EDITORIAL

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

The modern medical literature on infective endocarditis (IE) starts, one may say, with the Gulstonian lectures given by sir William Osler at the Royal College of Physicians in 1885, published later that same year in the British Medical Journal (1). The clinical triad fever, murmur and embolic phenomena, is a sharp short clinical definition of this severe disease. Much of what followed is basically an extension of the triad:

- Fever is considered a minor criterion of IE, and the inflammation generated by the infection is also translated into inflammatory markers, be them rheumatoid factor (2), or erythrocyte sedimentation rate, ESR, and C-reactive protein, CRP (3), the latter more frequently requested as routine laboratory tests;

- Murmur, especially a new regurgitant one, is a hallmark of valvular damage, a major criterion when detected echocardigraphically (2), but other murmurs may signal underlying valve disease, and may be minor criteria as they may be predisposing lesions for IE (2). With medical progress and the use of echocardiography, valvular damage may be further characterized, with the visualization of the anatomical hallmark of IE, vegetations. Echocardiography, especially transesophageal, may reveal complications such as abscess, perforation, pseudoaneurysm and fistulae (4, 5). Further imaging techniques such as computed tomography angiography (CTA), 18- fluorodeoxyglucose positron emission computed tomography (18FDG PET CT), single photon emission computed tomography (SPECT CT), and magnetic resonance imaging (MRI) have incremented anatomical and functional evaluation of heart structures (6). But the investigation often will start with hearing a murmur on heart auscultation.

- Emboli, which may manifest as peripheral lesions such as Osler's nodes, Janeway lesions, subconjunctival hemorrhages, splinter hemorrhages, petechiae and purpura. Emboli to the central nervous system (CNS) may manifest as stroke but they may be asymptomatic in the CNS as well as in inner organs. As a matter of fact, splenic emboli occur in 20 to 35% of patients with left-sided IE, but the vast majority is asymptomatic as less than 5% eventually evolve as abscess (7). Depending on the radiological method used, abnormalities of the CNS may be detected in 10 to 85% of left-sided IE (8-11). Therefore, radiological methods are of great value in identifying emboli, such as ultrasonography (of the abdomen and pelvis), CT (chest, abdomen, brain), CTA, 18FDG PET CT, SPECT CT and MRI (7). Eventually, in 2015, the ESC consensus «officialized» the role of many of these images attributing minor or major criteria to several radiological findings (6).

However, microbiological results are crucial in the diagnosis of IE, and it was at its infancy at Osler's time (1).

Many physicians and scientists have contributed to the study of endocarditis along the decades (1, 12, 13). The Duke criteria were proposed in 1994, «for more accurate diagnosis and classification of patients with suspected endocarditis and to provide better entry criteria for epidemiologic studies and clinical trials», with a clear goal of including echocardiography, which had become a major asset for IE diagnosis (2). The diagnostic criteria followed the outline of the rheumatic fever criteria (the Jones' criteria) (14) giving different weights to clinical, microbiological and echocardiographic findings. These are shown in Table 1.

The 1994 Duke diagnostic criteria were reviewed in 2000, and called the modified Duke criteria (15). This update brought few changes, as outlined in green in Table 1 and which can be summarized as: i) the category "possible IE" should be defined as having at least 1 major criterion and 1 minor criterion or 3 minor criteria; ii) the minor criterion "echocardiogram consistent with IE but not meeting major criterion" should be eliminated, given the widespread use of transesophageal echocardiography; iii) bacteremia due to S. aureus should be considered a major criterion, regardless of whether the infection is nosocomially acquired or whether a removable source of infection is present; iv) positive Q-fever serology should be changed to a major criterion.

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It took the group of experts on endocarditis to publish an opinion paper following this over 2 decades later (16), and it is this document this editorial is about. This time the criteria take on the name DUKE-ISCVID, with the recognition of the International Society for Cardiovascular Infectious Diseases members' role in formulating them.

The summary of the proposals of the updated Duke-ISCVID criteria (2023) are highlighted in blue on Tables 1 and 2.

Table 1. The Duke criteria and further modifications (in green the 2000 modifications, in blue the 2023 Duke-ISCVID update). Adapted from Durack et al. 1994 (2), Li et al 2000 (15) and Fowler et al. 2023 (16)

Major microbio-logical criteria	**Blood culture results:** **Typical microorganisms:** Microorganisms that commonly cause IE isolated from two or more separate blood culture sets: -*Staphylococcus aureus* and *Staphylococcus lugdunensis* -*Streptococci, including Abiotrophia* spp, *Granulicatella* sp. and *Gemella*, and excluding *Streptococcus pneumoniae e Streptococcus pyogenes* -HACEK group -*Enterococcus* faecalis,* **OR** **Persistently positive blood cultures for atypical germs:** Microorganisms that are not typical for IE – isolated from three or more separate blood culture sets Positive serology for Coxiella burnetii with phase I IgG antibodies > 1:800 on IF or C.burnetii isolated from a single blood culture Indirect immunofluorescence assay with IgM or IgG antibodies to *Bartonella henselae* or *Bartonella quintana* with IgG titer > 1:800 Positive PCR or other nucleic acid-based technique for *Coxiella burnetii, Bartonella* spp or *Tropheryma whipple*i from blood In the presence of intracardiac prosthetic material, blood cultures positive for the following microorganisms: Coagulase negative staphylococci *Corynebacterium* striatum and C. *jeikeium*, *Serratia marcescens* and *Pseudomonas aeruginosa* *Cutibacterium acnes* Non -tuberculous mycobacteria (especially *M. chimaerae*) *Candida spp*
Major criteria for endocardial involvement	**Echocardiographic findings or findings on cardiac computed tomography:** -Vegetations -Valve leaflet perforation -Valvar aneurysm -Abscess -Pseudoaneurysm -Intracardiac fistula OR New valvular regurgitation OR New partial dehiscence of a prosthetic valve OR **^{18}FDG PET/CT imaging with 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 more than 3 months following valve surgery** OR **Surgical findings** Evidence of infective endocarditis documented by direct visual inspection during cardiac surgery

Table 1. The Duke criteria and further modifications (in green the 2000 modifications, in blue the 2023 Duke-ISCVID update). Adapted from Durack et al 1994 (2), Li et al 2000 (15) and Fowler et al 2023 (16). (Continued from page 16)

Minor criteria	A.Predisposition: -Previous history of infective endocarditis -Prosthetic valve -Previous valve repair -Congenital heart disease -More than mild regurgitation or stenosis of any etiology -Endovascular cardiac implantable electronic devices -Hypertrophic obstructive cardiomyopathy -Injection drug use B.Documented temperature greater than 38oC (100.4o F) C.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 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.

*" Community-acquired enterococci, in the absence of a primary focus" are the terms used in the modified Duke criteria (15).
HACEK= *Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella,* and *Kingell*

We will now briefly discuss in what way the new proposals may make a difference for everyday practice.

For the good :

Predisposition: Including as minor criteria predispositions which are well recognized in IE, such as a previous episode and a previous valve repair, and others which are frequently more seen in modern practice, such as intracardiac devices and percutaneously implanted valves.

Physical examination: Valuing physical examination in times when medics less and less value it: *« New valvular regurgitation identified on auscultation, if echocardiography is not available, is considered a minor criterion.»*

Microbiology: less burocratic blood culture collection, since no time schedule is defined for blood taking as long as at least 2 separate venipunctures are done at different times, and not necessarily at different sites.

The inclusion of *Staphylococcus lugdunensis* and *Abiotrophia, Granulicatella,* and *Gemella* (these last three previously referred to as nutritionally variant streptococci) as typical organisms. Furthermore, it is sensible to specify that *Enterococcus faecalis* (and no other species) be considered typical (since it is rare that other species of enterococci are associated with IE); however, the question of how we should weigh whether the enterococcal infection is acquired in the community or in healthcare-associated scenarios is not discussed, nor how an associated focus of enterococcal infection should be dealt with (colonoscopy: should it be obtained systematically?).

The inclusion of *Bartonella henselae* or *B.quintana* serology as major criterion when presenting high titers, given the role of this pathogen in BCNE (17-19) .

Radiology: Validating radiological findings of embolic lesions and those proposed by the 2015 ESC document as minor and major criteria (6). Moreover, regarding 18FDG PET CT scan in recently operated patients, suggesting that if done less than 3 months after surgery, abnormal findings suggestive of IE be considered minor criteria. This is in tune with progressively better interpretation of PET CT scans, where the pattern of heterogeneous uptake is highly suggestive of infection, irrespective of the date of surgery (20).

Table 2. Definite, possible and rejected infective endocarditis according to the Duke criteria and further modifications (in green the 2000 modifications, in blue the 2023 Duke-ISCVID update). Adapted from Durack et al 1994(2), Li et al 2000(15) and Fowler et al 2023(16).

DEFINITE INFECTIVE ENDOCARDITIS
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 2.Active endocarditis identified in or on a vegetation; from cardiac tissue; from an explanted prosthetic valve or sewing ring; from an ascending aortic graft (with concomitant evidence of valve involvement); from a CIED; or from an embolus
Clinical Criteria **2 Major Criteria** **or** **1 Major Criterion and 3 Minor Criteria** **or** **5 Minor Criteria**
POSSIBLE ENDOCARDITIS 1 Major Criterion and 1 Minor Criterion **OR** 3 minor criteria
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

Surgery : Often, in clinical practice, the physicians in charge of patients with IE take into account the description of findings reported in the surgical notes on those patients who have had valve surgery for IE. It has been our practice for many years to judge the duration of antibiotic therapy post-surgery guided by the macroscopic findings at surgery and by the histopathology of valves (21, 22). The Duke-ISCVID update has considered the surgical findings as major criteria for endocardial involvement in IE when documented by visual inspection during heart surgery. An important note of caution is given: appropriate samples for histopathology and microbiological studies must still be sent!

For the not so good: there are troublesome microorganisms included in the list of major criteria when the patient has prosthetic material, which will very probably lead to overtreatment, particularly for the patient who is still in the intensive care unit (ICU) or medical ward and who has had a recent cardiac procedure (the scenario of early prosthetic valve IE). Furthermore, patients with valve prosthesis who are hospitalized for whatever reason and end up with a fever may have bacteremia or fungemia from other sources, with a low likelihood of IE. With this categorization, nearly all patients will have possible IE, as they have the prosthesis (a predisposition, which is a minor criterion)(2), plus fever (if they were cultured, it is very likely they had fever or elevated C-reactive protein (CRP) , the latter St Thomas minor criteria) (3) and the positive blood culture as a major criterion. Adding up, this makes 1 major and 1 or 2 minor criteria, and therefore, possible IE (2). This situation will trigger clinicians to start intravenous antibiotics. Removing the culprit intravenous line followed by a rapid improvement in the patients clinical status may be comforting but insufficient evidence against IE, especially if the weight of a major criterion is given to Gram negatives, coagulase negative staphylococci and candida.

It is well known that coagulase negative staphylococci occur very frequently in bloodstream infections (BSI), as do Gram negatives and *Candida* spp. In a recent study on BSI conducted retrospectively of patients in 41 acute-care hospitals in the Becton Dickinson Insights Research and Database (the distribution of hospitals in this database is similar to the hospital distribution in the United States as a whole), the included patients were adults, and had been admitted between 2015 and 2019 (23). The microorganisms isolated from BSI in 403 patients with a central line present on the

day of the event or before were, in order of greater frequency, *Candida* spp, in 26%, coagulase negative staphylococci, in 20.6%, Enterobacteriacae in 16.8% , enterococci in 15.9% and *S.aureus* in 12.4% (23). Another large study, EUROBACT-2, involved 2600 ICU patients from 333 ICUs in 52 countries (mostly European) in 2019 (24). Sources of infection were predominantly pneumonia in 26.7%, intravascular catheters in 26.4%, and abdomen in 15.1%. Overall, there were 2927 bacterial and fungal isolates, most commonly Gram-negatives, in 59%, with a predominance of *Klebsiella* spp., *Acinetobacter* spp., Escherichia coli and Pseudomonas spp. (247/1726; 14.3%). Gram-positive pathogens accounted for 31.1% of isolates and were mainly *Enterococcus* spp. (34.5%) and coagulase-negative staphylococci (273/910, 30%) (24).

Serratia marcescens and *Pseudomonas aeruginosa,* although not rare in BSI, are uncommon causes of IE. Non-HACEK Gram negative IE represents approximately 2% to 6% of all cases of IE, and has been associated with healthcare, including urinary tract procedures, intravenous lines and early prosthetic valve IE (25). However, a recent study across 13 hospitals in Pennsylvania, USA (26), identified 123 cases through electronic records between April 2010 and December 2021, and found a high proportion of intravenous drug users (52%) and of *S.marcescens,* similar to older series from the 80's and 90's in which drug users prevailed. Other series of non-HACEK Gram negative IE did not show a predominance of *S.marcescens* nor of *P.aeruginosa; E.coli* and *K.pneumoniae* figure more frequently or just as frequently as these do (25, 27-34). Although it is positive to stimulate clinicians to think of IE and pursue the diagnosis with TOE or PET CT, this will add a great deal of cost and invasive procedures. The key point is how often does bacteremia with these germs actually result in IE in patients with prosthetic material? What are the evidences in the literature? One must remember that a "typical" microorganism is not necessarily a frequent cause of IE, but its identification in an episode of bacteremia is strongly associated with IE (16), so, how often are coagulase negative staphylococci, the mentioned Gram negatives and Candida associated with IE to have the status of major criterion?

In summary, my viewpoint it that, in the setting of possibly associated line infections or other bacteremia in ICUs or in the wards one must be cautious of labeling these microorganisms major criterion. Obviously this is a very different scenario from patients who have prosthetic devices presenting a community-acquired infectious syndrome and their blood cultures turn up positive with these germs, especially if blood cultures are persistently positive.

Finally, another downside of the 2023 update is specifying that, regarding vascular phenomena, the radiological evidence be of cerebral abscess and splenic abscess (16). In fact, splenic emboli to the CNS and spleen are very frequent in left-sided IE, but abscesses in both areas are rare (7, 35).

What the update's proposals bring for the future

There have been some developments (16S/18S rRNA gene polymerase chain reaction (PCR), new sequencing techniques, and fluorescence in situ hybridization) in the microbiological diagnosis of IE and the update of the modified Duke criteria includes them in the following manner:

"Positive PCR or other nucleic acid-based technique (amplicon 16S or 18S, or metagenomic or shotgun sequencing) identifying *Coxiella burnetii, Bartonella* or *Tropheryma whipplei* should be considered major criteria; if other microorganisms are identified by these same methods; they should be considered minor."

It must be said that these methods are at the present moment restricted to research institutes or to some private hospital services, and the vast majority of clinicians will not be able to request in situ hybridation, metagenomic or even PCR tests for their patients. It remains to be seen how these possibilities come gradually into practice.

Furthermore, the availability and interpretation of the new radiological methods are still poor, as recently reviewed by Besson et al. (36), and we hope these exams become more widely available and standardized methodologically.

To conclude, the authors of the updated modified Duke criteria recognize that the proposed 2023 Duke-ISCVID IE criteria should undergo external validation studies (16), as the previous versions did. We are keen to see publications on the issue coming out in the next months and years. And importantly, we thank the timely review these experts have published.

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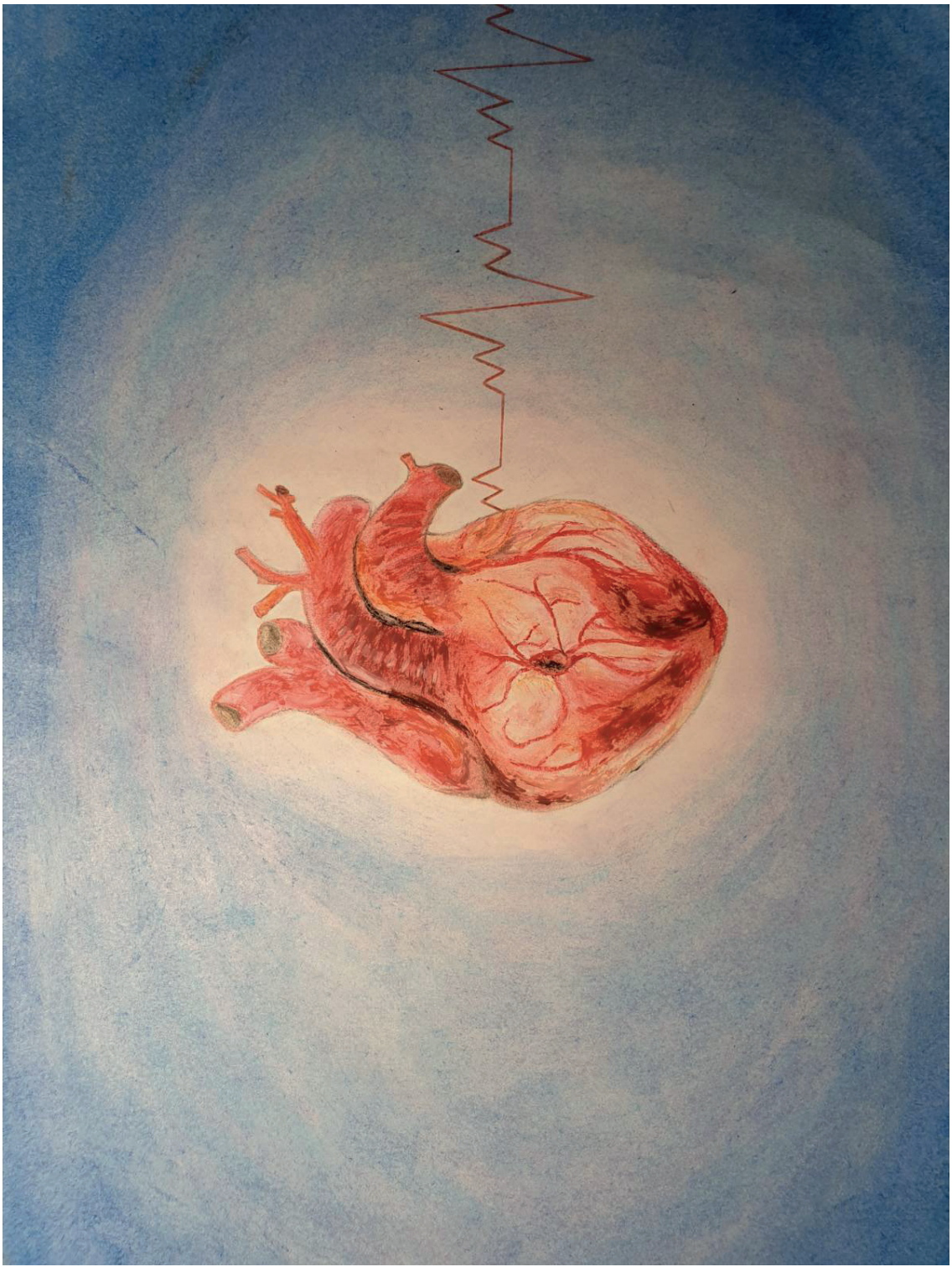

«Heart»

The human heart is an organ that pumps blood throughout the body via the circulatory system, supplying oxygen and nutrients to the tissues and removing carbon dioxide and other wastes.

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