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VIEWPOINTS

The 2023 Duke-International Society for Cardiovascular Infectious Diseases Criteria for Infective Endocarditis: Updating the Modified Duke Criteria

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(See the Editorial Commentary by Paras on pages 527–8.)

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, polymerase chain reaction, amplicon/metagenomic sequencing, in situ hybridization), imaging (positron emission computed tomography with 18F-fluorodeoxyglucose, 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 Duke-ISCVID Criteria available online as a "Living Document."

Keywords. endocarditis; Duke Criteria; PET/CT; echocardiography; ISCVID.

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

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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 here. 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 on identifying either microorganisms or histopathologic evidence of active IE in operative or postmortem 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 polymerase chain reaction (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 2 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 on a recent cohort study of more than 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 because of the high risk of IE in patients with bacteremia [14]. *Enterococcus faecalis* was added as a typical pathogen regardless of the primary source and setting of infection based on 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 on the relatively high risk of IE in patients with bacteremia because of these pathogens [16]. Non-*faecalis* enterococci were omitted as typical organisms because of 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 *Corynebacterium jeikeium* [18], *Serratia marcescens* and *Pseudomonas aeruginosa* [9], *Cutibacterium acnes* [19], nontuberculous mycobacteria (especially *Mycobacterium chimaerae*) [20], and *Candida* species.

In the 2023 Duke ISCVID Criteria, "typical" microorganisms isolated from 2 or more separate blood culture sets (each set consisting of 1 aerobic and 1 anaerobic bottle) constitute a Major Criterion. By contrast, microorganisms that occasionally or rarely cause IE must be isolated in 3 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 2 blood culture sets should be obtained. Although 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 1 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 the result of either bacteria whose growth in

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 identified[a] 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[e]

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

[a]By culture, staining, immunologic techniques, polymerase chain reaction (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, Grocott, or silver stains such as Warthin-Starry, Steiner, or Dieterle) should be interpreted cautiously, particularly in patients with a prior episode of IE because such tests can remain positive for extended periods following successful treatment. Antibiotic therapy before 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].

[b]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.

[c]Acute endocarditis—vegetations or cardiac/aortic tissue lesions of native or prosthetic valves showing active inflammation without significant healing or organizational change.

[d]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.

[e]Firm alternate diagnosis explaining IE signs and symptoms consists of either microbiologic or nonmicrobiologic causes. Firm alternate microbiologic diagnosis includes (1) identifiable source for bloodstream infection with a nontypical IE pathogen, (2) rapid resolution of bloodstream infection, and (3) absence of evidence for IE on cardiac imaging. Firm alternate nonmicrobiologic diagnosis includes (1) presence of non-IE cause for cardiac imaging findings (eg, marantic or nonbacterial thrombotic endocarditis) and (2) absence of microbiologic evidence for IE.

blood cultures is inhibited by prior antibiotics or microorganisms that are not isolated by routine culture techniques (eg, *Coxiella burnetii*, *Bartonella* species) [22]. Other pertinent causes of "initial" BCNE are microorganisms that either grow slowly in the microbiology laboratory and/or require special media for cultivation (eg, *Brucella*, Tropheryma whipplei, Legionella, fungi, *Abiotrophia, Granulicatella*) [22, 23]. In the Modified Duke Criteria, *C. burnetii* anti-phase I immunoglobulin G (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 IgG titer of ≥:800 for *Bartonella quintana* or *Bartonella 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 has been demonstrated in small cohorts with bacteremia and IE [27–29]. A major advantage of amplicon or metagenomic sequencing is rapid turnaround time, often yielding results in 24 to 48 hours after initiation of an assay; a major disadvantage is high cost.

Although the usefulness of amplicon or metagenomic sequencing in patients with BCNE needs to be further evaluated,

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 whipplei* 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,[e] 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 confirmation[n]

II. MINOR CRITERIA

A. Predisposition

– **Previous history of IE**
– Prosthetic valve[o]
– Previous valve repair[o]
– 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[q]

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

[a] *Staphylococcus aureus*; *Staphylococcus lugdunensis*; *Enterococcus faecalis*; all streptococcal species (except for *Streptococcus pneumoniae* and *Streptococcus 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 *Corynebacterium* jeikeium, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Cutibacterium acnes*, nontuberculous mycobacteria (especially *M. chimaerae*), and *Candida* spp.

[b] "Blood culture set" is defined as a simultaneously drawn pair of 1 aerobic and 1 anaerobic bottle. "Positive" blood culture set is defined as microbial growth from at least 1 of the bottles. Blood cultures from separate venipuncture sites are strongly recommended whenever possible for evaluating suspected IE.

[c] Amplicon (16S or 18S) or metagenomic (shotgun) sequencing.

[d] Or equivalent titre results on other methodologies.

[e] Oscillating intracardiac mass on valve or other cardiac tissue, **endovascular CIED** or other implanted material in the absence of an alternative anatomic explanation.

[f] Interruption of valvular endocardial tissue continuity.

[g] Elongation with saccular outpouching of valvular tissue.

[h] Perivalvular (or perigraft) soft tissue lesion with variable degree of evolution to an organized collection.

[i] Perivalvular cavity communicating with the cardiovascular lumen.

[j] Communication between 2 neighboring cardiac chambers through a perforation.

[k] For prosthetic valve endocarditis (PVE), intense, focal/multifocal, or heterogeneous FDG uptake patterns; for native valve endocarditis and cardiac device leads, any abnormal uptake pattern [53–55].

[l] Performed at least 3 months after prosthetic valve surgical implantation [40].

[m] 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 Criterion. PET/CT can be useful in detecting extracardiac foci of infection [51, 57].

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

[o] Placed either by open-heart surgical or transcatheter approach.

[p] 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].

[q] Defined as either:
(1) Unexplained presence of either acute kidney injury (AKI, defined later) or acute on chronic kidney injury (defined later) plus 2 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) <60 mL/min/1.73 m^2.
Acute or chronic kidney injury: reduction by at least 1 ordinal level of function: eg, from "moderately decreased" to "severely decreased"; or from "severely decreased" to "kidney failure."
Interpretive ranges for eGFR: normal ≥60 mL/min/1.73 m^2; moderately decreased 30–59 mL/min/1.73 m^2; severely decreased 15–29 mL/min/1.73 m^2; kidney failure <15 ml/min/1.73 m^2.

[r] Excludes single positive blood cultures or sequencing based assays for microorganisms that commonly contaminate blood cultures or rarely cause IE.

[s] Applicable only when echocardiography is unavailable. Based on expert opinion.

the ISCVID Working Group believes 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

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). Although the hallmark echocardiographic evidence of IE is a valvular vegetation, other complications involving valvular leaflets (eg, perforation, pseudoaneurysm), paravalvular structures (eg, abscess, pseudoaneurysm, fistula), or prosthetic valves (eg, valvular dehiscence) can also be indicative of IE [30]. Transthoracic echocardiography 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 (eg, perforation, paravalvular lesions, fistula, prosthetic valve dehiscence) [31]. TEE is also recommended in many patients with hematogenous spondylodiscitis because of recent studies finding IE prevalence up to 33% [32]. Despite the high sensitivity and specificity of TEE, challenging clinical scenarios exist in which 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). Although CCT's ability to detect vegetations is lower than that of echocardiography, it has a higher sensitivity for the detection of paravalvular lesions because of its improved spatial resolution [33, 34]. For example, CCT had a better sensitivity than TEE to diagnose pseudoaneurysm or abscess (78% vs 69%), whereas TEE outperformed CCT for the detection of vegetations (94% vs 64%), valvular perforation (81% vs 41%), and paravalvular

leakage (69% vs 44%) [35]. The combination of both CCT and echocardiography had superior sensitivity for the diagnosis of all valvular and paravalvular lesions compared with either modality alone [36]. As a result, the ISCVID Working Group considers these 2 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 because of 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

Positron emission CT with 18F-fluorodeoxyglucose ([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 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 on 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]) compared with 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 IE diagnostic criteria for PVE, a change that improved the diagnostic yield compared with 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 Criterion, 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 postoperative inflammation from infection within the first 3 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 become 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 (eg, vegetations, abscess, valvular destruction, dehiscence or loosening of prosthetic valve, other direct evidence of IE) as a new Major Criterion in the 2023 Duke-ISCVID IE Criteria when other definitive criteria (eg, cardiac imaging, histology, 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 (eg, transcatheter valve implant/repair, 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 2 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 nonmicrobiologic alternate diagnoses. To reject IE because of a firm alternate microbiologic diagnosis, all of the following must apply: (1) identifiable source for bloodstream infection with a nontypical IE pathogen; (2) rapid resolution of bloodstream infection; and (3) absence of evidence for IE on cardiac imaging. IE could also be rejected with a firm alternate nonmicrobiologic diagnosis (eg, 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 3 positive blood cultures for nontypical pathogens to meet Major Microbiologic Criteria can be

Table 3. Updates to Modified Duke Criteria Proposed by 2023 Duke-International Society for Cardiovascular Infectious Diseases Infective Endocarditis (IE) Criteria

CRITERIA	Change
PATHOLOGIC CRITERIA	
Microorganism identification	Microorganisms identified in appropriate sample by PCR, amplicon or metagenomic sequencing, or in situ hybridization
MAJOR CLINICAL CRITERIA	
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.; and *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*, nontuberculous mycobacteria, and *Candida* spp.
Other microbiologic tests	Added new Major Criteria for fastidious pathogens: 1) PCR or amplicon/metagenomic sequencing identifies *C. burnetii*, *Bartonella* spp., or *T. whipplei* from blood; or 2) IFA ≥1:800 for IgG antibodies identifies *B. henselae* or *B. quintana.*
Imaging	
Echocardiography	Similar to earlier versions. Cornerstone of imaging criterion.
Cardiac computed 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 mo 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 mo of cardiac surgery.
Physical examination	New auscultation of regurgitant murmur when echocardiography is unavailable.

Abbreviations: [18F] FDG PET CT, positron emission computed tomography with 18F-fluorodeoxyglucose; CIED, cardiac implantable electronic device; IFA, immunofluorescence assay; PCR, polymerase chain reaction.

problematic because 3 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 more than 2 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 a 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 3 decades ago, a steady stream of diagnostic advances has been introduced and used to manage patients with IE. As a result, updating the Modified Duke Criteria after more than 2 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. The 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 5 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 on the ISCVID website, highlighting in yellow the new additions. Every 4 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 human immunodeficiency virus [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

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