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Recent Insights in Native Valve Infective Endocarditis:

Abbreviated Title
Recent Insights in NVIE

Authors
Professor Mark J Dayer, PhD FRCP[1]; Dr. Juan A Quintero-Martinez, MD[2]; Professor Martin H Thornhill, MBBS BDS MSc PhD[3]; Professor John B Chambers MD FESC FACC[4]; Professor Gosta B Pettersson MD PHD[5]; Professor Emeritus Larry M. Baddour, MD FIDSA FAHA[6].

Affiliations
[1]Somerset NHS Foundation Trust, Taunton, UK; Faculty of Health, University of Plymouth, Plymouth, UK; mark.dayer@somersetft.nhs.uk.
[2]Department of Internal Medicine, University of Miami Miller School of Medicine, Jackson Memorial Hospital, Miami, FL; quinteromartinez.juan@mayo.edu.
[3]Department of Oral and Maxillofacial Medicine, Surgery and Pathology, School of Clinical Dentistry, University of Sheffield, Sheffield, UK; m.thornhill@sheffield.ac.uk.
[4]Emeritus Professor of Clinical Cardiology at Guy's and St Thomas' NHS Trust, London, UK, and Kings College, London, UK; jboydchambers@aol.com.
[5]Cleveland Clinic, Consultant staff surgeon; petterg@ccf.org.
[6]Departments of Medicine and Cardiovascular Medicine, Division of Public Health, Infectious Diseases and Occupational Health, Mayo Clinic, Rochester, MN; baddour.larry@mayo.edu.

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Address for Correspondence

Professor Mark J Dayer
Department of Cardiology, Somerset NHS Foundation Trust, Musgrove Park, Taunton, Somerset, TA1 5DA, UK
+44 1823 342154
markdayer@gmail.com
@dayer_mark

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Article summarizing the latest advances in native valve endocarditis, including imaging, diagnosis, and prevention #MedEd #Endocarditis

Abstract (150 words)

This focused review highlights the latest issues in native valve infective endocarditis (NVIE). Native valve disease moderately increases the risk of developing IE. In 2023, new diagnostic criteria were published by the Duke-ISCVID group. New pathogens were designated as typical and findings on CT were included as diagnostic criteria. It is now recognized that a multidisciplinary approach to care is vital, and the role of an “endocarditis team” is highlighted. Recent studies have suggested that a transition from intravenous to oral antibiotics in selected patients may be reasonable, and the role of long-acting antibiotics is discussed. It is now clear that an aggressive surgical approach can be life-saving in some patients. Finally, there have been several recent studies that have suggested there is an association between dental and other invasive procedures and an increased risk of developing IE. Moreover, data indicate that antibiotic prophylaxis may be effective in some scenarios.

Condensed Abstract (91 words)

This review highlights the latest issues pertaining to native valve infective endocarditis (NVIE). In 2023, the Duke-ISCVID group outlined new diagnostic criteria including new typical pathogens and CT findings. A multidisciplinary approach featuring an "endocarditis team" is now deemed essential. The transition from intravenous to oral antibiotics, alongside the potential effectiveness of long-acting antibiotics, is discussed. Aggressive surgical intervention can be lifesaving. Recent research also suggests a link between dental and other invasive procedures and elevated IE risk, with antibiotic prophylaxis showing efficacy in preventing IE in those at high risk.

Key Words

- Infective endocarditis
- Diagnostic criteria
- Cardiac computed tomography
- [18F] Fluorodeoxyglucose positron emission tomography-computed tomography
- Endocarditis team

Abbreviations

[18F]FDG PET-CT	[18F]Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography
AHA	American Heart Association
AP	Antibiotic Prophylaxis
CCT	Cardiac Computed Tomography
ESC	European Society of Cardiology
FDA	Food and Drug Administration
IDPs	Invasive Dental Procedures
IDU	Injection Drug Use
IE	Infective Endocarditis
ISCVID	International Society of Cardiovascular Infectious Diseases
MRI	Magnetic Resonance Imaging
NVIE	Native Valve Endocarditis
TEE	Transesophageal Echocardiography
TTE	Transthoracic Echocardiography

Introduction

Infective endocarditis (IE) is a rare but devastating infection often characterized by multisystem complications; the mortality rate is 25% or more at one year. Native valve IE (NVIE) is the most prevalent form of IE, accounting for 90% of IE cases in one nationwide (US) study that included cases between 2003 and 2017.[1] This review will focus on recently published diagnostic criteria, management guidelines, trends, innovations, and controversies (Central Illustration) and builds on previous reviews published in this journal.[2,3] Related topics are addressed in separate reviews in this JACC Focus Summary.

Epidemiology and Risk Factors

IE incidence rates of 10-20 cases/100,000/annum have been reported.[4] In Europe, rates are probably increasing,[5] but in the US, IE rates have remained static[4] despite an ageing population,[6] increasing injection drug use (IDU)[7,8] and surgical and transvenous valve procedures.[9] However, the ability to conduct population-based investigations in the US to determine the incidence of IE is limited.

Individuals with certain native valve conditions that predispose to IE ("moderate risk group") have an increased risk akin to that of conditions (prosthetic valve placement or repair), for example, in the "high-risk" group . Other native cardiac conditions that predispose to the development of IE include certain types of congenital heart disease, and hypertrophic cardiomyopathy In contrast, the decline of rheumatic fever has lowered the IE rate from underlying rheumatic carditis. The proportion of cases due to NVIE, in the absence of injection drug use, could be falling, and data from California and New York support this notion.[10] However, findings from the Global Burden of Disease database highlighted the fact that the

incidence of IE in the US[11] and the World[12] was not evenly distributed and was dependent on the specific state or region.

Diagnosis

The 2023 Duke-International Society of Cardiovascular Infectious Diseases (ISCVID) Criteria and the 2023 European Society of Cardiology (ESC) Criteria

The original Duke criteria were published in 1994 and modified in 2000. Updated Duke-ISCVID criteria and ESC criteria were both published in 2023,.17, [13] The Duke-ISCVID criteria contain significant detail regarding microbiology and include newer imaging techniques, including CT and [18F]-FDG PET/CT in IE diagnosis However, they do not include SPECT/CT, unlike the ESC 2023 criteria, which also contain less detail regarding microbiology. In addition to clinical, microbiologic, and imaging criteria, surgical criteria were added to the Duke-ISCVID criteria which were not included in the ESC criteria. There are other more subtle differences in the minor criteria, including the presence of physical examination criteria in the Duke-ISCVID document. These differences can be seen in Tables 1 and 2.

Microbiology and the Risk of Underlying Infective Endocarditis

The likelihood of IE depends on both patient risk factors and the pathogen. It has become recommended practice to undertake echocardiography when *S. aureus* is isolated from blood cultures.[13] Whether this should be transthoracic or transesophageal is determined on a case by case basis, and remains a source of debate. The risk of having IE if an oral streptococcus is isolated from blood cultures is only slightly less, and IE is more likely if *E. faecalis* is isolated;

around 1 in 10 patients with blood cultures positive for *Staphylococcus aureus* will have IE, whereas it is nearer 1 in 6 with *E. faecalis.*[14]

Interestingly, the microbiology of IE across the world is now broadly similar with *S. aureus* and viridans group streptococci and the most common isolates.[15-18]

Imaging in IE

Imaging is key in diagnosing IE and echocardiography, CCT and [18]FDG PET-CT are now commonly used techniques, as reflected in the 2023 Duke-ISCVID criteria. We will not review MRI specifically, but it is an essential tool for imaging the brain and spine, which are frequently involved in IE cases.

Echocardiography

Transthoracic echocardiography (TTE) is the first-line imaging modality for IE evaluation (Table 3).[19] This modality can assess for valvular vegetations, along with other valvular complications, including abscesses, perforations, aneurysms, pseudoaneurysms and fistulas.[20,21] In addition, echocardiography provides a hemodynamic assessment of the severity of valvular lesions, which is essential to determine the need for surgical intervention.[22] In NVIE, the sensitivity of TTE ranges from 40% to 63%.

The sensitivity (90%-100%) of transesophageal echocardiography (TEE) is superior to that of TTE to detect IE.[23] TEE provides better characterization and measurement of vegetation length, which is useful for determining embolic risk and the need for early surgery.[13,24] Incorporating three-dimensional (3D) TEE can provide a more in-depth assessment of the impact of IE on the valve and can also be helpful in preoperative planning.[25,26]

TEE is recommended when a TTE is inconclusive, or when a TTE is negative but there is strong clinical suspicion and in most patients with a positive TTE.[13,25] However, TEE is not always superior. For example, TTE can be better than TEE when evaluating anterior structures, particularly right-sided IE, and small anterior root abscesses.[27] However, left-sided heart valves remain the most commonly involved; some studies have demonstrated they account for around 80% of cases, equally divided between aortic and mitral valves.[28]

Negative findings on echocardiography do not exclude an NVIE diagnosis, particularly in the early course of the disease, when vegetations or valvular complications may be too small to detect. When clinical suspicion is high, TTE or TEE can be repeated after several days; additional imaging modalities can also be considered.[25]

Cardiac Computerized Tomography

CCT has a direct and indirect role in diagnosing and managing NVIE. Firstly, vegetations can be seen directly on CCT, although the sensitivity and specificity are slightly lower than that for TEE.[29] The principal role, however, is to identify pseudoaneurysms and abscesses in the aortic root and fistulae, where it may be superior to TEE due to its improved spatial resolution.[29-32]

In addition, CCT is useful for surgical planning since it provides information on aortic and aortic valve calcification and the anatomy of coronary arteries. However, CCT is not mandatory in all cases.[25,33,34] Moreover, CCT can detect septic pulmonary emboli in patients with right-sided endocarditis.[35,36]

CCT is often a valuable adjunct for patients with contraindications to TEE, inconclusive echocardiographic findings, or suspected paravalvular disease.[29,30,33] The combination of CCT with echocardiography has superior diagnostic yield to detect valvular and paravalvular lesions.[19,37]

More broadly, CT scanning can also identify abscesses in the brain and spleen (new minor criteria) or identify the source of bloodstream infection, such as a gastrointestinal lesion, that led to IE.

[18F]Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography

[18F]FDG PET-CT can identify infections before structural tissue changes occur.[38] However, it has a limited role in NVIE due to its low sensitivity,[39,40] although specificity is high, at 98%.[41] These scans are more sensitive for prosthetic valve endocarditis (PVE), where there is a more pronounced inflammatory response and consequently a higher FDG uptake, making false negatives less likely.[42] However, these scans may also identify extra-cardiac pathology and complications in significant proportions of patients, which may assist management.[43]

Management

The Endocarditis Team

Today, a multidisciplinary team of experts is considered best practice for managing IE patients.[44,45] A team approach to managing IE results in management revisions in around half of patients[46] and improves outcomes, including survival.[47-51] For example, Ruch et al. demonstrated that mortality was lower (14.7% vs. 20.3%), time to surgery was reduced (10.3 days vs. 16.4 days), and length of stay was also reduced (31.9 days vs. 40.6 days) after the introduction of an endocarditis team.[49] A recent systematic review and meta-analysis also demonstrated an improvement in short-term mortality among patients managed by an IE team.[52]

A team is necessary because NVIE can involve many systems, and this expertise is needed in all aspects of IE diagnosis and management. The team, which should be at every heart valve

center, should meet regularly to review patients (Table 4).[3,53-55] However, decisions on urgent cases should never be delayed to the next meeting but should be discussed immediately by the relevant clinicians. In smaller centers, it will not be possible to assemble such a broad-based group, and it is important that the teams there have a close relationship with a cardiothoracic surgical center. This approach has been endorsed in the latest ESC guidelines.[13]

Antibiotic Therapy

This review will not re-document the different antibiotic regimens recommended by recent guidelines.[56] Rather, it focuses on newer areas of discussion and including the transition of treatment from intravenous to oral antibiotic therapy (transitional regimens) and the use of long-acting antibiotics.

Publication of the POET Study[57] prompted a reevaluation of transitional antibiotic regimens. Investigators conducted a randomized, non-inferiority, multicenter trial that included 400 adult patients with left-sided IE. Of note, patients were eligible for enrollment if they had responded to initial intravenous therapy and TEE showed no perivalvular abscess formation or valve abnormalities that required surgery. Approximately 73% of patients in each treatment arm had NVIE. Importantly, streptococci were the predominant pathogens in both groups. Results of a sub-study confirmed that target antibiotic levels in patients who received oral antibiotics were achieved in most patients.[58]

The results of this trial supported the conclusion that transitional regimens among clinically stable patients were non-inferior to intravenous treatment.

Dalbavancin and oritavancin are lipoglycopeptide antibiotics that are long-acting antibiotics and are active against *S. aureus,* including methicillin-resistant strains. Although not FDA approved for IE treatment and no clinical trial data are available, these long-acting antibiotics have been used with some success in selected case reports and case series.[59] Because they only

have to be dosed every 7 days or longer, and would obviate the need for an indwelling intravenous catheter, they could improve prolonged therapy compliance and have therefore garnered interest for NVIE treatment.

Surgery

Indications for Surgery

Surgery is an important component of treatment for many patients. Previous reviews have suggested rates of around 50%, but these have been based on data from cardiothoracic surgical centers.[60,61] However, recent nationwide or statewide studies have suggested rates of 25% or less.[10,62,63]

The indications for surgery in patients with active IE are well established.[64] For left-sided native valve IE, all guidelines agree on the principles: patients with uncontrolled infection, severe valve dysfunction, particularly with evidence of heart failure, invasive disease, or at high risk of embolism require surgery.

The Timing of Surgery in Patients with Active Endocarditis Without Central Nervous System Events

There is a trend towards earlier surgery.[65,66] American Association of Thoracic Surgery guidelines state: “Once there is an indication for surgery, the operation should not be delayed”.[64] The most frequent adverse event while waiting for surgery is an embolic event, which can be devastating. Acute mitral or aortic regurgitation with acute heart failure or cardiogenic shock is an emergency.

Although it is generally accepted that an effective antimicrobial regimen should be initiated pre-operatively and ongoing at the time of surgery, there is no recommendation for how long

the patient should be treated pre-operatively; a failure to respond to antibiotics or antibiotic escape can be an indication for earlier surgery, but careful evaluation for alternative sites of infection, or the development of an allergy to the antibiotic regimen, which can mimic sepsis, is required.

Surgery for Valve Dysfunction and to Reduce the Risk of Embolism

The main uncertainty for left-sided IE relates to defining when valve dysfunction without heart failure justifies early surgery and when the risk of embolism alone is an indication for surgery. Valve dysfunction in patients with IE often progresses rapidly, and acute moderate to severe aortic valve regurgitation is poorly tolerated. The most consistent risk factor for embolism that can be influenced by surgery is vegetation size, and those >10mm are more likely to embolise.[67,68] In the end, decisions on surgical intervention are often subjective.

The oft-cited randomized trial by Kang et al.[69] included patients with NVIE within seven days of diagnosis and a combination of vegetations >10mm and severe mitral or aortic valve dysfunction but without heart failure. Patients in the early surgery group were operated on within 48 hours, whereas there was no time stipulation for the control group; most (77%) had surgery during the initial hospitalization. There was no significant difference in mortality, but there was a significant reduction in embolic events at six weeks. There were no emboli in the early surgery group, whereas 8/39 patients had an embolic event within six weeks in the control group. There were no emboli in either group during the 6-week to 6-month follow-up period. This study has been criticized because of the low incidence of *S. aureus*, the presence of emboli prior to randomization and the small number of centers involved.

More recently, results of a retrospectively conducted French study have suggested that patients with intermediate length vegetations (10-15mm) and no other indication for surgery benefit

from surgery with significantly improved long-term survival compared with medical therapy alone.[70]

The Timing of Surgery in Patients with Active Endocarditis and Central Nervous System Involvement

The timing of surgery for patients with CNS involvement is complex, debated, and should finally be decided by the endocarditis team, including neurological and neurosurgical input. Whereas some recommend that all patients should have brain imaging before surgery,[71] The recent ESC guidelines suggest that brain imaging may be considered (Class IIb).[13]

Over the last five years, it has become clear that “smaller strokes”, as defined by the severity of neurological symptoms and by imaging, without hemorrhagic conversion are not reasons to postpone surgery. Patients who are unconscious or do not respond to commands should await neurological improvement before surgical intervention. Generally, if there has been an intracranial hemorrhage, a delay of 4 weeks is recommended, but this depends on the appearance and size of the cerebral lesion, the urgency of the cardiac indication, and the patient's general status.[72,73]

Risk Scores for Surgery in Patients with Infective Endocarditis

Several risk scores have been created to predict outcomes after surgery in patients with IE. The most recent attempt to develop a specific risk score, the APORTEI score was based on a meta-analysis published in 2020.[74]

Of note, there was a lack of agreement between the APORTEI score and the EuroSCORE I. The EuroSCORE I was more likely to underestimate mortality in low-risk patients and overestimate mortality in high-risk patients. Another limitation of such scores is the significant

variability in practice and outcomes between centers. There has been a recent review which provides a more in-depth discussion of risk models.[75]

Principles of Surgery

The principles of surgery are beyond the scope of this article. It is now generally accepted, however, that valves can be repaired in the context of IE and do not necessarily need replacement.

Aortic valve repair is seldom possible in the context of IE. Aortic valve repairs are, at present, principally autologous pericardiac patch repairs of small perforations.

For mitral valve IE, repair is considered better than replacement when possible. Indeed, the mitral valve repair rate in IE has been considered a possible quality metric.[76,77] A study by El Khoury's group, including patients with remote IE, suggested that up to 4 in 5 mitral valves could be repaired.[76] There was a suggestion that patients with a patch repair might have a worse outcome, but that did not reach significance. More recent studies enrolling only patients with active IE observed repair rates of nearer 2 in 5.[78] When more complex repair, including larger patches, was required, repair was no longer better than replacement.

Standard principles should be applied when deciding whether a biological or mechanical replacement is required.

Mortality

In Scotland between 2010-2014, 30-day mortality in patients hospitalized with IE was 13.8%, and 1-year mortality was 30.9%.[79] At any age, mortality declined over a 25-year time frame, but due to the ageing population, mortality of the overall cohort remained static.

In Denmark, patients with streptococcal IE had an in-hospital mortality of 11.1% and a 58.5% mortality after a median of 2.3 years.[80] Patients with *S. aureus* or enterococcal IE had significantly higher mortality. Nonetheless, both short-term and long-term mortality improved in Denmark between 1999 and 2018.[81]

Mortality rates in the US have fallen slightly (from 54/1,000,000 in 1999 to 50/1,000,000 in 2019), but not in all groups.[82] This study reported that mortality rates have increased in men, non-Hispanic whites and those living in rural areas, possibly due to social factors.

Prevention

Several recent studies have provided new evidence confirming an association between invasive dental procedures (IDPs) and IE in those at high risk.[83-87] Studies have also demonstrated a reduction in IE incidence in high-risk patients given antibiotic prophylaxis (AP) before IDPs.[85,87] A recent meta-analysis concluded that despite a lack of randomized data, AP prior to IDPs is likely to reduce the incidence of IE in those at high risk.[88]

Many cases of NVIE, however, are not caused by oral streptococci. Indeed, the incidence of staphylococcal and enterococcal IE appears to be rising. Recent large epidemiological studies have again raised the possibility that other invasive medical and surgical procedures (e.g., implantation of cardiac pacemakers/defibrillators, gastrointestinal endoscopy, bronchoscopy) may be temporally linked with the development of IE, particularly in those at high risk (Figure 1).[86,89] Many of these procedures were previously recommended for AP cover, but these recommendations were eliminated in the mid-2000s.

In their most recent guidelines published in August 2023, the ESC strengthened the level of their recommendation that high-risk patients should be given AP before invasive dental procedures from Class IIa to Class I because of the strength of the new evidence that has become available since their last review in 2015.[13] For patients with a history of previous IE,

the level of evidence has also increased from 'C' to 'B'. The ESC has also now added patients with ventricular assist devices to their list of high-risk conditions recommended for AP (class I, level C), recommended that AP should be considered in patients with transcatheter mitral and tricuspid valve repairs (Class IIa, level C), and recommended that AP may be considered in heart transplant recipients (Class IIb, level C). The updated ESC guidelines state that AP is not routinely recommended for those at intermediate risk but may be considered individually.

Because of the new evidence associating certain invasive medical and surgical procedures with subsequent IE (Figure 1),[86,89] the ESC guidelines also now state that "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 (Class IIb, level C). A recent AHA Scientific Advisory has also argued that there should be a reappraisal of the AHA guidelines considering these new data.[8]

Of note, the latest ESC guidelines,[13] like the current AHA guidelines,[90] no longer recommend clindamycin AP in those who are allergic to penicillin, preferring cephalexin, clarithromycin, azithromycin, and doxycycline as oral alternatives due to the increased risk of *Clostridioides difficile* infection with clindamycin.[91]

Not all cases of IE caused by oral streptococci follow an IDP, and daily activities such as toothbrushing, flossing, and chewing may result in a significant bacteremia that can cause IE, particularly in those with poor oral hygiene.[92,93] Indeed, a recent clinical trial showed that even in those at moderate risk, IE was significantly more likely in those with poor oral hygiene.[94] Maintenance of good oral hygiene and regular access to dental care could be more important in preventing oral streptococcal IE than AP for IDP (although evidence of the relative importance of these prevention measures is still needed). It is recommended that those at high IE risk should receive bi-annual dental examinations and education on maintaining daily good oral hygiene.[13,90]

Conclusions

The epidemiology of IE is changing, and the incidence of NVIE, excluding that due to IDU, varies, depending on geographic areas. Nonetheless, it still comprises the bulk of IE cases. Diagnostic criteria are expanding with the availability of additional techniques. A multidisciplinary team approach in the management of cases is now standard practice in many institutions. There is a trend towards initial courses of intravenous antibiotics with a transition to oral antibiotics in those who respond (also based on TEE findings) to initial parenteral therapy. Surgery, when indicated, is now performed earlier in the IE course with improved outcomes. Mortality is falling, but in-hospital and 1-year mortality rates remain unacceptably high.

There remain many challenges to improve the prevention, diagnosis, and management of IE. There is still much debate over antibiotic prophylaxis and other potential strategies to reduce the risk of developing IE. The duration of antibiotic therapy was established in the 1940s and 50s, and is currently being investigated with trial results pending. The timing of surgical intervention remains debatable.

Main Messages

- New data have been published regarding all aspects of native valve infective endocarditis.
- Updated diagnostic criteria have been published, incorporating new imaging modalities.
- Multidisciplinary teams and early surgery can be beneficial; early oral antibiotic transition is possible.

- New evidence has linked invasive procedures to endocarditis development and antibiotic prophylaxis to endocarditis prevention.

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Table 1. The Duke-ISCVID Criteria

Major		
Microbiologic Major Criteria	a) Positive blood cultures:	
		i. Microorganisms that commonly cause IE* isolated from two or more separate blood culture sets¶; or
		ii. Microorganisms that occasionally or rarely cause IE isolated from three or more separate blood culture sets¶
	b) Positive laboratory tests:	
		i. Positive PCR or other nucleic acid-based technique† for Coxiella burnetii, Bartonella species, or Tropheryma whipplei from blood; or
		ii. Coxiella burnetii antiphase I IgG antibody titer > 1:800††††, or isolated from a single blood culture; or
		iii. Indirect immunofluorescence assays (IFA) for detection of IgM and IgG antibodies to Bartonella henselae or Bartonella quintana with IgG titer > 1:800††††
Imaging positive for IE	a) Echocardiography and Cardiac Computed Tomography Imaging	
		i. Echocardiography and/or Cardiac CT showing vegetation§, valvular/leaflet perforation‡, valvular/leaflet aneurysm**, abscess¶¶, pseudoaneurysm††, or intracardiac fistula§§; or
		ii. Significant new valvular regurgitation on echocardiography as compared to previous imaging. Worsening or changing of pre-existing regurgitation is not sufficient; or
		iii. New partial dehiscence of prosthetic valve as compared to previous imaging
	b) [18F]-FDG PET/CT	
		i. Abnormal metabolic activity‡‡ involving a native or prosthetic valve, ascending aortic graft (with concomitant evidence of valve involvement), intracardiac device leads or other prosthetic material*** ¶¶¶
	c) Note reference to SPECT/CT has been removed compared with the ESC 2015 criteria	
Surgical Major Criteria	Evidence of IE documented by direct inspection during heart surgery neither Major Imaging Criteria nor subsequent histologic or microbiologic confirmation§§§§	
Minor		
Predisposition?	Previous history of IE, Prosthetic valve†††, Previous valve repair†††, Congenital heart disease§§§, More than mild regurgitation or stenosis of any etiology, Endovascular CIED, Hypertrophic obstructive cardiomyopathy, Injection drug use	
Fever?	Temperature >38 °C or >100.4 °F	
Vascular Phenomena?	Major Arterial Emboli, Septic Pulmonary Infarcts, Cerebral or Splenic Abscess, Mycotic Aneurysm, Intracranial Hemorrhage, Conjunctival Hemorrhages, and Janeway's Lesions	
Immunologic Phenomena?	Immune Complex-Mediated Glomerulonephritis‡‡‡, Osler's Nodes, Roth's Spots, and Rheumatoid Factor	
Microbiological Evidence?	a) Microbiologic evidence, falling short of a Major Criterion:	
		i. Positive blood cultures for a microorganism consistent with IE but not meeting the requirements for Major Criterion****
		ii. Positive culture, PCR or other nucleic acid-based test (amplicon or shotgun sequencing, in situ hybridization) for an organism consistent with IE**** from a sterile body site other than cardiac tissue, cardiac prosthesis, or embolus; or a single finding of a skin bacterium by PCR on a valve or wire without additional clinical or microbiological supporting evidence.
Imaging Criteria	Abnormal metabolic activity as detected by [18F]-FDG PET/CT within 3 months of implantation of prosthetic valve, ascending aortic graft (with concomitant evidence of valve involvement), intracardiac device leads or other prosthetic material	
Physical Examination Criteria¶¶¶¶	New valvular regurgitation identified on auscultation if echocardiography is not available. Worsening or changing of pre-existing murmur not sufficient	

*	Staphylococcus aureus; Staphylococcus lugdunensis; Enterococcus faecalis; all streptococcal species (except for S. pneumoniae and S. pyogenes), Granulicatella and Abiotrophia spp., Gemella spp., HACEK group microorganisms (Haemophilus species, Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae). In the setting of intracardiac prosthetic material, the following additional bacteria should be included as "typical" pathogens: coagulase negative staphylococci, Corynebacterium striatum and C. jeikeium, Serratia marcescens, Pseudomonas aeruginosa, Cutibacterium acnes, non-tuberculous mycobacteria (especially M chimaerae), and Candida spp.
¶	"Blood culture set" is defined as a simultaneously drawn pair of one aerobic and one anaerobic bottle. "Positive" blood culture set is defined as microbial growth from at least one of the bottles. Blood cultures from separate venepuncture sites are strongly recommended whenever possible for evaluating suspected IE.
†	Amplicon (16S or 18S) or metagenomic (shotgun) sequencing.
††††	Or equivalent titre results on other methodologies.
§	Oscillating intracardiac mass on valve or other cardiac tissue, endovascular CIED or other implanted material in the absence of an alternative anatomic explanation.
‡	Interruption of valvular endocardial tissue continuity.
¶¶	Elongation with saccular outpouching of valvular tissue.
††	Perivalvular cavity communicating with the cardiovascular lumen.
§§	Communication between two neighboring cardiac chambers through a perforation.
‡‡	For PVE, intense, focal/multifocal or heterogeneous FDG uptake patterns; for NVE and cardiac device leads any abnormal uptake pattern.
***	Performed at least 3 months after prosthetic valve surgical implantation.
¶¶¶	Some prosthetic valves may have intrinsic non-pathological FDG uptake. An isolated FDG-PET positive generator pocket in the absence of intracardiac infection, does not qualify as a Major Criteria. PET/CT can be useful in detecting extracardiac foci of infection.
§§§§	Addition of this major criterion should not be interpreted as giving license to not send appropriate samples for histopathology and microbiological studies.
†††	Placed either by open-heart surgical or transcatheter approach.
§§§	Includes cyanotic CHD (tetralogy of Fallot, univentricular heart, complete transposition, truncus arteriosus, hypoplastic left heart); endocardial cushion defects; ventricular septal defect; left-sided lesions (bicuspid aortic valve; aortic stenosis and insufficiency, mitral valve prolapse, mitral stenosis and insufficiency); right-sided lesions (Ebstein anomaly, anomalies of the pulmonary valve, congenital tricuspid valve disease); patent ductus arteriosus; and other congenital anomalies, with or without repair.
‡‡‡	Defined as either:
	i. Unexplained presence of either acute kidney injury (AKI, defined below) or acute on chronic kidney injury (defined below) plus two of the following: hematuria, proteinuria, cellular casts on inspection of urinary sediment, or serologic perturbations (hypocomplementemia, cryoglobulinemia, and/or presence of circulating immune complexes); or
	ii. renal biopsy consistent with immune complex-mediated renal disease.
	AKI: new unexplained reduction of estimated glomerular filtration rate (eGFR) < 60mL/Min/1.73sq m.
	Acute on chronic kidney injury: reduction by at least one ordinal level of function: e.g., From "Moderately decreased" to "Severely decreased"; or from "Severely Decreased" to "Kidney failure".
	Interpretive Ranges for eGFR: Normal > 60 ml/min/1.73 sq m; Moderately decreased 30 - 59 ml/min/1.73 sq m; Severely decreased 15 - 29 ml/min/1.73 sq m; Kidney failure < 15 ml/min/1.73 sq m.
****	Excludes single positive blood cultures or sequencing based assays for microorganisms which commonly contaminate blood cultures or rarely cause IE.
¶¶¶¶	Applicable only when echocardiography is unavailable. Based upon expert opinion.

Definite IE		
	Pathologic criteria	Microorganisms identified* in the context of clinical signs of active endocarditis in a vegetation; from cardiac tissue; from an explanted prosthetic valve or sewing ring; from an ascending aortic graft (with concomitant evidence of valve involvement); from an endovascular intracardiac implantable electronic device (CIED); or from an arterial embolus; or
		Active endocarditis† (may be acute¶ or subacute/ chronic§) identified in or on a vegetation; from cardiac tissue; from an explanted prosthetic valve or sewing ring; from an ascending aortic graft (with concomitant evidence of valve involvement); from a CIED; or from an embolus

	Clinical criteria	Two major criteria; or
		One major and three minor criteria; or
		Five minor criteria
Possible IE		1 major criterion and 1 minor criterion; or
		3 minor criteria
Rejected		1. Firm alternate diagnosis explaining signs/symptoms‡; or
		2. Lack of recurrence despite antibiotic therapy for less than 4 days
		3. No pathologic evidence of IE at surgery or autopsy after antibiotic therapy for <4 days
		4. Does not meet criteria for possible IE, as above

IE	Infective Endocarditis
TEE	Trans-Esophageal Echocardiogram
TTE	Trans-Thoracic Echocardiogram
HACEK	Haemophilus spp., Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella spp., Kingella kingae
Ig	Immunoglobulin
[18F]-FDG PET/CT	[18F]-Fluorodeoxyglucose Positron Emission Tomography-computed Tomography
SPECT/CT	Single photon-emission computed tomography
Cardiac CT	Cardiac computed tomography

Table 2. The ESC 2023 Critieria[13]

Major Criteria		
Blood culture positive for IE		a) Typical microorganisms consistent with IE from 2 separate blood cultures:
		i. Viridans streptococci, Streptococcus gallolyticus (bovis), HACEK group, Staphylococcus aureus, Enterococcus faecalis
		b) Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:
		i. At least 2 positive cultures of blood samples drawn >12 hours apart; or
		ii. All of 3 or a majority of 4 separate cultures of blood (with first and last samples drawn at least 1 hour apart)
		c) Single positive blood culture for Coxiella Burnetii or phase I IgG antibody titer >1:800 (was minor criterion)
Imaging positive for IE		a) Valvular, perivalvular/periprosthetic and foreign material anatomic and metabolic lesions characteristic of IE detected by any of the following imaging techniques:
		i. Echocardiography (TTE and TEE)
		ii. Cardiac CT
		iii. [18F]-FDG-PET/CT
		iv. SPECT/CT
Minor Criteria		
Predisposition		Predisposing conditions (i.e. predisposing heart condition at high or intermediate risk of IE or PWIDs; see section 3 of the ESC guidelines for a detailed explanation
Fever		Temperature >38 °C or >100.4 °F
Embolic vascular dissemination (including those asymptomatic detected by imaging only)		a) Major systemic and pulmonary emboli/infarcts and abscesses
		b) Haematogenous osteoarticular septic complications (i.e. spondylodiscitis)
		c) Mycotic aneurysms.
		d) Intracranial ischaemic/haemorrhagic lesions
		e) Conjunctival haemorrhages
		f) Janeway's lesions
Immunologic Phenomena		Glomerulonephritis, Osler's Nodes, Roth's Spots, and Rheumatoid Factor
Microbiological Evidence		a) Positive blood culture but does not meet a major criterion (Excludes single positive culture for coagulase-negative staphylococci and organisms that do not cause endocarditis)
		b) Serological evidence of active infection with organisms consistent with IE

Definite IE		
	Pathologic criteria	Microorganisms found by culture or histology in a vegetation that has embolized, or an intracardiac abscess; or
		Pathologic lesions: vegetation or intracardiac abscess confirmed by histology showing active endocarditis
	Clinical criteria	Two major criteria; or
		One major and three minor criteria; or
		Five minor criteria
Possible IE		1 major criterion and 1 minor criterion; or

	3 minor criteria
Rejected	1. Firm alternate diagnosis for manifestations of endocarditis; or
	2. Resolution of symptoms suggesting IE with antibiotic therapy for ≤4 days; or
	3. No pathologic evidence of IE at surgery or autopsy after antibiotic therapy for <4 days
	4. Does not meet criteria for possible IE, as above

IE	Infective Endocarditis
TEE	Trans-Esophageal Echocardiogram
TTE	Trans-Thoracic Echocardiogram
HACEK	Haemophilus spp., Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella spp., Kingella kingae
Ig	Immunoglobulin
[18F]-FDG PET/CT	[18F]-Fluorodeoxyglucose Positron Emission Tomography-computed Tomography
SPECT/CT	Single photon-emission computed tomography
Cardiac CT	Cardiac computed tomography

Table 3. Summary of the Principal Benefits and Limitations of Differing Imaging Techniques

Transthoracic Echocardiography	Transesophageal Echocardiography	Cardiac CT	MRI	Nuclear Imaging
Benefits				
Easy access, widely available, safe, effective, can assess valvular vegetations and complications, and provides hemodynamic assessment	Increased sensitivity over TTE to assess prosthetic valves, small vegetations and perivalvular complications.	Good sensitivity to detect perivalvular complications in both prosthetic and native valves. Can detect embolic complications.	Detection of peripheral emboli, particularly brain and spine. Can detect the extent of infection beyond the valve in prosthetic valve IE. Can evaluate complex cardiac anatomy in patients with congenital heart disease; of particular value in paediatric patients where radiation exposure a concern.	When positive, is highly specific for the diagnosis of native valve endocarditis. May identify metastatic infection. May identify source of infection, in particular malignancy.
Limitations				
Low sensitivity to detect small vegetations, perivalvular complications and poor assessment of prosthetic valves	Requires introducing a probe through the oropharynx and esophagus which can be contraindicated in certain diseases. Reduced sensitivity in patients with prosthetic valves and cardiac implanted devices.	Low sensitivity to detect small vegetations. Patients are exposed to radiation.	Not a primary diagnostic tool for IE, as does not have the spatial or temporal resolution to evaluate vegetations on native valves.	Low sensitivity for diagnosing native valve infective endocarditis; of greater value in prosthetic valve IE and when there are indwelling devices. High radiation exposure.

Table 4. Good Practice Recommendations for Endocarditis Multidisciplinary Team Meetings[95]

Objective	Documentation	Participants
• Review of imaging and clinical data of all patients • Determine indications for intervention • Determine appropriateness of intervention and frailty (especially in multi-morbid or elderly patients) • Determine most appropriate intervention along with risk and timing • Assign appropriate surgeon with special expertise • Regular progress assessment • Clinicopathological feedback • Discussion of all adverse events including possible methods of avoiding them	• MDT outcomes should be recorded • Documentation should include date of MDT and participants • MDT outcome disseminated to referrer, primary care physician, and patient • MDT outcome database maintained to audit against actual intervention • Referring centre should be kept updated	• Cardiac surgeon (expertise in complex valve surgery) **(key member)** • Cardiologist with expertise in valve disease **(key member)** • Cardiologist or physiologist/scientist with expertise in imaging/echo **(key member)** • Multidisciplinary team administrator **(key member)** • Infection specialist **(key member)** • Other specialists as required – for example, dentists, allergy specialists, home health teams

Figure 1. Attributable Risk – Predicted Additional IE Cases Per 100,000 Procedures

The attributable risk is presented for invasive procedures with a significant positive temporal association with subsequent IE and is expressed as the predicted additional number of IE cases per 100,000 procedures. GI = gastrointestinal, IPs = invasive procedures, transf = transfusion, exch = exchange. Reproduced from Thornhill et al.[86]

Central Illustration. Native Valve Infective Endocarditis