardiography in patients with bacteraemia

Aetiology of bacteraemia	Name of the score	Score (points)	Screening echocardiography
S. aureus	VIRSTA	≥3	Yes
		<3	No
	PREDICT	≥4	Yes
		<4	No
	POSITIVE	≥4	Yes
		<4	No
E. faecalis	DENOVA	≥3	Yes
		<3	No
Streptococci	HANDCOC	≥3	Yes
		<3	No

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

Hybrid nuclear imaging modalities, single photon emission computed tomography (SPECT/CT) and positron emission tomography/computed tomography (PET/CT), enable the simultaneous assessment of metabolic and anatomical information. Detection of infection in SPECT/CT imaging relies on the use of autologous radiolabelled leucocytes (^{111}indium-oxine or ^{99m}technetium-hexamethylpropyleneamine oxime [99mTc-HMPAO]) that accumulate time-dependently in late compared with early images. PET/CT is performed using a single acquisition time point after administration of ^{18}F-fluorodeoxyglucose ([18F]FDG), which is incorporated by activated leucocytes, monocyte-macrophages, and CD4$^+$ T-lymphocytes accumulating at the sites of infection. The simultaneous acquisition of an electrocardiogram (ECG)-gated cardiac CT angiography (PET/CTA) provides the advantage of detecting IE-related local lesions in the cardiac CT images. These diagnostic procedures have shown to be particularly useful for detecting infection in the presence of cardiac prosthetic valves and other implantable materials.[15–17]

Studies have reported that the addition of [18F]FDG-PET/CT to the modified Duke criteria increased the sensitivity from 52–70% to 91–97% and, in a recent study, the addition of [18F]FDG-PET/CT to echocardiography increased the sensitivity to 96%.[18–20] The main contribution of [18F]FDG-PET/CT and white blood cell (WBC) SPECT/CT is in high clinical suspicion of prosthetic valve endocarditis (PVE) in which, despite a proper clinical and imaging diagnostic algorithm, IE diagnosis remains 'possible' or even 'rejected' by the traditional criteria.[19–22] The incorporation of PET/CT in the diagnostic criteria for IE in the *2015 ESC Guidelines for the management of infective endocarditis* was shown to increase sensitivity of Duke criteria from 57% to 84%, at the cost of a relative decrease in specificity from 96% to 71%.[23] Further, the presence of [18F]FDG-PET/CT uptake as a major criterion in the ESC 2015 diagnostic criteria was found in 41% of patients without major echocardiographic criteria for IE.[23] However, when considering the subgroup of patients with high clinical suspicion of IE, the absolute increase in true-positive findings is higher than the absolute decrease in false positives using the ESC 2015 diagnostic criteria instead of the Duke criteria.

2.2.2.1. Technical considerations and interpretation of positron emission tomography/computed tomography

To facilitate visualization of presumed sites of valve infection, suppression of [18F]FDG uptake by normal myocardium requires proper patient preparation.[15,24,25] Interpretation of PET/CT studies needs specific expertise and knowledge of potential physiological and pathological conditions that may resemble IE uptake to reduce false-positive results (i.e. the presence of surgical adhesives).[25–28] Focal or heterogeneous valvular/prosthetic or perivalvular/periprosthetic uptake patterns of high intensity detected by [18F]FDG-PET/CT are considered abnormal and, hence, consistent with infection.[29–31] The probability of IE increases with the intensity of the uptake at the valves/prostheses. Since prolonged antimicrobial therapy can reduce [18F]FDG intensity despite persistent infections, the duration of the ongoing treatment should be considered. Moreover, reported data have demonstrated that inflammation and post-surgical changes can be differentiated from infection in most cases, regardless of the time from surgery.[26,32] The key point is proper interpretation of images with special knowledge of the characteristic uptake patterns, taking into account the type of surgery and prosthetic materials, and use of the technique in the indicated clinical scenarios.[33,34] The main findings of PET/CT and PET/CTA are described in *Supplementary Tables S3* and *S5*. [18F]FDG uptake patterns are illustrated in *Figure S1*.

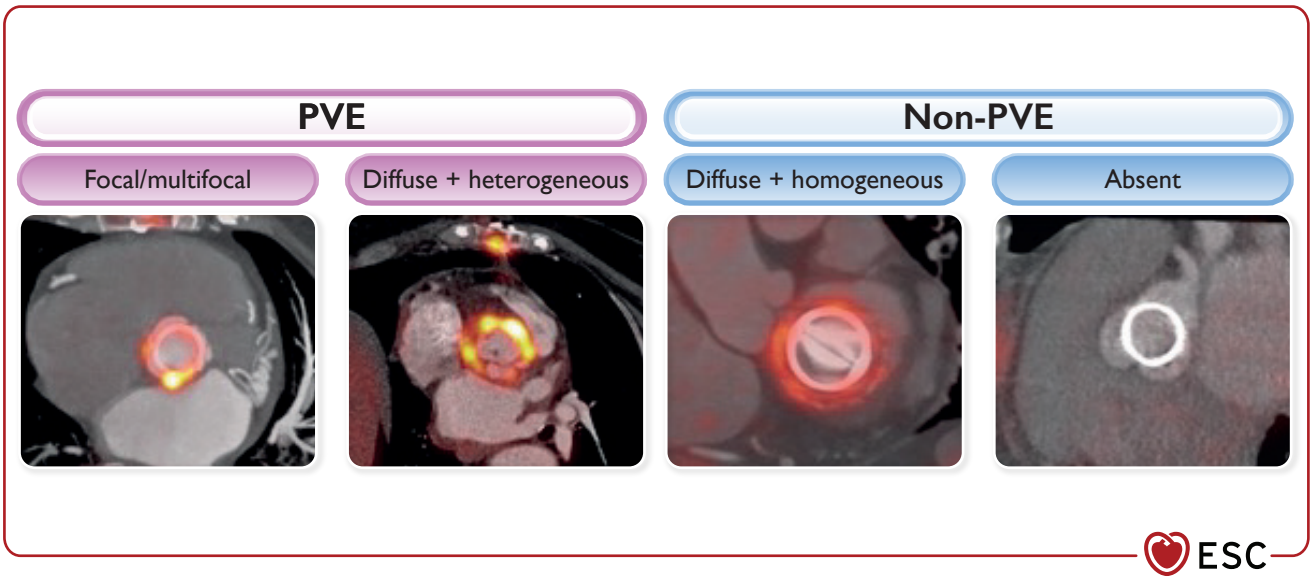

Figure S1 [18F]-fluorodeoxyglucose positron emission tomography/computed tomography uptake distribution patterns in patients with prosthetic heart valves. CTA, computed tomography angiography; PET, positron emission tomography; PVE, prosthetic valve endocarditis. PET/CTA fusion images of the valve plane. Characteristic infection (left) and inflammation (right) patterns. Adapted from Roque *et al.*[34]

Table S5 **^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography cardiac imaging findings in prosthetic valve endocarditis**

	Qualitative (visual) analysis	Semi-quantitative analysis
Metabolic findings	• [^{18}F]FDG uptake distribution pattern: focal/multifocal or diffuse-heterogeneous distribution. • Location of [^{18}F]FDG uptake: at the valve (intravalvular in the leaflets), valvular/prosthetic (following the supporting structure of the valve), or perivalvular/periprosthetic (next to the valve/prosthesis). • Moderate-intense [^{18}F]FDG visual intensity as compared with other organs considered a normal reference (considering ongoing antimicrobial therapy). • Uptake associated with anatomic lesions. • Hypermetabolism of spleen and/or bone marrow as indirect sign of IE.	Commonly used parameters for quantification: • SUVmax: maximum standardized uptake value. • SUVmean: mean standardized uptake value. • SUVratio: prosthesis-to-background (hepatic or blood pool) SUV. • The probability of infection increases as the SUVmax and/or SUVratio values are higher (considering ongoing antimicrobial therapy) There are no standardized threshold or cut-off values Reported reference values can be taken into account: • SUVmax >5 (95% CI, 4–15) • SUVratio >2.5 (95% CI, 2–6).
Anatomic findings	Visualization of lesions characteristic of IE: • Valvular: severe leaflet thickening,[a] vegetation,[a] leaflet perforation[a]. • Perivalvular or periprosthetic complications: abscess, pseudoaneurysm, infected collection, fistula,[a] prosthetic valve dehiscence[a].	

[18F]FDG, ^{18}F-fluorodeoxyglucose; CTA, computed tomography angiography; ECG, electrocardiogram; IE, infective endocarditis; SUV, standardized uptake value; SUVmax, maximum standardized uptake value; SUVmean, mean standardized uptake value; SUVratio, prothesis-to-background SUV.
[a]Only visualized with the use of intravenous iodinated contrast and ECG-gated cardiac CTA.

2.3. Diagnostic criteria

Table S6 Definition of infective endocarditis according to the modified Duke criteria

Major criteria
Pathologic criteria • Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or • Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis
Blood culture positive for IE

• Typical microorganisms consistent with IE from 2 separate blood cultures:
  • Oral streptococci, *Streptococcus gallolyticus*, HACEK group, *Staphylococcus aureus*; or
  • Community-acquired enterococci, in the absence of a primary focus; or
• Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:
  • At least 2 positive cultures of blood samples drawn >12 h apart; or
  • All of 3 or a majority of >4 separate cultures of blood (with first and last sample drawn at least 1 h apart).
• Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titre >1:800.

Evidence of endocardial involvement
Echocardiogram positive for IE (TOE recommended in patients with prosthetic valves, rated at least 'possible IE' by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients), defined as follows: • Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or • Abscess; or • New partial dehiscence of prosthetic valve.
New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)
Minor criteria
• Predisposition, predisposing heart condition, or injection drug use. • Fever, temperature >38°C. • Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway lesions. • Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor. • Microbiological evidence: positive blood culture but does not meet a major criterion as noted above[a] or serological evidence of active infection with organism consistent with IE.

HACEK, *Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella,* and *Kingella*; IE, infective endocarditis; Ig, immunoglobulin; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography.
[a]Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.
Adapted from Li *et al.*[35]

3. Prognostic assessment at admission

3.1. Predictors of poor outcome on admission

Four main factors affect prognosis at admission: patient characteristics, the presence or absence of cardiac and non-cardiac complications, the infecting microorganism, and echocardiographic findings (*Table S7*).[7,36–38] Increasing age, prosthetic valve involvement, HF, septic shock, cerebral complications, history of haemodialysis, periannular complications (especially abscess), and *S. aureus* infection are particularly strong predictors of poor in-hospital outcome.[7,36–39] In addition, patients with persistently positive blood cultures 48–72 h after initiation of antibiotic treatment are at high risk, and benefit significantly from surgery.[40]

Table S7 Predictors of poor outcome in patients with infective endocarditis[a]

Patient characteristics • **Older age.** • **Prosthetic valve IE.** • **Haemodialysis.** • **Unsuitable for surgery (e.g. frailty).** • Diabetes mellitus. • High Charlson Comorbidity Index.
Clinical complications of IE • **Heart failure.** • **Cerebral complications.** • **Septic shock.** • Renal failure.
Microbiological features • ***S. aureus*.** • Fungi. • Non-HACEK Gram-negative bacilli. • Persistent bacteraemia.
Echocardiographic findings • **Periannular complications.** • Left-sided infective endocarditis. • Vegetation size >10 mm. • Severe left-sided valve regurgitation. • Reduced left ventricular ejection fraction. • Pulmonary hypertension. • Prosthetic valve dysfunction. • Severe diastolic dysfunction or echocardiographic signs of elevated left ventricular diastolic pressures.

HACEK, *Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella,* and *Kingella*; HF, heart failure; IE, infective endocarditis.
[a]Factors in bold are those consistently listed as strong predictors of adverse outcome in published studies.

Surgery is an independent predictor of survival in IE, particularly in high-risk patients, and those with uncontrolled infection and/or HF.[37,41] Among patients who need emergency or urgent surgery, older age, pre-operative renal failure, PVE, septic shock, persistent infection, periannular complications, and multivalve involvement are predictors of mortality.[42–44] Several surgical risk scoring systems have been developed (see *Section 8.1*), but none are used in daily clinical routine. Patients with unrecognized surgery indication or prohibitive surgical risk have the worst prognosis, particularly in elder patients.[45–47]

Table S7 lists the predictors of poor outcome in IE, as determined by numerous studies. Factors that are protective against adverse outcomes include >1 month duration of symptoms prior to presentation, oral streptococcus infection, and surgery.[37,38]

4. Antimicrobial therapy: principles and methods

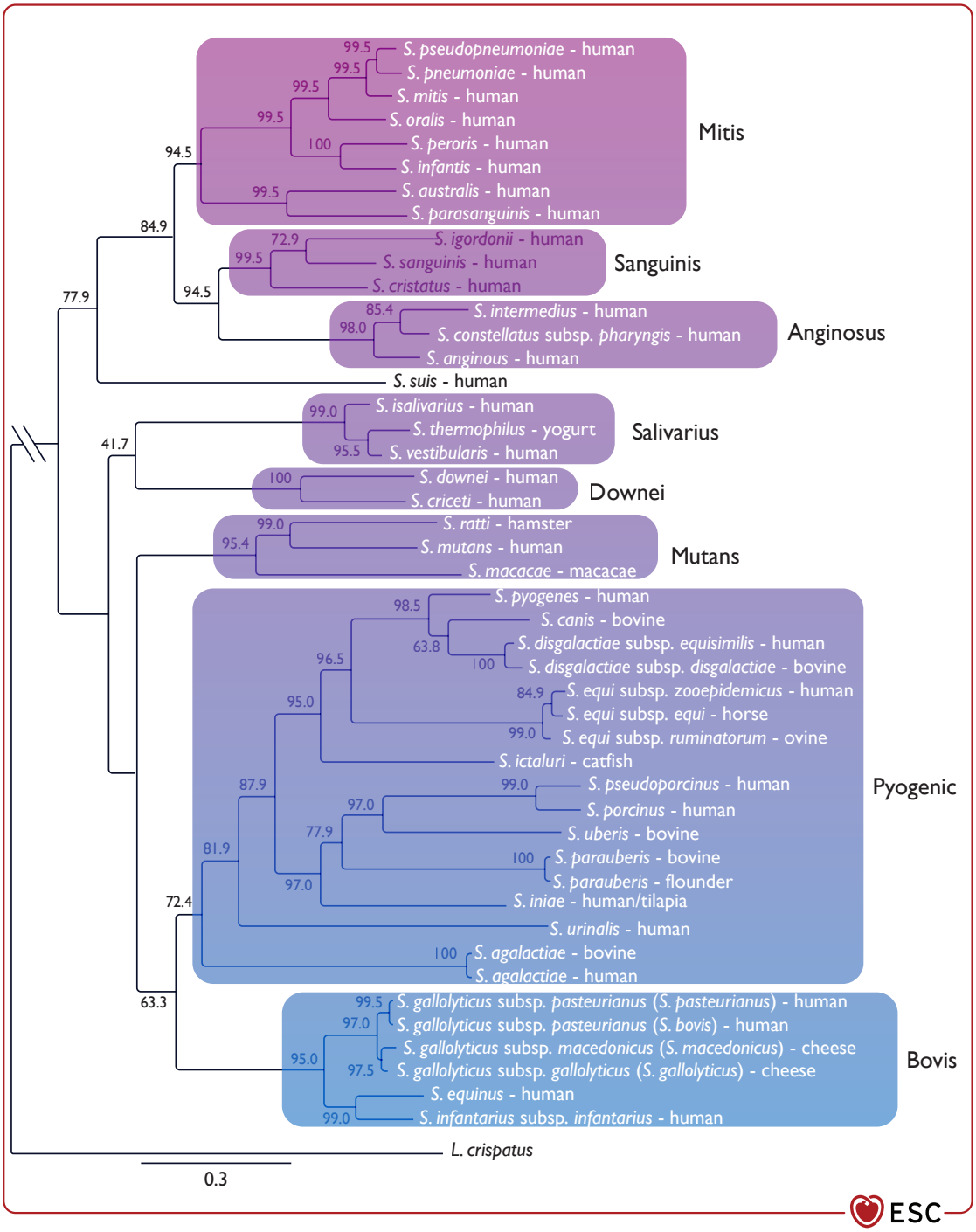

Figure S2 Phylogeny of the indicated streptococcal species derived from a core set of 136 concatenated genes. Numbers on branches show bootstrap support for each relationship. The colour shading indicates the eight major groups. Reproduced with permission from Abranches *et al.*[48]

Table S8 General recommendations, treatment phases, and clinical scenarios to consider outpatient parenteral or outpatient oral antibiotic therapy for infective endocarditis

General recommendations		
Outpatient parenteral or oral antibiotic therapy can be considered if: • Patient is clinically stable. • Home environment is stable, preferably with a cohabitant caregiver. • Patient is self-reliant or home healthcare can be provided. Contraindications: • Heart failure. • Severe valvular regurgitation, vegetations >10 mm, progression, or local complications. • Neurological involvement. • Renal impairment. • Malabsorption. • PWID.		
Timing and indications in various clinical scenarios		
Critical phase (rapid shift to OPAT or oral step-down treatment, 0–2 weeks): • Consider OPAT in NVE caused by oral streptococci or *S. gallolyticus.* • Oral step-down treatment may be considered after a minimum of 10 days of i.v. antibiotic treatment.		
NVE	**PVE**	**CIED**
• >10 days of i.v. antibiotic treatment after admission or performed surgery. • IE by any causative agent except highly difficult-to-treat microorganisms[a]. • Negative blood cultures at 72 h. • TOE ruling out severe aortic regurgitation and prosthetic valve dysfunction. • No anticoagulation issues.	• >10 days of i.v. antibiotic treatment after admission. • IE caused by oral streptococci, *S. gallolyticus,* or *E. faecalis.* • Cardiac surgery not indicated • Negative blood cultures at 72 h. • TOE ruling out severe aortic regurgitation and prosthetic valve dysfunction. • No anticoagulation issues.	• >7 days of i.v. antibiotic treatment after non-complicated early lead extraction (<1 week from admission). • IE by any causative agent except highly difficult-to-treat microorganismsa. • No signs of pocket infection. • Negative blood cultures at 72 h after reimplantation of CIED. • Normal echocardiography.
Continuation phase (postponed shift to OPAT or oral step-down treatment, beyond week 2): • Consider oral step-down treatment if: i.v. minimum 10 days, and *Streptococcus* spp., *E. faecalis*, *S. aureus*, or CoNS.		
NVE	**PVE**	**CIED**
• >3 weeks of i.v. antibiotic treatment after admission or surgery performed. • IE by any causative agent except highly difficult-to-treat microorganisms[a]. • Negative blood cultures at 72 h. • TOE ruling out severe aortic regurgitation and prosthetic valve dysfunction. • No anticoagulation issues. • No severe sequelae or clinical complications. • No need for daily and/or complex cures.	• >3 weeks of i.v. antibiotic treatment after admission or surgery performed. • Patients undergoing cardiac surgery and not infected with highly difficult-to-treat microorganism[a] and without severe complications. • Negative blood cultures at 72 h. • TOE ruling out severe aortic regurgitation and prosthetic valve dysfunction. • No anticoagulation issues. • No severe sequelae or clinical complications. • No need for daily and/or complex cures.	• >2 weeks of i.v. antibiotic treatment after device removal/reimplantation. • Associated right-sided IE with vegetations >2 cm. • Associated with left-sided IE (apply then criteria for NVE/PVE) • Late or complicated lead extraction • IE by any causative agent except highly difficult-to-treat microorganisms. • No signs of pocket infection. • Negative blood cultures at 72 h after reimplantation of CIED. • Normal echocardiography. • No severe sequelae or clinical complications. • No need for daily and/or complex cures.

CIED, cardiac implantable electronic device; CoNS, coagulase-negative staphylococci; IE, infective endocarditis; i.v., intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; NVE, native valve endocarditis; OPAT, outpatient parenteral antibiotic therapy; PVE, prosthetic valve endocarditis; PWID, people who inject drugs; TOE, transoesophageal echocardiography.
[a]Highly difficult-to-treat microorganism: microorganisms requiring i.v. antibiotic combinations that cannot be administered by means of OPAT 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*).

Table S9 Combinations of antibiotics for oral step-down treatment

Penicillin-and methicillin-susceptible *S. aureus* & CoNS	Methicillin-susceptible *S. aureus* & CoNS	Methicillin-resistant CoNS	*E. faecalis*	Penicillin-susceptible streptococci	Penicillin-resistant streptococci
Amoxicillin 1 g × 4 Rifampin 600 mg × 2	Dicloxacillin 1 g × 4 Rifampin 600 mg × 2	Linezolid 600 mg × 2 Fusidic acid 750 mg × 2	Amoxicillin 1 g × 4 Moxifloxacin 400 mg × 1	Amoxicillin 1 g × 4 Rifampin 600 mg × 2	Linezolid 600 mg × 2 Rifampin 600 mg × 2
Amoxicillin 1 g × 4 Fusidic acid 750 mg × 2	Dicloxacillin 1 g × 4 Fusidic acid 750 mg × 2	Linezolid 600 mg × 2 Rifampin 600 mg × 2	Amoxicillin 1 g × 4 Linezolid 600 mg × 2	Amoxicillin 1 g × 4 Moxifloxacin 400 mg × 1	Moxifloxacin 400 mg × 1 Rifampin 600 mg × 2
Moxifloxacin 400 mg × 1 Rifampin 600 mg × 2	Moxifloxacin 400 mg × 1 Rifampin 600 mg × 2		Amoxicillin 1 g × 4 Rifampin 600 mg × 2	Amoxicillin 1 g × 4 Linezolid 600 mg × 2	Linezolid 600 mg × 2 Moxifloxacin 400 mg × 1
Linezolid 600 mg × 2 Rifampin 600 mg × 2	Linezolid 600 mg × 2 Rifampin 600 mg × 2		Linezolid 600 mg × 2 Moxifloxacin 400 mg × 1	Linezolid 600 mg × 2 Rifampin 600 mg × 2	
Linezolid 600 mg × 2 Fusidic acid 750 mg × 2	Linezolid 600 mg × 2 Fusidic acid 750 mg × 2		Linezolid 600 mg × 2 Rifampin 600 mg × 2	Linezolid 600 mg × 2 Moxifloxacin 400 mg × 1	

CoNS, coagulase-negative staphylococci.

5. Timing of surgery after stroke

Table S10 Peri-operative physiologic derangements impacting neurological outcomes after stroke in patients with infective endocarditis and proposed measures to mitigate risk in patients undergoing valve surgery

Peri-operative physiological derangements with potential to negatively impact neurologic status	Action to decrease risk
Pre-operative anaemia	• Low threshold for transfusion. • Infection control. • i.v. iron when appropriate.
Need for anticoagulation for CPB	• Maintain a target ACT in therapeutic range during CPB. • Optimization of pre-operative coagulopathy.
Loss of pulsatility on CPB	• Unmodifiable.
Altered cerebral autoregulation during anaesthesia/CPB	• Maintain optimal mean systemic pressure at all times.
Systemic hypo/hypertension during surgery and early post-operatively	• Maintain optimal mean systemic pressure at all times.
Altered haematocrit and decreased blood oxygen content	• Low threshold for transfusion in peri-operative period and avoidance of further haemodilution.
Hypothermia degree and hypocapnia	• CO_2 range maintenance. Avoidance of more than mild hypothermia (unless aortic arch surgery or long aortic crossclamp time anticipated).
Risk of micro- and macroembolism	• Avoid excess manipulation of heart prior to aortic clamping. • Surgical debris control during valvular debridement. • Proper deairing prior to separating from CPB.
Increased tissue oedema and third spacing	• Avoid further haemodilution and unnecessary volume expansion. • Haemofiltration during CPB in patients with pre-operative hypervolaemia/oedema.
Induction of coagulopathy	• Meticulous surgical technique. • Haemofiltration. • Aggressive control of haemostasis disturbances, even in the absence of bleeding.
Complexity of surgical reconstruction and CPB duration	• Unmodifiable.
Potential need for IABP or other temporary mechanical circulatory support	• Unmodifiable.

Continued

Need for antiplatelet or antithrombotic therapy after surgery	• Non-mechanical valve substitutes. • Left atrial appendage occlusion when atrial fibrillation is present. • Limit antiplatelet/antithrombotic therapy early after surgery. • Guide therapy with repeat cerebral imaging.
Valve substitute choice	• Avoid mechanical valves in patients with extensive strokes or felt to be at risk of bleeding transformation.
Risk of post-operative bleeding and subsequent haemodynamic instability	• Meticulous surgical technique. • Aggressive correction of coagulopathy. • Haemofiltration during CPB. • Low threshold for mediastinal packing and delayed chest closure.
Need for extensive blood product use to achieve haemostasis	• Pre-operative optimization (vitamin K, anaemia correction). • Haemofiltration during CPB. • Meticulous surgical technique. • Low threshold for mediastinal packing delayed chest closure.
Expected prolonged sedation and inability to assess neurologic evolution	• Follow-up cerebral imaging if feasible.

ACT, active clotting time; CPB, cardio-pulmonary bypass; IABP, intra-aortic balloon pump; i.v., intravenous.
Several peri-operative variables should be addressed in order to lower the risk of neurological deterioration and haemorrhagic transformation post-stroke.[49–55]

6. Management of specific situations

6.1. Prosthetic valve endocarditis

6.1.1. Definition and pathophysiology

In cases of peri-operative contamination, the infection usually involves the sewing ring and polyfilament braided sutures and, from there, expands to the annulus, leading to perivalvular abscess, dehiscence, pseudoaneurysms, and fistulae.[56–58] In late PVE, additional mechanisms may exist including haematogenous spread of microorganisms from systemic infections. The infection is frequently located on high turbulence areas such as paravalvular leaks, the junctions between prosthesis leaflets and the commissure posts, and the hinges of mechanical leaflets. If the sewing ring and sutures are affected, perivalvular abscess, dehiscence, pseudoaneurysms, and fistulae can be observed. The formation of pseudoaneurysms, abscesses, and fistulae are more common in patients with an aortic valved graft conduit.[58]

Bacteraemia can also lead to late PVE after TAVI, which should be managed in the same manner as other PVE.[59,60]

The consequence of PVE is usually new prosthetic regurgitation. Less frequently, large vegetations may cause prosthetic valve obstruction.

6.2. Infective endocarditis affecting cardiac implantable electronic devices

Table S11 The PADIT score for predicting risk of hospitalization for device infection at 1 year after CIED implantation

Predictor	PADIT risk score points
Prior procedure(s) on the same pocket	
None	0
One	1
Two or more	4
Age (years)	
<60	2
60–69	1
≥70	0
Depressed renal function (GFR <30 mL/min)	1
Immunocompromised[a]	3
Type of procedure[b]	
Pacemaker	0
ICD	2
CRT	4
Revision/upgrade	5

CIED, cardiovascular implanted electronic device; CRT, cardiac resynchronization therapy; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; ICD, implantable cardioverter defibrillator; PADIT, Previous procedure on same pocket; Age; Depressed renal function; Immunocompromised; Type of procedure.
Total scores range from 0–15, with low (0 to 4), intermediate (5 to 6), and high (≥7) risk corresponding to rates of hospitalization for infection of 0.51%, 1.42%, and 3.41%, respectively.[61]
[a]Immunocompromised: immunosuppression, chemotherapy, radiation, long-term or recent high dose steroids or having a disease that is sufficiently advanced to suppress resistance to infection (e.g. leukaemia, lymphoma, HIV infection).
[b]Categories are mutually exclusive.

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