



LE ENDOCARDITI INFETTIVE: IL PUNTO DI VISTA DELL'INFETTIVOLOGO

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Disclosures

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Infective Endocarditis

Li M et al. Lancet 2024;404(10450):377-392

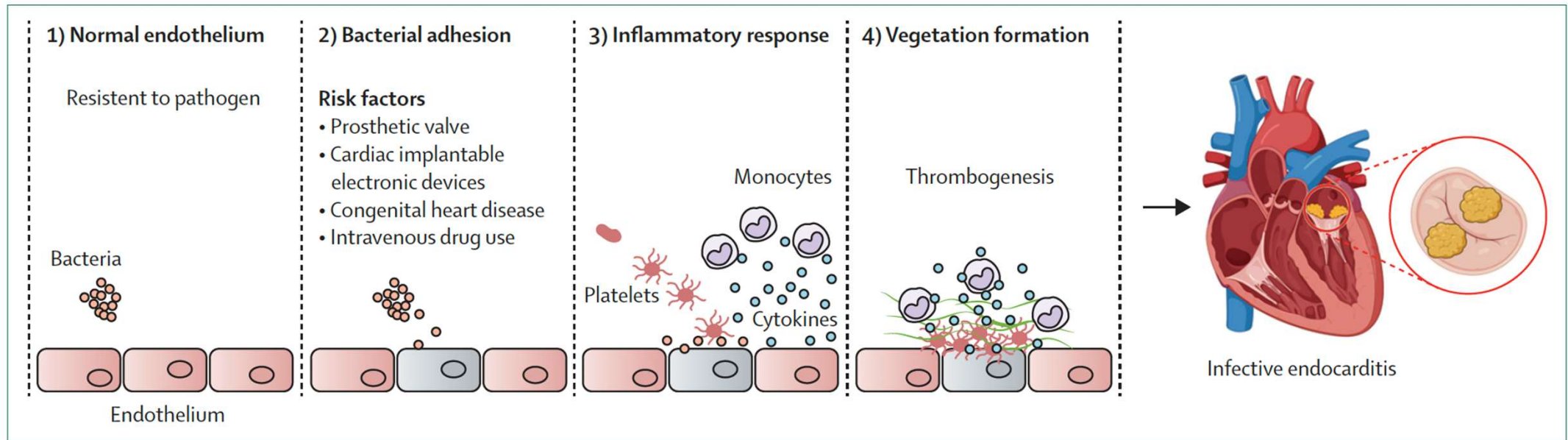
- **First described more than 350 years ago, now a global health concern**
 - Infections of endocardium: valvular, mural, cordal
 - Native or prosthetic heart valves, septal defect, indwelling cardiac device
- **Over recent decades → shifts in causation and epidemiology**
- **Imaging and Microbiology in evolution**
- **Multidisciplinary management:**
 - Infectious diseases, Microbiology, Cardiology & Cardiosurgery, Radiology, Neurology
- **Evidence:**
 - More observational studies available than randomised controlled trials

Geller SA. Autops Case Rep 2013;3:5-12

Lerner PI, Weinstein L. NEJM 1966;274;199-206 & 259-266 & 388-393

Pathophysiology of Infective Endocarditis

Li M et al. Lancet 2024;404(10450):377-392



Infective Endocarditis: Symptoms

Li M et al. Lancet 2024;404(10450):377-392

- **Most predominant clinical symptoms, in 3116 patients**
 - Fever in 2421 cases & congestive heart failure in 848 cases **78% & 27%**
 - Cardiac murmurs, identified as the most frequent sign, were reported in 2010 cases **65%**
- **Other symptoms and signs were less common:**
 - Septic shock in 209 cases, syncope in 81, cardiogenic shock in 72 **7-3-2%**
 - Janeway lesions in 109, Osler's nodes in 59, and Roth's spots in 44 cases **3-2-1%**
- **Symptomatic embolic complications at admission in 788 (25%) cases**
 - Cerebral in 352, splenic in 177 cases **11-6%**
 - Pulmonary in 199, renal in 78, 93 for other peripheral events **6-2-3%**
 - Conduction abnormalities on admission in 358 of 3116 total cases: BAV-I & BAV-III **11-8-3%**
- **Paravalvular abscess in 367 cases** **12%**

Infective Endocarditis: Etiology

Li M et al. Lancet 2024;404(10450):377-392

- **80% of cases:**
 - Staphylococci, Streptococci, Enterococci
 - Majority = *Staphylococcus aureus*, followed by viridans group streptococci
 - Gram-negative bacilli also potential microorganisms, but rare
 - Fungus-associated, mostly by *Candida spp.*, in immunosuppressed (1–2% of cases)
 - Polimicrobial etiology possible and resistant bacteria increasing
- **Positive blood cultures**
 - 45-79%
- **Atypical bacteria & negative blood cultures variable**

Blood Cultures-negative Infective Endocarditis

Delgado V. et al. Eur Heart J 2023

Pathogens	Proposed therapy ^a	Treatment outcome
<i>Brucella</i> 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
<i>C. burnetii</i> (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
<i>Bartonella</i> 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%
<i>Legionella</i> 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
<i>Mycoplasma</i> spp.	Levofloxacin (500 mg/12 h) i.v. or orally for ≥6 months ^e	Optimal treatment unknown
<i>T. whipplei</i> (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

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IE, infective endocarditis; Ig, immunoglobulin; i.v., intravenous.

Adapted from Brouqui et al.³⁸³

^aOwing 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.

Focus on Age, Intravascular Devices & Enterococci

Cecchi E et al, Int J Cardiol 2015

- **677 prospectively collected episodes**
 - 17 Italian centers 2007 to December 2010
 - Median age of 62 years (IQR: 49-74)
 - Predisposing cardiopathy in 50%
- **Etiology**
 - CNS and enterococci were relatively more frequent in patients with intravascular devices and prosthesis
 - *S. viridans* in left native valve
- **Diagnosis**
 - Made by TTE & TEE in 62% and 94% of cases, respectively
- **Mortality**
 - in-hospital mortality was 14% and 1-year mortality was 21%
- → **Older patients with comorbidities and intravascular devices**
- → **Acute** onset
- → **High frequency of Enterococci**

Updating Infective Endocarditis Diagnostic Criteria to Recognize *Enterococcus faecalis* as a Typical Endocarditis Bacterium

Dahl A et al. Clin Infect Dis 2022;75(6):1097102

- **Previous modified Duke criteria considered *E. faecalis* as a microbiological “Major” diagnostic criterion**
 - Bacteremia both community-acquired and without known focus
- **Proposal to upgrade *E. faecalis* as a “typical” endocarditis bacterium**
- **Improved sensitivity from 70% to 96%**
 - From modified Duke criteria to Enterococcal adjusted Duke criteria
 - Prospective study of 344 patients with *E. faecalis* bacteremia evaluated with echocardiography
- **Probably it is the time to designate *E. faecalis* as a “typical” endocarditis pathogen**
 - Regardless the place of acquisition or the portal of entry

The 2023 Duke-International Society for Cardiovascular Infectious Diseases Criteria for Infective Endocarditis: Updating the Modified Duke Criteria Fowler VG et al Clin Infect Dis 2023;77(4):518-26

Table 1. Definitions of Infective Endocarditis According to the 2023 Duke-International Society for Cardiovascular Infectious Diseases Infective Endocarditis (IE) Criteria, With Proposed Changes in Bold Type

I. DEFINITE ENDOCARDITIS

A. Pathologic Criteria

- (1) **Microorganisms identified² 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
- (2) **Active endocarditis^b (may be acute^c or subacute/chronic^d) 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 arterial embolus**

B. Clinical Criteria

- (1) 2 Major Criteria
or
- (2) 1 Major Criterion and 3 Minor Criteria
or
- (3) 5 Minor Criteria

II. POSSIBLE ENDOCARDITIS

- A. 1 Major Criterion And 1 Minor Criterion
or
- B. 3 Minor Criteria

III. REJECTED ENDOCARDITIS

- A. Firm alternate diagnosis explaining signs/symptoms^a
or
- B. Lack of recurrence despite antibiotic therapy for less than 4 d.**
or
- C. No pathologic or macroscopic evidence of IE at surgery or autopsy, with antibiotic therapy for less than 4 d
or
- D. Does not meet criteria for possible IE, as above

The 2023 Duke-International Society for Cardiovascular Infectious Diseases Criteria for Infective Endocarditis: Updating the Modified Duke Criteria Fowler VG et al Clin Infect Dis 2023;77(4):518-26

Table 2. Definitions of Terms Used in the 2023 Duke-International Society for Cardiovascular Infectious Diseases Infective Endocarditis (IE) Criteria for the Diagnosis of IE, With Proposed Changes in Bold Type

I. MAJOR CRITERIA

A. Microbiologic Major Criteria

(1) Positive blood cultures

i. Microorganisms that commonly cause IE^a isolated from 2 or more separate blood culture sets (Typical)^b

or

ii. Microorganisms that occasionally or rarely cause IE isolated from 3 or more separate blood culture sets (Nontypical)^b

(2) Positive laboratory tests

i. Positive polymerase chain reaction (PCR) or other nucleic acid-based technique^c for *Coxiella burnetii*, *Bartonella* species, or *Tropheryma whippelii* from blood

or

ii. *Coxiella burnetii* antiphase I immunoglobulin G (IgG) antibody titer >1:800 [24]^d, 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 immunoglobulin G (IgG) titer ≥ 1:800 [24, 25]^d

B. Imaging Major Criteria

(1) Echocardiography and **cardiac computed tomography (CT) imaging**

i. Echocardiography and/or cardiac CT showing vegetation,^a valvular/leaflet perforation,^f valvular/leaflet aneurysm,^g abscess,^h pseudoaneurysm,ⁱ or intracardiac fistula^j

or

ii. Significant new valvular regurgitation on echocardiography as compared with previous imaging. Worsening or changing of preexisting regurgitation is not sufficient.

or

iii. New partial dehiscence of prosthetic valve as compared with previous imaging [52]

(2) **Positron emission computed tomography with 18F-fluorodeoxyglucose ([18F]FDG PET/CT imaging)**

Abnormal metabolic activity^k involving a native or prosthetic valve, ascending aortic graft (with concomitant evidence of valve involvement), intracardiac device leads or other prosthetic material^{l,m}

C. Surgical Major Criteria

Evidence of IE documented by direct inspection during heart surgery neither Major Imaging Criteria nor subsequent histologic or microbiologic confirmationⁿ

The 2023 Duke-International Society for Cardiovascular Infectious Diseases Criteria for Infective Endocarditis: Updating the Modified Duke Criteria Fowler VG et al Clin Infect Dis 2023;77(4):518-26

II. MINOR CRITERIA

- A. Predisposition
 - **Previous history of IE**
 - Prosthetic valve^o
 - Previous valve repair^p
 - Congenital heart disease^p
 - More than mild regurgitation or stenosis of any etiology
 - **Endovascular intracardiac implantable electronic device (CIED)**
 - Hypertrophic obstructive cardiomyopathy
 - Injection drug use
- B. Fever *Documented temperature greater than 38.0 °C (100.4 °F)*
- C. Vascular Phenomena *Clinical or radiological evidence of arterial emboli, septic pulmonary infarcts, **cerebral or splenic abscess**, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions, purulent purpura*
- D. Immunologic Phenomena *Positive rheumatoid factor, Osler nodes, Roth spots, or immune complex-mediated glomerulonephritis^a*
- E. Microbiologic Evidence, Falling Short of a Major Criterion
 - 1) Positive blood cultures for a microorganism consistent with IE but not meeting the requirements for Major Criterion^r
 - or
 - 2) **Positive culture, PCR, or other nucleic acid based test (amplicon or shotgun sequencing, *in situ* hybridization) for an organism consistent with IE^r from a sterile body site other than cardiac tissue, cardiac prosthesis, or arterial embolus; or a single finding of a skin bacterium by PCR on a valve or wire without additional clinical or microbiological supporting evidence [51]**
- F. Imaging Criteria
 - Abnormal metabolic activity as detected by [18F]FDG PET/CT within 3 mo of implantation of prosthetic valve, ascending aortic graft (with concomitant evidence of valve involvement), intracardiac device leads or other prosthetic material***
- G. Physical Examination Criteria^s
New valvular regurgitation identified on auscultation if echocardiography is not available. Worsening or changing of preexisting murmur not sufficient

Computed Tomography in Infectious Endocarditis

Dalebout EM et al. J Soc Cardiovasc Angiogr Interv 2024

	Transesophageal echocardiography	Cardiac computed tomography
Vegetation	Oscillating or non-oscillating mass adjacent to valves, chordae, cardiac device leads or other structures	Low to intermediate attenuated mobile mass attached to valves or other cardiac structure. Can also appear as thickened valve leaflets
Perforation	Discontinuity of valvular tissue with color Doppler flow through the defect	Defect in leaflet tissue
Fistula	Abnormal blood flow through communicating cardiac chambers or cavities seen by color Doppler flow	Communicating trajectory between two cardiac cavities filled with contrast
Abscess	Thickened, irregularly shaped, paravalvular area or mass appearing echodense or echolucent	Area filled with intermediate to low density fluid and high attenuated rim. Surrounding structures can show inflammatory changes or mass effect
Pseudoaneurysm	Pulsatile paravalvular echo-free space detected with color Doppler	Attenuated cavities, enhancing corresponding with cardiac chambers or vessels
Paravalvular leak and dehiscence	Discontinuity between the prosthetic valve and annulus with regurgitation detected by color Doppler. Rocking prosthesis motion can be seen	Hyperdense area in between the valve and the annulus, connecting proximal and distal structures. Rocking motion can be seen on cine images due to larger circumferential dehiscence

Figure 5.

Overview of signs of endocarditis that can be seen on echocardiography and computed tomography.^{8,10,37–39}

Summary of Three Metanalysis: CT Vs. TEE in Infectious Endocarditis

Dalebout EM et al. J Soc Cardiovasc Angiogr Interv 2024

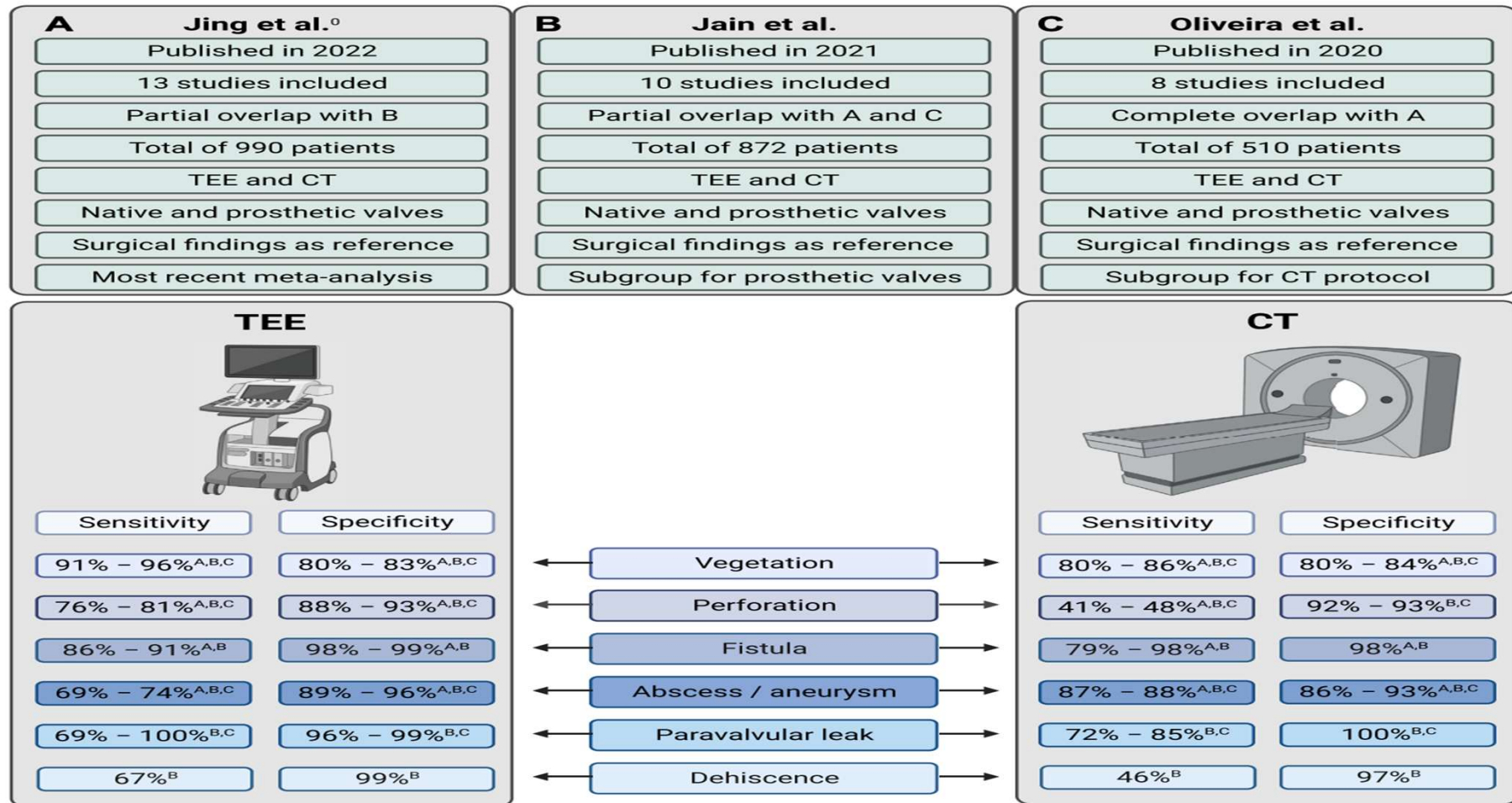


Figure 6. Summary of 3 meta-analyses considering the diagnostic accuracy of transesophageal echocardiography (TEE) and computed tomography (CT) for infective endocarditis. The most important study characteristics are provided and the range of pooled sensitivity and specificity for different signs of endocarditis. (A) Meta-analysis by Jing et al.⁴⁰; (B) meta-analysis by Jain et al.⁸; (C) meta-analysis by Oliveira et al.⁹

Make Modern Microbiology Matter More in the 2023 European Society of Cardiology Guidelines for Infective Endocarditis

Oldberg K & Rasmussen M Clin Infect Dis 2024;79(2):336-8

Both the 2023 Duke–International Society for Cardiovascular Infectious Diseases (ISCVID) criteria for the diagnosis of infective endocarditis (IE) and the 2023 European Society of Cardiology (ESC) guidelines for the management of IE have recently been published [1, 2]. The 2023 ESC guidelines were published after the Duke–ISCVID criteria and could have included the updated diagnostic criteria presented in the Duke–ISCVID criteria. Instead, the ESC guidelines refer to the modified Duke criteria from 2000 [3] with some minor changes. This has resulted in 2 diagnostic criteria for IE, which is unfortunate for researchers in the field and ultimately for patients.

Whereas the 2023 ESC guidelines stress that a multidisciplinary approach is needed to optimally manage patients with IE, the working group is hardly multidisciplinary and there is no microbiologist in the group. Thus, the guidelines, in terms of microbiological diagnostics, fail to elaborate on potentially important aspects of managing patients with IE [4]. We believe that there is a need for more microbiological input in the future when new guidelines are written.

The 2023 ESC guidelines present diagnostic criteria for IE where some changes in the microbiological aspects were introduced. These include introduction of the term “oral streptococci” instead of “viridans streptococci” and “*Streptococcus gallolyticus*” instead of “*Streptococcus bovis*.” Both changes are problematic since some viridans streptococci, such as *Streptococcus anginosus*, are instead “intestinal streptococci,” and *S. gallolyticus* is just one of several species in the bovis group [5]. It is therefore unclear which streptococci should be regarded as typical IE pathogens according to the 2023 ESC diagnostic criteria. Table 1 summarizes some of the problematic features of the ESC 2023 guidelines together with a short proposal for possible actions that can be taken to address these concerns.

The ESC 2023 diagnostic criteria for IE do not make use of the improvements in species determination of bacteria, in particular, streptococci, that have occurred since the first publication of the Duke criteria in 1994. For example, it has become evident that patients with bacteremia with streptococci of the mutans, bovis, or sanguinis groups often have IE, whereas patients with bacteremia caused by anginosus group streptococci rarely have IE [6, 7]. In addition, several pathogens are not mentioned in the ESC 2023 diagnostic criteria despite having a propensity similar to that of *Staphylococcus aureus* or “oral streptococci” to cause IE. Such bacterial genera and species include *Abiotrophia*, *Aerococcus*, *Corynebacterium striatum*, *Corynebacterium jeikeium*, *Gemella*, *Granulicatella*, and *Staphylococcus lugdunensis*, and these should all be regarded as typical pathogens [8]. Some of these pathogens are recognized as typical IE pathogens in the Duke–ISCVID criteria [2].

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<https://doi.org/10.1093/cid/ciae222>

Guidelines Conflicts

Oldberg K & Rasmussen M Clin Infect Dis 2024;79(2):336-8

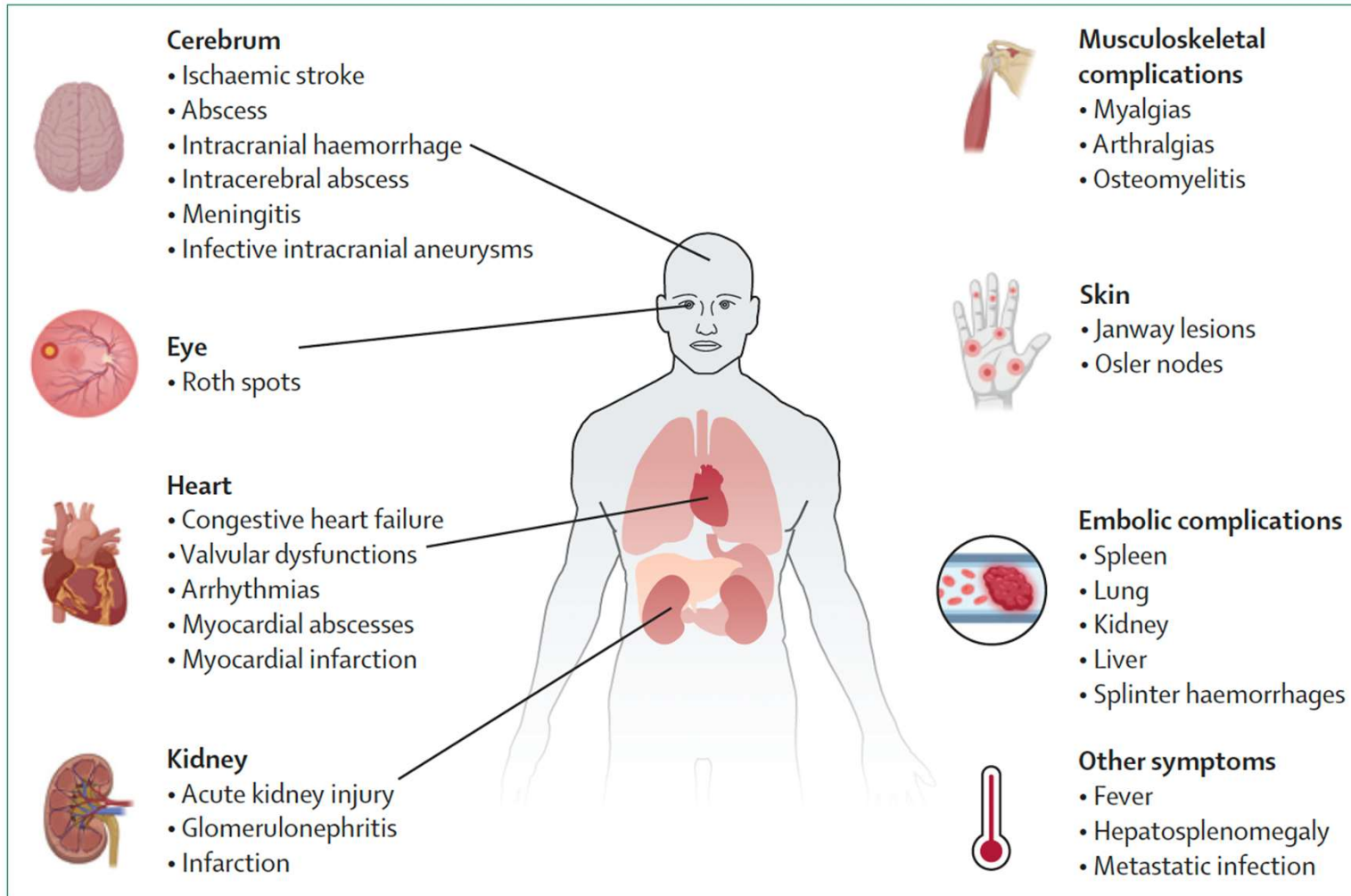
Table 1. Problems With Microbiological Aspects of the European Society of Cardiology 2023 Guidelines and Proposed Action

Feature	European Society of Cardiology 2023 Problem	Suggested Alternative
Typical pathogens	"Oral streptococci"	Viridans streptococci
	" <i>Streptococcus gallolyticus</i> "	<i>Streptococcus bovis</i> group
	No mention of other <i>Streptococcus</i> -like pathogens	<i>Aerococcus</i> , <i>Abiotrophia</i> , <i>Granulicatella</i> , <i>Gemella</i> , <i>Corynebacterium jeikeium</i> , <i>Corynebacterium striatum</i> , and <i>Staphylococcus lugdunensis</i> as typical pathogens
Blood cultures	"With first and last samples drawn ≥ 1 h apart"	Makes culturing more difficult without evidence of improved sensitivity; delete this claim
	"Blood cultures should be obtained at 30-minute intervals"	Makes culturing more difficult without evidence of improved sensitivity; delete this claim
	No recommendation on follow-up blood culture	Recommend follow-up blood cultures for <i>Staphylococcus aureus</i> to assess likelihood of IE
	No mention of TTP	Mention that a short TTP is linked to higher risk for IE
	No mention of incubation time	Prolonged incubation (>5 d) may be needed for <i>Cutibacterium</i> in suspected prosthesis valve IE
Strategy	"Blood cultures remain negative at 48 h"	This is also common in culture-positive IE; wait for 5 days before taking action
	"Systematic serological testing"	Not necessary if antibiotics have been given before blood cultures
	Serology for <i>Aspergillus</i>	Not to be used; consider beta-D-glucan or galactomannan
	Serology for <i>Legionella</i> and <i>Mycoplasma</i>	Extremely rare causes of IE; do not recommend
	"Nonbacterial endocarditis should systematically be considered and assays for" "should be performed"	The diagnostic benefit of these tests is doubtful, and the word "should" is far too strong
Other	Figure 4	A new figure is needed
	Table 9	Revise according to the suggestions presented here

Abbreviations: IE, infective endocarditis; TTP, time to positivity.

Infective Endocarditis: Complications

Li M et al. Lancet 2024;404(10450):377-392



Diagnosi Autoptica = EI Acuta

- **1527 autopsie eseguite nel periodo 1996-99**
= 94% dei decessi ospedalieri
- **EI = 31 casi; 26 valutabili:**
 - Tutte EI sinistre (5 MV, 8 AV, 1 MV + AV)
 - 14 con errata diagnosi: polmoniti, meningiti, leptospirosi, cirrosi, artrite reumatoide
 - Alcolismo fattore in comune
- **Durata media dei sintomi: 8.5_±4.8 giorni**
- **Degenza media: 1.6_±1.44 giorni**

Updating Infective Endocarditis Diagnostic Criteria to Recognize *Enterococcus faecalis* as a Typical Endocarditis Bacterium

Dahl A et al. Clin Infect Dis 2022;75(6):1097102

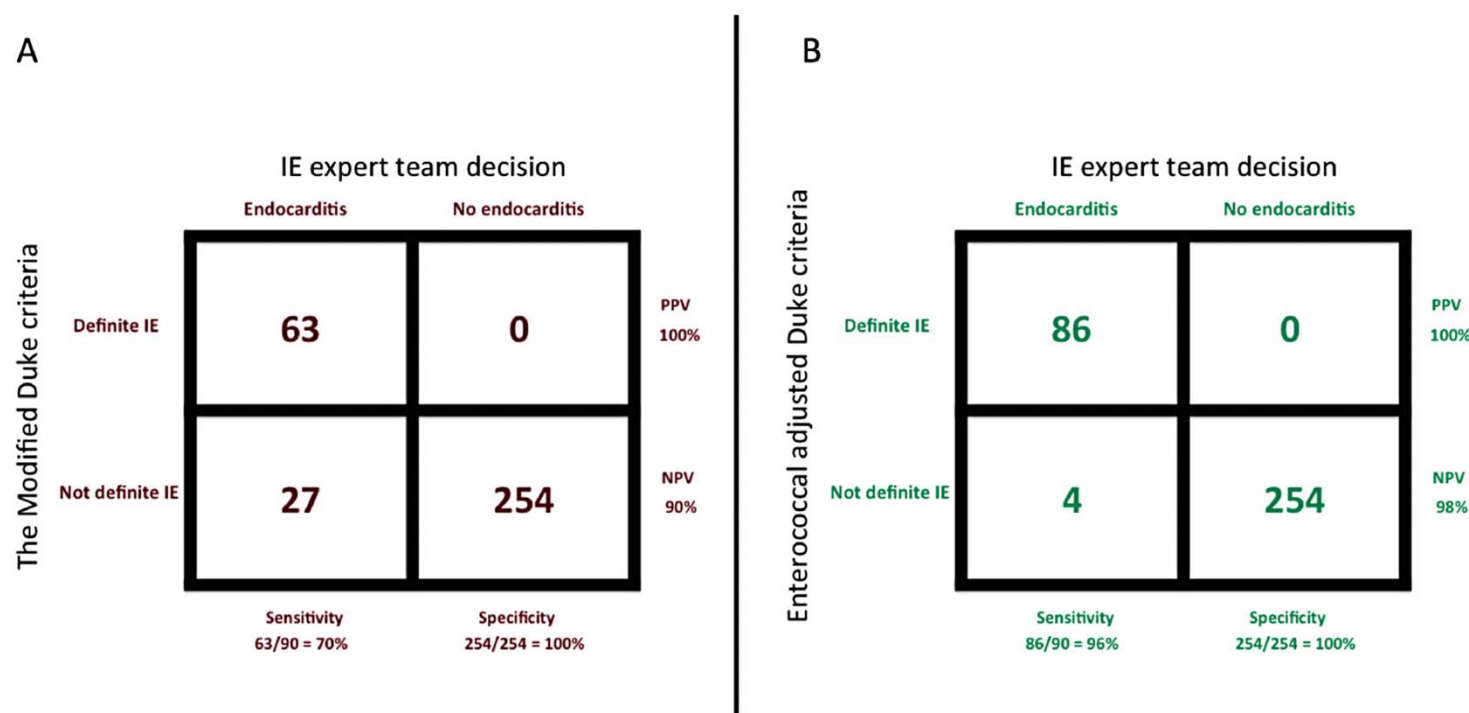
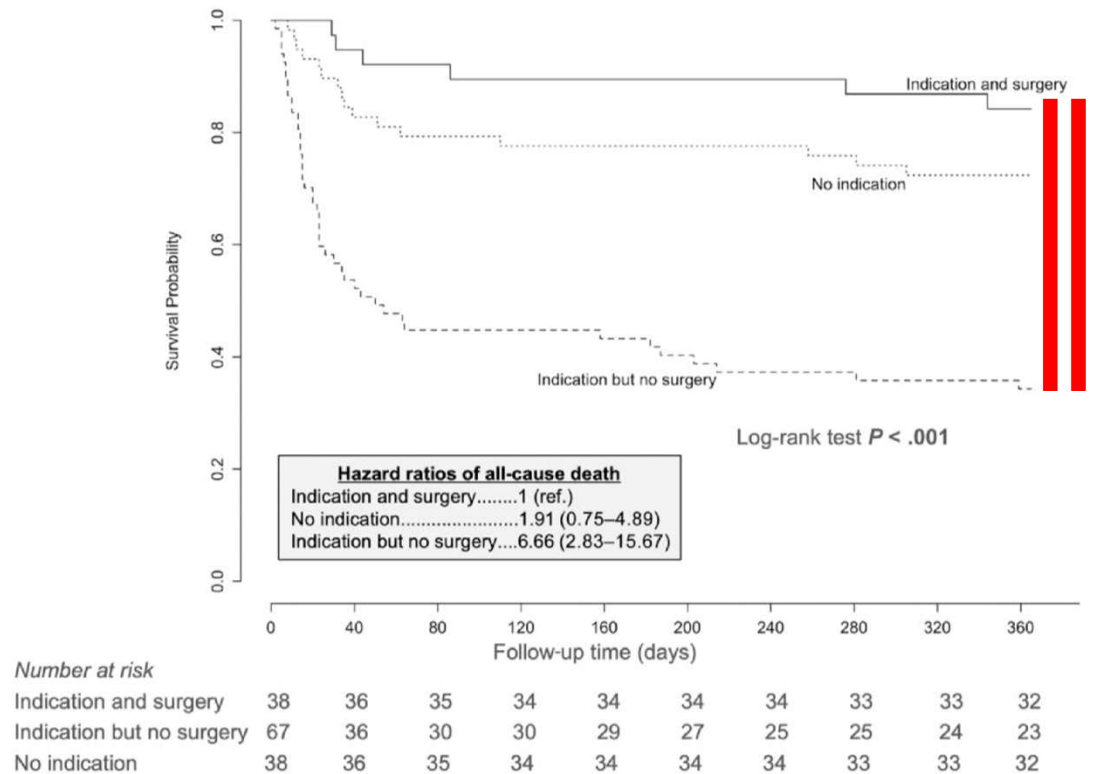


Figure 1. Diagnostic performance of the modified Duke criteria (A) and the enterococcal adjusted Duke criteria (B) in 344 patients with *E. faecalis* bacteremia. The modified Duke criteria had a sensitivity of 70% and an NPV of 90% (a). The *Enterococcal adjusted Duke Criteria* had a sensitivity of 96% and a NPV of 98% (b). Abbreviations: IE, infective endocarditis; NPV, negative predictive value; PPV, positive predictive value.

Mortality of Left-side Infective Endocarditis With & Without Surgery in Elderly (MoISE) Study

Hemar V et al Clin Infect Dis 2023;77(10):1440-8

A Survival probability according to surgical indication



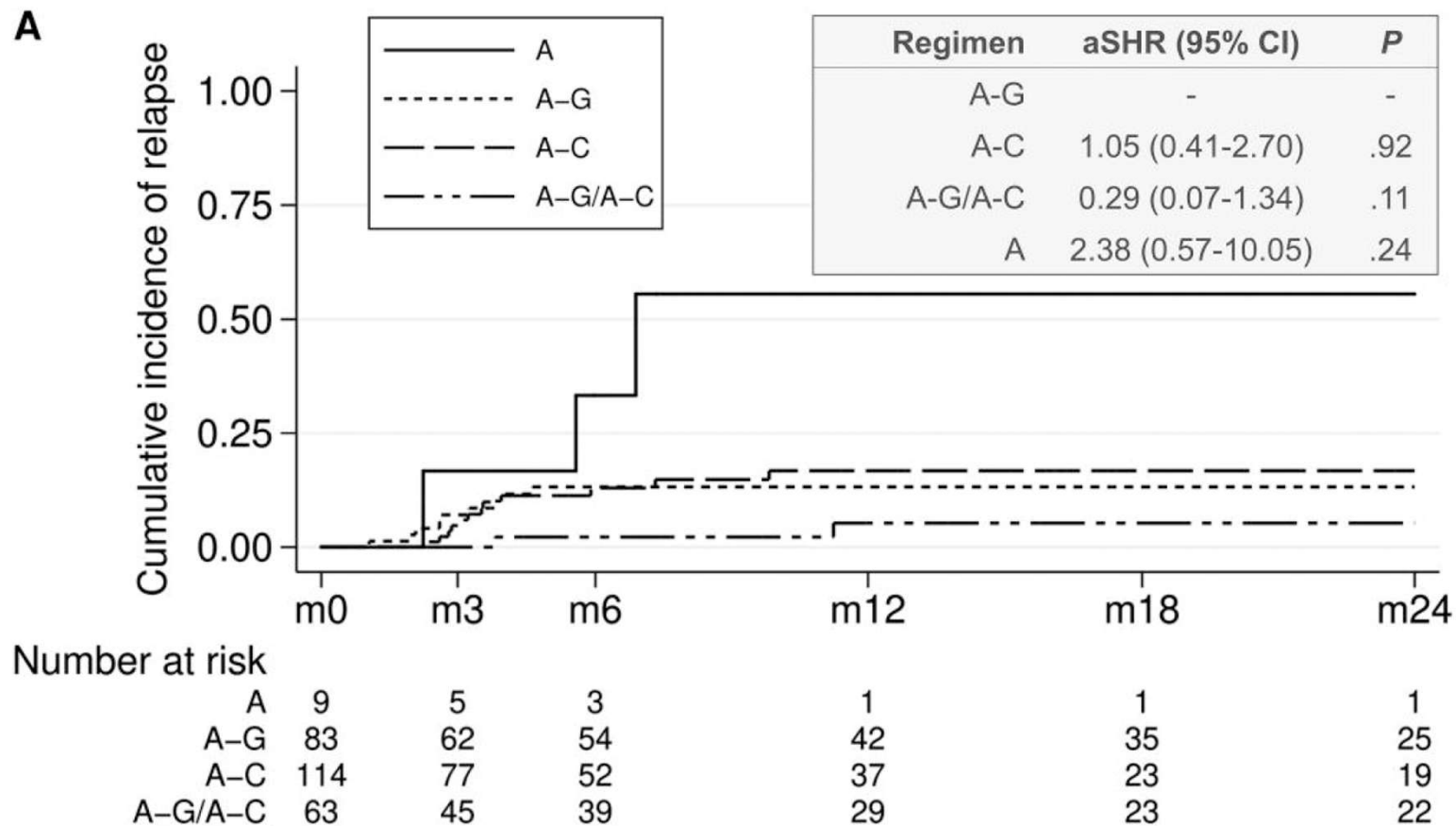
Mortality of Left-side Infective Endocarditis With & Without Surgery in Elderly (MoISE) Study

Hemar V et al Clin Infect Dis 2023;77(10):1440-8

- **163 patients**
 - Median age, 84 years; men, 59%; prosthetic LSIE, 45%
 - Potential surgical indications 105 (64%)
 - Cardiosurgery 38 (36%)
- **Cardiosurgery associated with:**
 - Younger age & more likely men with aortic involvement
 - Lower Charlson comorbidity index
- **Better functional status at admission**
- **1-year mortality rate**
 - LSIE patients without surgical indications 28%
 - Lower in operated compared with no intervention despite a surgical indication
 - 16% vs 66%, $P < .001$
- **Geriatric specialist in the endocarditis team? Discuss opportunities & futilities**

Effect of Different Treatments on Enterococcal Infective Endocarditis Risk of Relapse

Danneels P et al. Clin Infect Dis 2023



Endocarditi Infettive: Sintesi

- **Abbiamo guadagnato in metodologia**
 - Da soggettivo a oggettivo
 - Quanta interpretazione "culturale-clinica" abbiamo perso?
- **Approccio più tecnico & interdisciplinare**
 - Manca un'interdisciplinarieta' "complementare"
 - Le linee guida sono scritte più da cardiologi
- **Abbiamo perso in àmbiti squisitamente soggettivi & descrittivi**
 - Individualizzazione diagnostico-terapeutica
 - Endocarditi "acute" e "subacute"
 - Batteriemie e timing delle complicanze come fattore predittivo di endocardite
- **Progressi nella cardiochirurgia (precoce) & terapia orale**

**“Il cuore assiste spesso impassibile al
dramma di cui egli stesso è teatro”**

Enciclopedia Medica Italiana

1971

Giuseppe Giunchi & Franco De Rosa

Unexpected Infective Endocarditis: Towards a New Alert for Clinicians

La Canna G et al. J Clin Med 2024;13(17):5058

- **Daily clinical practice & evolving epidemiology**
 - Variations in the populations at risk
 - Increased incidence in subjects without at-risk cardiac disease
 - Emergent at-risk populations for IE:
 - Immunocompromised patients, comorbidity burden (e.g., cancer, diabetes, dialysis)
 - Long-term central venous catheters or recurrent healthcare interventions
 - Healthy subjects &, virulent bacteria
- **Possible overlooking, challenging diagnosis and delayed treatment**

Infective Endocarditis: Knowledge Gaps

Li M et al. Lancet 2024;404(10450):377-392

Knowledge gaps that need strong evidence from further research

Proposed study designs

Diagnosis

Diagnostic schema	Which diagnostic schema is the most accurate? What is the diagnostic accuracy of the different schema in diverse care settings?	A
Microbiology	What is the accuracy of diagnostic testing for <i>Bartonella</i> infective endocarditis?	A
Microbiology	What is the accuracy of diagnostic testing for <i>Coxiella burnetii</i> (Q fever) infective endocarditis?	A
Microbiology	What is the accuracy of diagnosis of culture-negative infective endocarditis using molecular rapid diagnostic tests, or the determination of bacterial or fungal cell-free DNA in blood samples?	A
Microbiology	What is the role of molecular and biochemical indicators to establish the diagnosis in fungal endocarditis?	B
Microbiology	What is the effect of molecular rapid diagnostic tests on outcomes in infective endocarditis?	C
Imaging	What is the standard method to assess the size of the vegetations?	A
Imaging	What is the diagnostic performance of intracardiac echocardiography in prosthetic valve endocarditis?	A
Imaging	What is the role of scoring systems in the identification of patients who might require a transoesophageal echocardiogram in the diagnosis of infective endocarditis?	B
Imaging	What is the role of repeat echocardiograms in patients with an initial negative study suspected of having infective endocarditis or in patients with an established diagnosis of infective endocarditis?	B
Imaging	What is the role of [¹⁸ F]FDG-PET-CT in native valve endocarditis?	B
Imaging	What is the ability of [¹⁸ F]FDG-PET-CT to affect clinical outcomes of infective endocarditis?	C