Clinical Infectious Diseases

VIEWPOINTS ARTICLE

The 2023 Duke-ISCVID Criteria for Infective Endocarditis: Updating the Modified Duke Criteria

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DOI: 10.1093/cid/ciad271

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The microbiology, epidemiology, diagnostics, and treatment of infective endocarditis (IE) have changed significantly since the Duke Criteria were published in 1994 and modified in 2000. The International Society for Cardiovascular Infectious Diseases (ISCVID) convened a multidisciplinary Working Group to update the diagnostic criteria for IE. The resulting 2023 Duke-ISCVID IE Criteria propose significant changes, including new microbiology diagnostics (enzyme immunoassay for *Bartonella* species, PCR, amplicon/ metagenomic sequencing, *in situ* hybridization), imaging ([18F]FDG PET/CT, Cardiac Computed Tomography), and inclusion of intraoperative inspection as a new Major Clinical Criterion. The list of "typical" microorganisms causing IE was expanded and includes pathogens to be considered as typical only in the presence of intracardiac prostheses. The requirements for timing and separate venipunctures for blood cultures were removed. Last, additional predisposing conditions (transcatheter valve implants, endovascular cardiac implantable electronic devices, prior IE) were clarified. These diagnostic criteria should be updated periodically by making the ISCVID-Duke Criteria available online as a "Living Document".

Keywords: Endocarditis; Duke Criteria; PET/CT; Echocardiography; ISCVID

INTRODUCTION

The Duke Criteria for diagnosis of infective endocarditis (IE) were originally published in 1994 [1] and modified in 2000[2]. Their primary purpose was to serve as a research tool to standardize the definition of a clinically protean condition. Their presence paved the way for a steady stream of multinational investigations[3-7] that transformed our understanding of the disease. However, the microbiology, diagnostics, epidemiology, and treatment of IE have changed significantly since the debut of these criteria. For example, endovascular cardiac implantable electronic devices (CIEDs), including permanent pacemakers and cardioverter-defibrillators, are now present in at least 10% of contemporary IE case series[6], and constitute a significant risk factor for infection[8, 9]. Transcatheter implanted valves are infected at rates comparable to surgically implanted valves, and are an increasing component of prosthetic valve endocarditis (PVE). In

2015, the European Society of Cardiology[10] proposed changes to the Modified Duke Criteria; however, recent advances require further modifications of the formal diagnostic criteria for IE.

In response to this need, in 2021 the International Society for Cardiovascular Infectious Diseases (ISCVID) convened a Working Group of 25 subject matter experts from 5 continents and 6 IE-related subspecialties (Cardiovascular Pathology, Cardiovascular Surgery, Cardiology, Radiology, Clinical Microbiology, and Infectious Diseases), to prepare an update of the diagnostic criteria for IE. These **2023 Duke-ISCVID IE Criteria** are presented below. In this Consensus document, the ISCVID Working Group presents the rationale for the modification of the previous diagnostic criteria, and a summary of the proposed changes.

Definite IE - pathologic criteria

The Pathologic Criteria for Definite IE in the Modified Duke Criteria relied upon identifying either microorganisms or histopathologic evidence of active IE in operative or post-mortem specimens. The 2023 Duke-ISCVID IE Criteria clarify and extend these criteria by incorporating recent genetic, molecular, and tissue staining techniques by which etiologic microorganisms can be detected (**Table 1**). A variety of newer laboratory diagnostics, including 16S/18S rRNA gene PCR, new sequencing techniques[11], and fluorescence *in situ* hybridization[12], can enhance our ability to diagnose IE. For example, fluorescence *in situ* hybridization combined with PCR/sequencing (FISHseq) in the analysis of infected prosthetic heart valves demonstrated a 30% increase in the detection/ clarification of causative microorganisms over routine blood and valve cultures [12]. The ISCVID Working Group incorporated these new diagnostic approaches into the Pathologic Criteria of Definite IE in the 2023 Duke-ISCVID 2023 Criteria.

Clinical criteria

The ISCVID Working group concludes that the original structure for differentiating Definite, Possible, and Rejected IE on the basis of Major and Minor Clinical Criteria should remain unchanged. One new domain, Surgical, was added to the two previous domains (Microbiologic and Imaging) comprising the Clinical Criteria (**Table 2**).

Microbiologic criteria

Blood cultures

The microbiological diagnostic criteria are depicted in **Table 2**. Blood cultures remain the gold standard for diagnosing IE and for directing antimicrobial therapy. There is no change in the original strategy to group microorganisms that ‘typically’ or ‘occasionally or rarely’ cause IE. In the 2023 Duke-ISCVID Criteria, a "typical" microorganism is not necessarily a frequent cause of IE, but its identification in an episode of bacteremia is strongly associated with IE. Conversely, an atypical microorganism is a bacterium whose identification in a bacteremia is associated with

a low risk of IE. Additional bacteria were added to the 'typical microorganism' group to reflect recent epidemiologic data. Based upon a recent cohort study of over 6500 cases of streptococcal bacteremia, all streptococcal species except *Streptococcus pneumoniae* and *Streptococcus pyogenes* are now recognized as typical IE pathogens[13]. *Staphylococcus lugdunensis* was added due to the high risk of IE in patients with bacteremia[14]. *Enterococcus faecalis* was added as a typical pathogen irrespective of the primary source and setting of infection, based upon recent findings that such a designation increased the sensitivity of diagnosing IE from 70% to 96% without losing specificity[15]. Several "streptococci-like bacteria", including *Granulicatella* and *Abiotrophia species (previously included as "nutritionally variant strains")*, and *Gemella* species were identified as typical IE pathogens based upon the relatively high risk of IE in patients with bacteremia due to these pathogens[16]. Non-*faecalis* enterococci were omitted as typical organisms due to their infrequency as a cause of IE[17]. Finally, the ISCVID Working Group agreed that the clinical context in which an episode of bacteremia occurred influenced consideration of what bacteria should be considered "typical" IE pathogens. Thus, the following additional bacteria should be included as "typical" pathogens in the setting of intracardiac prosthetic material: coagulase negative staphylococci[7], *Corynebacterium striatum* and *C. jeikeium*[18], *Serratia marcescens* and *Pseudomonas aeruginosa[9]*, *Cutibacterium acnes*[19], non-tuberculous mycobacteria, (especially *M. chimaerae*)[20], and *Candida* species.

In the 2023 Duke ISCVID Criteria, "typical" microorganisms isolated from two or more separate blood culture sets (each set consisting of one aerobic and one anaerobic bottle) constitute a Major Criterion. By contrast, microorganisms that occasionally or rarely cause IE must be isolated in three or more separate blood cultures to constitute a Major Criterion. In response to changing clinical practice and a better understanding of the pathogenesis of endovascular infection, the ISCVID Working Group expert consensus was that complex requirements for blood cultures specifying the timing and the need for separate venipunctures should be discontinued. For adults with suspected bacteremia, at least two blood culture sets should be obtained. While best practice recommendations endorse separate venipuncture for each blood culture whenever possible[21], it is no longer required by the Duke Criteria. Patients should only be considered to have polymicrobial IE if the criteria for Definite IE are met and more than one bloodstream pathogen fulfills Major Microbiologic Criteria. If only one bloodstream pathogen meets Major Microbiologic Criteria, then IE is attributed solely to that predominant organism.

Other microbiologic tests

The ISCVID Working Group identified additional microbiologic tests that could constitute a Major Criterion, especially when conventional blood cultures fail to identify a causative pathogen. Blood culture negative endocarditis (BCNE) occurs in ~ 10% of IE cases from industrialized regions [6]. BCNE is most commonly due either to bacteria whose growth in blood cultures is inhibited by prior antibiotics, or to microorganisms which are not isolated by routine culture techniques (e.g., *Coxiella burnetii* or *Bartonella species*)[22]. Other pertinent causes of "initially" BCNE are microorganisms that either grow slowly in the microbiology laboratory

and/or require special media for cultivation (e.g., *Brucella*; *Tropheryma whipplei; Legionella*; fungi; *Abiotrophia, Granulicatella*)[22, 23]. In the Modified Duke Criteria, *C. burnetii* anti-phase I IgG antibody titer > 1:800 was identified as a Major Criterion based on extensive experience in confirmed cases of Q Fever IE[24]. In the current revision, the ISCVID Working Group accepts an Enzyme Immunoassay (EIA) IgG titer of $\geq$ 1:800 for *B. quintana* or *B. henselae* as a Major Criterion based on recent epidemiologic, serologic and clinical surveys of confirmed cases of *Bartonella* IE [24, 25].

Finally, identification of *C. burnetii, Bartonella* species, or *T. whipplei* by PCR or other nucleic acid-based techniques from blood[23] was added as a new Major Criterion (Table 2). Two newer techniques, amplicon or hypothesis free metagenomic ('shotgun') sequencing, are increasingly used to identify the etiology of BCNE. The sensitivity and specificity of these assays have been verified by spiking plasma samples with known microorganisms[26], and their utility have been demonstrated in small cohorts with bacteremia and IE[27-29]. A major advantage of amplicon or metagenomic sequencing is rapid turn-around time, often yielding results in 24-48 hours after initiation of an assay; a major disadvantage is high cost.

While the usefulness of amplicon or metagenomic sequencing in patients with BCNE needs to be further evaluated, the ISCVID Working Group believe that a positive result for *C. burnetii, Bartonella* species, or *T. whipplei* from an amplicon or metagenomic sequencing platform should constitute a Major Criterion, comparable to immunoassays or PCR. Amplicon or metagenomic sequencing has unresolved issues for the diagnosis of other causes of BCNE, including differentiating 'true positive' from 'contamination' and IE from other causes of bacteremia. Thus, positive serum amplicon or metagenomic sequencing results for organisms other than *C. burnetii, Bartonella*, and *T. whipplei* bacteria should be considered as a Minor Criterion pending further data.

Imaging criteria

Echocardiography and Cardiac Computed Tomography (CCT)

Echocardiography remains the first-line imaging modality for detecting anatomic evidence of IE[30] and continues to be a critical Major Criterion in the 2023 Duke-ISCVID IE 2023 Criteria (Table 2). While the hallmark echocardiographic evidence of IE is a valvular vegetation, other complications involving valvular leaflets (e.g., perforation or pseudoaneurysm), paravalvular structures (e.g., abscess, pseudoaneurysm or fistula), or prosthetic valves (e.g., valvular dehiscence) can also be indicative of IE[30]. Transthoracic echocardiography (TTE) has a lower sensitivity for the diagnosis of IE compared with transesophageal echocardiography (TEE). Hence, TEE is usually mandatory in cases of suspected IE, especially in the setting of prosthetic valves, cardiac devices, or when complications are suspected (e.g., perforation, paravalvular lesions, fistula, or prosthetic valve dehiscence)[31]. TEE is also recommended in many patients with hematogenous spondylodiscitis due to recent studies finding IE prevalence up to 33%[32].

Despite the high sensitivity and specificity of TEE, challenging clinical scenarios exist where echocardiography cannot confirm or exclude the diagnosis of IE. In such cases, and in all cases of IE in patients with intracardiac implants or with suspicion of paravalvular extension, newer diagnostic techniques may help to confirm the diagnosis.

The ISCVID Working Group added cardiac computed tomography (CCT) as an additional imaging modality in the 2023 Duke-ISCVID IE Criteria (Table 2). While CCT's ability to detect vegetations is lower than that of echocardiography, it has a higher sensitivity for the detection of paravalvular lesions due to its improved spatial resolution[33, 34]. For example, CCT had a better sensitivity than TEE to diagnose pseudoaneurysm or abscess (78% vs 69%), while TEE outperformed CCT for the detection of vegetations (94% vs 64%), valvular perforation (81% vs 41%) and paravalvular leakage (69% v s 44%)[35]. The combination of both CCT and echocardiography had superior sensitivity for the diagnosis of all valvular and paravalvular lesions compared to either modality alone[36]. As a result, the ISCVID Working Group considers these two imaging modalities as complementary in patients with suspected IE. In addition, CCT may be a useful adjunct when TEE is contraindicated, or when TEE images are suboptimal due to calcifications or intracardiac implants.

The ISCVID Working Group agrees that the findings of significant new valvular regurgitation and prosthetic valve dehiscence constitute a Major Criterion, *if they are found to be new when compared to prior imaging studies*.

Positron Emission Computed Tomography with 18F-fluorodeoxyglucose ([18F]FDG PET/CT)

[18F]FDG PET/CT is now included in the 2023 Duke-ISCVID IE Criteria as an imaging modality (Table 2). [18F]FDG PET/CT overcomes the diagnostic limitations of echocardiography when evaluating prosthetic material [37], allowing reclassification of a large portion of suspected prosthetic valve endocarditis (PVE) cases from "possible" to "definite" IE. Because the role of [18F]FDG PET/CT to reject IE remains controversial, the ISCVID Working Group currently focused upon its positive predictive value. When added into the Duke Criteria as a Major Criterion, [18F]FDG PET/CT significantly improves the identification of definite PVE (pooled sensitivity: 0.86 [0.81–0.89]; pooled specificity: 0.84 [0.79–0.88]) as compared to echocardiography alone[38]. [18F]FDG PET/CT has special value in the diagnosis of cardiac infection in patients with complex cardiac implants, such as multiple prosthetic valves, combined aortic valves and grafts, and congenital heart disease [39]. [18F]FDG PET/CT was included as a Major Criterion in the 2015 European Society of Cardiology (ESC) IE diagnostic criteria for PVE, a change which improved the diagnostic yield compared to the modified Duke Criteria. Thus, the current indication for [18F]FDG PET/CT is for patients with a high clinical suspicion of PVE but nondiagnostic echocardiography. Intense, focal/multifocal or heterogeneous FDG uptake patterns detected at least 3 months after prosthetic valve surgical implantation [40] are included as a Major Criterion by the ISCVID Working Group. Abnormal FDG uptake on CIED

leads is also considered a Major Criteria, although a negative scan cannot exclude infection if suspicion is high. In native valves, [18F]FDG PET/CT is insufficiently sensitive to exclude IE (sensitivity 0.31 [0.21-0.41]), but has a very high positive predictive value. Thus, a significant and visually abnormal uptake on native valves was also included as a Major Criteria by the ISCVID Working Group [38, 41]. The concern of differentiating between post-operative inflammation from infection within the first three months following implantation of a prosthetic valve is being progressively overcome[42]. Consequently, the ISCVID Working Group includes [18F]FDG PET/CT findings during this period as a Minor Criterion until more data on the routine use of early PET/CT scans becomes available.

New major criterion – surgical evidence

The intraoperative inspection of cardiac pathology by cardiovascular surgeons is invaluable in a case of suspected IE, particularly if further pathologic or microbiologic confirmation is not available. As a result, the ISCVID Working Group has added intraoperative evidence of IE (e.g., vegetations, abscess, valvular destruction, dehiscence or loosening of prosthetic valve, or other direct evidence of IE) as a new Major Criterion in the 2023 Duke-ISCVID IE Criteria when other definitive Criteria (e.g., cardiac imaging, histology, or microbiology) IE are unavailable (Table 2).

New minor clinical criteria

Clinical features added to the list of possible Minor Criteria by the ISCVID Working Group as predisposing conditions included additional types of cardiac prosthetic material (e.g., transcatheter valve implant/ repair and endovascular leads of CIEDs), an updated list of congenital heart conditions [43, 44] and a prior diagnosis of IE[45]. The ISCVID Working group recognized additional vascular phenomenon, including cerebral abscess and splenic abscess. Last, the ISCVID Working group developed a practical definition of immune complex mediated glomerulonephritis within the immunologic phenomena category.

Rejected IE

The Working group updated two of the 3 possible means by which the diagnosis of IE could be rejected (Table 1). Rejection criteria A, "Firm alternate diagnosis explaining signs/symptoms" was clarified to consist of either microbiologic or non-microbiologic alternate diagnoses. In order to reject IE due to a firm alternate microbiologic diagnosis, all of the following must apply: a) identifiable source for bloodstream infection with a nontypical IE pathogen; b) rapid resolution of bloodstream infection; and c) absence of evidence for IE on cardiac imaging. IE could also be rejected with a firm alternate non-microbiologic diagnosis (e.g., marantic endocarditis) and no microbiologic evidence for IE. Rejection criteria B was clarified to read "Lack of recurrence despite antibiotic therapy for less than 4 days."

Limitations

The 2023 Duke-ISCVID criteria contain limitations that should be addressed in future versions as more data become available. The requirement for three positive blood cultures for non-typical pathogens to meet Major Microbiologic Criteria can be problematic, as three blood cultures are typically only drawn when there is a suspicion of IE. Simultaneously altering multiple components of a diagnostic criteria that have been unchanged for over two decades could also become problematic. Some of the newly added diagnostic criteria, such as metagenomic sequencing or advanced cardiac imaging, are likely to be unavailable in hospitals in rural setting or low income countries.

Validation studies

When the Duke Endocarditis Service developed new criteria for the diagnosis of IE in 1994[1] , the intent was to improve sensitivity while maintaining specificity, compared with the von Reyn-Beth Israel Criteria[46]. When initially published, the Duke Criteria had not been externally validated. However, within a few years several external validation studies confirmed that the Duke Criteria had an improved sensitivity[47] and specificity[48] for the diagnosis of IE. Likewise, the Modified Duke Criteria, published in 2000, were only validated after publication. Thus, the 2023 Duke-ISCVID IE criteria proposed here should also undergo external validation studies. Databases collected after PET-scans became widely available and were routinely used to help diagnose IE should be used for this purpose. Sensitivity should be tested in patients with pathologically confirmed IE. Specificity should be tested in patients with high clinical suspicion of IE for whom the diagnosis of IE is firmly ruled out, either through negative valve histopathology at valve surgery or autopsy, or in bacteremic patients with negative imaging who are cured with only short course of antibiotics. Finally, these guidelines are intended to supplement but never replace clinical judgment in managing patients with suspected IE.

CONCLUSION

Since the original Duke Criteria were published almost three decades ago, a steady stream of diagnostic advances have been introduced and utilized to manage patients with IE. As a result, updating the Modified Duke Criteria after over two decades is essential to ensure that they remain relevant. In this report a multidisciplinary, multinational working group of subject matter experts proposes changes to IE diagnostic criteria that reflect advances in practice (**Table 3**).

The primary goal of the 2023 Duke-ISCVID IE diagnostic criteria is to catalyze research in IE by providing an internationally reproducible definition of the syndrome. ISCVID Council proposes that diagnostic criteria for IE should be updated periodically, with validation of their sensitivity and specificity, to reflect diagnostic advances. The ISCVID will be responsible for periodically updating these recommendations on its website as a living document (http://iscvid.org/). ISCVID

has created an ad hoc committee to carry it out, composed by the first and last author of this manuscript plus five additional members (a cardiologist, an imaging expert, a microbiologist, an infectious disease specialist, and a cardiac surgeon) who will annually review the news that appears in the peer-reviewed literature. The changes suggested by this committee will be discussed and approved by the ISCVID council members and published in the living document in the ISCVID website, highlighting in yellow the new additions. Every four years and depending on existing developments, the updated recommendations could be submitted to a peer-reviewed journal for publication. This "Living Document" approach is currently undertaken with treatment guidelines for HIV[49] and hepatitis C[50]. The ISCVID is actively working to advance the field of IE research and treatment by proposing these updated diagnostic criteria, establishing a basis for future modifications in IE diagnostic criteria.

NOTES

ACKNOWLEDGEMENTS: Work contained in this manuscript was made possible by grant 1R01-AI165671 (VGF) from the National Institutes of Health. JMM received a personal 80:20 research grant from Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, during 2017–23.

DISCLOSURES: **ASB** reports research grants from NIAID; Akagera Medicines; ContraFect Corporation and Riovant Pharmaceuticals; payment for expert testimony from Hanson, Skemp & Sleik, La Crosse, Wisconsin.

AWK: Research grant: Karius; Honoraria: Pfizer, Data Safety Monitoring Board; Personal Fees Consulting: Debio Pharma; Royalties: Up To Date: Common Stock: Pfizer, Abbvie, Johnson and Johnson; participation in Winter Course in Infectious Diseases.

CAM reports personal fees from Edwards Lifesciences (Clinical Events Committee) and Cytosorbents Corp.

EDM reports research funding for his Institution from MSD, Pfizer, Angelini, Infectopharm, Advanz pharma, Menarini, and Shionogi; and personal consulting fees from Genentech, Roche, Angelini, Trx, Medtronic, and Abbvie; fees to participate in advisory boards for Pfizer; role as Secretary of the International Society for Cardiovascular Infectious Diseases; speaker's honoraria from Pfizer, Shionogi, Advanz pharma; as well as personal fees from Bio-Merieux, Sanofi-Aventis, and DiaSorin.

EF reports independent research grants for valvular heart diseases from the Novo Nordisk Foundation.

FV reports research funding outside the scope of the present study by bioMérieux; two patents pending in antimicrobial resistance detection (PCT/EP2022/069857 July 2022; FR 2200268 Jan 2022); and shares in Weezion.

JMM reported consulting honoraria and/or research grants from Angelini, Contrafect, Cubist, Genentech, Gilead Sciences, Jansen, Lysovant, Medtronic, MSD, Novartis, Pfizer, and ViiV Healthcare, outside the submitted work.

VGF reports personal consulting fees from Novartis, Debiopharm, Genentech, Achaogen, Affinium, Medicines Co., MedImmune, Bayer, Basilea, Affinergy, Janssen, Contrafect, Regeneron, Destiny, Amphliphi Biosciences, Integrated Biotherapeutics; C3J, Armata, Valanbio; Akagera, Aridis, Roche, and Pfizer (paid to author); grants from NIH, MedImmune, Allergan, Pfizer, Advanced Liquid Logics, Theravance, Novartis, Merck; Medical Biosurfaces; Locus; Affinergy; Contrafect; Karius; Genentech, Regeneron, Deep Blue, Basilea, Janssen; Royalties from UpToDate, stock options from Valanbio and ArcBio; Honoraria from Infectious Diseases Society of America for his service as Associate Editor of *Clinical Infectious Diseases*; travel support from Contrafect to 2019 ECCMID; and a sepsis diagnostics patent pending.

MMH reports payment from Up To Date (paid to author) and participation on an Advisory Board for Takeda Island.

SDP reports event payment from Agilent and Cariomyopathy UK (paid to institution); role as councilor for Association for European Cardiovascular Pathology (unpaid).

LD reports payment for expert testimony in IVC filter litigation for Cordis, Braun, and Bard; and stock or stock options from Asensus Surgical (Transenterix).

DTD reports payment for expert testimony for two worker's compensation claims and one medico-legal claim (paid to author); membership on the ISCVID Council; stock in Becton Dickinson Company, Moderna, Merck, and Illumina; and stock options in Magnolia Medical, Inc.

AD reports research grant support from the Lundbeck Foundation (unrelated to this work).

XD reports grants or contracts with Pfizer and Sanofi Pasteur (paid to institution).

All other authors: No relevant disclosures.

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Table 1. Definitions of Infective Endocarditis According to the 2023 Duke-ISCVID IE Criteria, with Proposed Changes in Bold Type.

I. DEFINITE ENDOCARDITIS

A. Pathologic Criteria

(1) 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

(2) 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

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‡

or

B. Lack of recurrence despite antibiotic therapy for less than 4 days.

or

C. No pathologic or macroscopic evidence of IE at surgery or autopsy, with antibiotic therapy for less than 4 days

or

D. Does not meet criteria for possible IE, as above

* by culture, staining, immunologic techniques, PCR or other nucleic acid based tests including amplicon (16S, 18S, internal transcribed spacers) sequencing, metagenomic (shotgun) sequencing, or in situ hybridization on fresh or paraffin-fixed tissue. Molecular techniques and tissue staining (Gram stain, Periodic acid Schiff with diastase [PASD], Grocott, or silver stains such as Warthin-Starry, Steiner, or Dieterle) should be interpreted cautiously, particularly in patients with a prior episode of IE since such tests can remain positive for extended periods following successful treatment. Antibiotic therapy prior to tissue procurement may also significantly alter microorganism morphology and staining characteristics. Test specificity is influenced by several factors and false positives can occur. Test interpretation should always be in the context of clinical and histological evidence of active endocarditis. A single finding of a skin bacterium by PCR on a valve or wire without additional clinical or microbiological supporting evidence should be regarded as Minor Criterion and not Definite IE[51]

†Active endocarditis - Vegetations, leaflet destruction, or adjacent tissue of native or prosthetic valves showing variable degrees of inflammatory cell infiltrates and healing. Many specimens demonstrate mixed features.

¶Acute endocarditis – Vegetations or cardiac/aortic tissue lesions of native or prosthetic valves showing active inflammation without significant healing or organizational change.

§Subacute/ Chronic endocarditis – Vegetations or cardiac/aortic tissue lesions of native or prosthetic valves demonstrating evidence of healing or attempted healing: maturing granulation tissue and fibrosis showing variable mononuclear cell infiltration and/or calcification. Calcification can occur rapidly in injured tissue and vegetations, or be part of the underlying valvular disease that was the original nidus for IE.

‡ "Firm alternate diagnosis explaining IE signs and symptoms consists of either microbiologic or non-microbiologic causes. Firm alternate microbiologic diagnosis includes a) identifiable source for bloodstream infection with a nontypical IE pathogen; b) rapid resolution of bloodstream infection; and c) absence of evidence for IE on cardiac imaging. Firm alternate non-microbiologic diagnosis includes a) presence of non-IE cause for cardiac imaging findings (e.g., marantic or nonbacterial thrombotic endocarditis); and b) absence of microbiologic evidence for IE.

Table 2. Definitions of Terms Used in the 2023 Duke-ISCVID IE Criteria for the Diagnosis of Infective Endocarditis, with Proposed Changes in Bold Type.

Major Criteria

A. Microbiologic Major Criteria

(1) 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**[¶]

(2) 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[24] [††††], 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 [24, 25] [††††]

B. Imaging Major Criteria

(1) 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[52]

(2) [18F]FDG PET/CT Imaging

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. Surgical Major Criteria

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

II. MINOR CRITERIA

A. 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

B. Fever

Documented temperature greater than 38.0 degrees Centigrade (100.4 degrees Fahrenheit)

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's nodes, Roth's spots, or immune complex-mediated glomerulonephritis‡‡‡

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[****]
2) **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[51]**

F. 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

G. 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 venipuncture sites are strongly recommended whenever possible for evaluating suspected IE.

† Amplicon (16S or 18S) or metagenomic (shotgun) sequencing

§ 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 (or perigraft) soft tissue lesion with variable degree of evolution to an organized collection

†† 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 [53-55]

*** performed at least 3 months after prosthetic valve surgical implantation [40]

¶¶¶ some prosthetic valves may have intrinsic non-pathological FDG uptake[42, 56]. 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[51, 57].

††† ***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 [58-60].

‡‡‡ defined as either:

1) 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

2) 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.

†††† **or equivalent titre results on other methodologies.**

§§§§ Addition of this major criterion should not be interpreted as giving license to not send appropriate samples for histopathology and microbiological studies.

Table 3. Updates to Modified Duke Criteria Proposed by 2023 Duke-ISCVID IE Criteria.

PATHOLOGIC CRITERIA	Change
Microorganism identification	Microorganisms identified in appropriate sample by PCR, amplicon or metagenomic sequencing, or *in situ* hybridization
MAJOR CLINICAL CRITERIA	Change
Microbiology	
Blood cultures	Removed requirements for timing and separate venipunctures for blood cultures.
Definition of typical organisms	Added typical pathogens: 1) *S. lugdunensis*; *E. faecalis;* all streptococci except *S. pneumoniae* and *S. pyogenes*; *Granulicatella spp.; Abiotrophia spp.; & Gemella* spp. 2) Organisms to be considered "typical" IE pathogens in the setting of intracardiac prosthetic material: coagulase negative staphylococci, *Corynebacterium striatum; C. jeikeium*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Cutibacterium acnes*, non-tuberculous mycobacteria, and *Candida* spp.
Other Microbiologic tests	Added new Major Criteria for fastidious pathogens: 1) PCR or amplicon/metagenomic sequencing identifies *C. burnetii*, *Bartonella* sp., or *T. whipplei* from blood; or 2) IFA $\geq$ 1:800 for IgG antibodies identifies *B. henselae* or *B. quintana.*
Imaging	
Echocardiography	Similar to earlier versions. Cornerstone of imaging criterion.
Cardiac Computerized Tomography	Added new Major Criterion. Findings equivalent to echocardiography.
[18F]FDG PET/CT	Added new Major Criterion. Findings for native valve, cardiac device, or prosthetic valve > 3 months after cardiac surgery are equivalent to echocardiography.
Surgical	Added new Major Criterion. Intraoperative inspection constitutes Major Criterion in absence of Major Criterion by cardiac imaging or histopathology.
MINOR CLINICAL CRITERIA	
Predisposition	Added Transcatheter valve implant/ repair, endovascular CIED, and prior diagnosis of IE.
Fever	Unchanged.
Vascular phenomena	Added splenic and cerebral abscess.

Immunologic phenomena	Added definition for immune complex mediated glomerulonephritis.
Microbiological	Added PCR or amplicon/metagenomic sequencing evidence of typical pathogen.
Imaging	Added PET/CT evidence < 3 months of cardiac surgery.
Physical examination	New auscultation of regurgitant murmur when echocardiography is unavailable.