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BRIEF REPORT

Lower Specificity of the European Society of Cardiology 2023 Diagnostic Criteria for Infective Endocarditis When Spondylodiscitis Is Regarded as a Vascular Phenomenon

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The ESC diagnostic criteria for infective endocarditis (IE) added spondylodiscitis as a minor criterion. This resulted in that 11 of 1807 patients with *Staphylococcus aureus*, streptococcal, or *Enterococcus faecalis* bacteremia, were reclassified from possible to definite IE, of whom only two were treated as IE.

Keywords. infective endocarditis; spondylodiscitis; bacteremia; *Staphylococcus aureus*; diagnostic criteria.

Infective endocarditis (IE) and spondylodiscitis (SD) are 2 types of infection that result from a hematogenous spread of bacteria to the heart valves or the spine, respectively. These conditions sometimes occur simultaneously, but only a minority of patients with IE have SD [1] and only a minority of patients with SD have IE [2]. The typical feature of IE is the formation of vegetations on the heart valves that can detach and lead to embolization in distant organs. When IE and SD is present simultaneously, either condition can occur first. SD is therefore not necessarily a result of embolization from the IE vegetation. The European Society for Cardiology (ESC) recently published diagnostic criteria for IE presented in the ESC2023 guidelines for the management of endocarditis. These criteria state that SD should be regarded as a vascular phenomenon, that is, an embolization, and thus constitute a minor criterion for the diagnosis of IE [3]. Previous versions of the Duke criteria as well as the Duke–International Society for Cardiovascular Infectious Diseases (ISCVID) criteria, also presented in 2023, do not regard SD as a vascular phenomenon [4, 5], and the ESC2023 criteria provide no explanation for addition of SD as a minor vascular criterion.

We investigated how the addition of SD as a minor vascular criterion affects the performance of the ESC2023 diagnostic criteria in relation to the Duke–ISCVID criteria in a cohort of patients with bacteremia with typical IE-causing pathogens. These cohorts have previously been used to develop risk stratification systems for IE [6–8]. In total, 1807 episodes of bacteremia were reanalyzed: 1098 with *Staphylococcus aureus* [8], 312 with non–beta-hemolytic streptococci (generation cohort) [7], and 397 with *Enterococcus faecalis* (generation cohort) [6]. The original reports used the ESC2015 definition of IE, which led to 132 episodes (7.3% of episodes) being classified as definite IE. Sixty-eight IE episodes were identified in *S. aureus* bacteremia (6.2%), 20 in streptococcal bacteremia (6.4%), and 44 in *E. faecalis* bacteremia (11%). Using the Duke–ISCVID criteria, an additional 2 episodes were reclassified to definite IE, 1 of which was perceived and treated as IE [9].

In our cohort, SD was identified in 97 episodes (8.8%) of *S. aureus* bacteremia, 8 episodes (2.6%) of streptococcal bacteremia, and 9 episodes (2.3%) of *E. faecalis* bacteremia. Using the ESC2023 criteria, recognizing SD as a minor vascular criterion, a new minor criterion was identified in 87 (*S. aureus*), 7 (streptococci), and 9 (*E. faecalis*) episodes, respectively, since some patients had another vascular phenomenon. This resulted in an additional 11 episodes being reclassified from possible IE (with Duke–ISCVID) to definite IE (with ESC2023). Of the reclassified episodes, 6 were caused by *S. aureus*, 1 by streptococci, and 4 by *E. faecalis*. A description of the episodes is given in Table 1. In 9 of these 11 episodes, the patients were not perceived to have and were not treated for IE. None of the patients had findings suggestive of IE on echocardiography or other imaging modalities. None of the patients experienced a relapse within 6 months. If the decision to treat a patient as having IE was used as the reference standard, the specificity decreased by 9 episodes, corresponding to a decrease in specificity from 100% with the Duke–ISCVID criteria to 99% with the ESC2023 criteria. The sensitivity of the ESC2023 criteria was increased by 2 episodes in our cohorts, using the decision to treat as IE as the standard, corresponding to an increase in sensitivity from 80% with the Duke–ISCVID to 81% with ESC2023.

SD is most often seen without IE. This demonstrates that SD is not commonly caused by embolization from an IE. The hematogenous spread of bacteria to the spine should therefore not be regarded as a vascular phenomenon as suggested in the ESC2023 criteria. Moreover, regarding SD as a minor criterion,

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Table 1. Features of Patients Reclassified to Definite Infective Endocarditis (IE) Using the European Society of Cardiology 2023 Criteria for Diagnosis of IE

Age, Sex	Bacteria	Treated as Infective Endocarditis	Number of Positive Blood Cultures	Echocardiography	Positron Emission Tomography–Computed Tomography	Minor Criteria	Acquisition	Comments
40, Female	*Staphylococcus aureus*	No	2	TTE-neg	ND	Fever, SD, PWID	Community	Also arthritis
51, Male	*S. aureus*	No	2	TEE-neg	ND	Fever, SD, PWID	Community	Only 6 d IV antibiotics
55, Male	*S. aureus*	No	2	TTE-neg	ND	Fever, SD, PWID and pIE	Community	…
58, Male	*S. aureus* (methicillin-resistant *S. aureus*)	No	2	TEE-neg	ND	Fever, SD, PWID	Community	…
29, Male	*S. aureus*	Yes	2	TEE-neg	ND	Fever, SD, PWID	Community	Also arthritis
50, Male	*S. aureus*	Yes	2	TEE-neg	ND	Fever, SD, PWID	Community	Arthritis and empyema
78, Female	*Streptococcus gordonii*	No	2	TTE-neg	ND	Fever, SD, NVD	Community	…
77, Male	*Enterococcus faecalis*	No	2	TEE-neg	ND	Fever, SD, NVD	Community	Only 5 d IV antibiotics
63, Male	*E. faecalis*	No	2	TEE-neg	ND	Fever, SD, PV, pIE	Community	…
80, Male	*E. faecalis*	No	3	TEE-neg	Neg	Fever, SD, PV	Nosocomial	Positron emission tomography–computed tomography-neg for IE but shows SD
74, Female	*E. faecalis*	No	2	TTE-neg	ND	Fever, SD, CIED	Community	…

Abbreviations: CIED, cardiac implantable electronic device; IE, infective endocarditis; IV, intravenous; ND, not done; neg, negative; NVD, native valve disease; pIE, previous infective endocarditis, PV, prosthetic valve; PWID, person who injects drugs; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; SD, spondylodiscitis.

at least in our bacteremia cohort, decreases specificity of the criteria with only a small increase in sensitivity. Interestingly, all 6 episodes of *S. aureus* bacteremia that were reclassified to definite IE were found in persons who inject drugs. Two of these episodes were treated as IE, whereas 4 were not. Four episodes of *E. faecalis* bacteremia were reclassified from possible to definite IE, and in proportion to the total number of episodes, reclassification was more common in *E. faecalis* than in *S. aureus* bacteremia. These 4 episodes were in persons with different types of predisposition for IE, and interestingly, none of them was treated for IE. There was no relapse in bacteremia in episodes that did not receive IE treatment. However, it should be kept in mind that a long per oral antibiotic treatment was given in all episodes, as this is the standard treatment of SD. This can possibly lead to cure of a missed IE.

In another recent study, also on bacteremia with *S. aureus*, the authors found that the addition of SD as a vascular phenomenon appeared to be unhelpful for the performance of the ESC2023 criteria [10]. Based on the above arguments, we suggest that the ESC2023 guidelines remove SD from the list of vascular phenomena/minor criteria. Moreover, we propose that the endocarditis community agree on 1 set of diagnostic criteria for IE by harmonizing the Duke–ISCVID and ESC2023 criteria. This would facilitate both care for patients with IE and research on IE.

Notes

Acknowledgments. The authors thank all of the coworkers who participated in the original data collection.

Data availability statement. Pseudonymized data will be shared upon reasonable request.

Potential conflicts of interest. The authors: No reported conflicts of interest. The authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Ethical approval statement. The appropriate ethics approvals were accounted for in the original publications [6–8].

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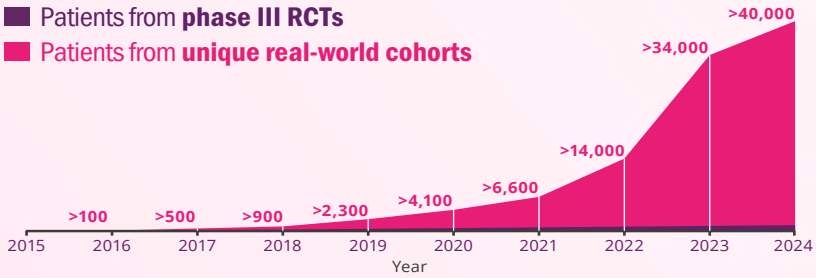

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ABBREVIATIONS

3TC, lamivudine; **CD4,** cluster of differentiation 4; **DTG,** dolutegravir; **FDA,** United States Food and Drug Administration; **FTC,** emtricitabine; **HIV,** human immunodeficiency virus; **ITT-E,** intention-to-treat exposed; **NRTI,** nucleoside/nucleotide reverse transcriptase inhibitor; **RCT,** randomised controlled trial; **RNA,** ribonucleic acid; **TAF,** tenofovir alafenamide fumarate; **TDF,** tenofovir disoproxil fumarate; **XTC,** emtricitabine.

FOOTNOTES

*Data extracted from a systematic literature review of DTG+3TC real-world evidence. Overlap between cohorts cannot be fully excluded.

**The reported rate reflects the sum-total of resistance cases calculated from GEMINI I and II (n=1/716, through 144 weeks), STAT (n=0/131, through 52 weeks), and D2ARLING (n=0/106, through 24 weeks).[5–7]

†GEMINI I and II are two identical 148-week, phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority, controlled clinical trials testing the efficacy of DTG/3TC in treatment-naïve patients. Participants with screening HIV-1 RNA ≤500,000 copies/mL were randomised 1:1 to once-daily DTG/3TC (n=716, pooled) or DTG + TDF/FTC (n=717, pooled). The primary endpoint of each GEMINI study was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[13]

‡STAT is a phase IIIb, open-label, 48-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of DTG/3TC in 131 newly diagnosed HIV-1 infected adults as a first line regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24.[6]

§D2ARLING is a randomised, open-label, phase IV study designed to assess the efficacy and safety of DTG/3TC in treatment-naïve people with HIV with no available baseline HIV-1 resistance testing. Participants were randomised in a 1:1 ratio to receive DTG/3TC (n=106) or DTG + TDF/XTC (n=108). The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48.[7] Results at week 24 of the study.

||The reported rate reflects the sum-total of resistance cases calculated from TANGO (n=0/369, through 196 weeks) and SALSA (n=0/246, through 48 weeks).[8,9]

¶TANGO is a randomised, open-label, trial testing the efficacy of DOVATO in virologically suppressed patients. Participants were randomised in a 1:1 ratio to receive DOVATO (n=369) or continue with TAF-containing regimens (n=372) for up to 200 weeks. At Week 148, 298 of those on TAF-based regimens switched to DOVATO. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL (virologic non-response) as per the FDA Snapshot category at Week 48 (adjusted for randomisation stratification factor).[8,13]

#SALSA is a phase III, randomised, open-label, non-inferiority clinical trial evaluating the efficacy and safety of switching to DTG/3TC compared with continuing current antiretroviral regimens in virologically suppressed adults with HIV. Eligible participants were randomised 1:1 to switch to once-daily DTG/3TC (n=246) or continue current antiretroviral regimens (n=247). The primary endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[9]

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