EDITORIAL

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Guidelines in review: Comparison of ESC and AHA guidance for the diagnosis and management of infective endocarditis in adults. Are the differences clinically relevant? The European perspective

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Article by Murphy et al. in this issue of the journal presents a summary and comparison of the most recent guidance on the use of imaging in the evaluation and management of infective endocarditis (IE) provided by the American Heart Association (AHA) IE writing committee and the Task Force for the management of IE of the European Society of Cardiology (ESC).[1–3] This commentary aims at discussing main differences between the recommendations of the U.S. and European guidelines as they relate to the use of imaging.

Diagnosis of IE is often challenging particularly at the early stage. It may present with very different clinical patterns depending on organs involved, the underlying cardiac disease, the micro-organisms involved, the presence or absence of complications, and the patient's characteristics. The systematic diagnosis of IE is based on the Duke classification[4,5] that stratifies patients with suspected IE into three categories: definite, possible, and rejected IE. The Duke classification is mainly based on the results of blood cultures and either transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE), because positive blood culture and echocardiography are defined as the two major criteria for IE. Both U.S. and European recommendations acknowledge that although the Duke classification has been extensively validated, it has limitations in clinical practice and must not replace clinical judgement.[2,3,6,7] In particular, diagnosis of IE is difficult in patients with a prosthetic valve or an intracardiac device.[6,7] Early and accurate diagnosis of endocarditis is crucial, because delay in adequate treatment impairs outcome.[2,3]

Echocardiography is the main diagnostic tool in endocarditis and is recommended as the first-line imaging modality in suspected IE.[2,3] As highlighted in the review by Murphy et al., TEE is needed in most patients with high clinical suspicion of endocarditis and in the presence of initially positive TTE.[1–3] The European guideline also specifically recommend TEE always in the presence of suspected prosthetic valve endocarditis (PVE) due to its better sensitivity and specificity in this setting compared with TTE.[2] The echocardiographic findings of IE include vegetation, perivalvular abscess, perivalvular pseudoaneurysm or intracardiac fistula, valvular perforation or valvular aneurysm, and a new dehiscence of a prosthetic valve.[2,3,6] Both U.S. and European recommendations acknowledge that although echocardiography plays a major role in the diagnosis of IE and gives a definite diagnosis of IE in majority of patients, atypical or doubtful results are not rare, particularly at the early stage of the disease, and in patients with suspected prosthetic valve endocarditis (PVE) or intracardiac device infection.[2,3] Thus, the Duke criteria have a lower sensitivity for the diagnosis of PVE, when compared with native valve IE.[6,7]

Besides echocardiography, contrast-enhanced computed tomography (CT), magnetic resonance imaging

(MRI), radiolabeled white blood cell (WBC) single-photon emission computed tomography (SPECT)/CT, and [18]F- fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT are evolving as important supplementary methods for patients with suspected IE and diagnostic difficulties, particularly in patients with suspected PVE.[8] Multimodality imaging may improve identification of endocardial involvement and extra cardiac complications of IE.

The value of cardiac CT has been acknowledged in both European and AHA/ACC guidelines,[2,9] but a recent AHA scientific statement on IE considered that more studies were needed to define the usefulness of nuclear imaging in IE.[3] Conversely, the ESC considered that the published data are sufficiently strong and convincing to propose new criteria (the 2015 ESC Modified Diagnostic criteria).[2] The Task Force proposed the addition of three further points in the diagnostic criteria of IE [2]: (1) The identification of paravalvular lesions by cardiac CT should be considered a major criterion; (2) In suspected PVE, abnormal activity around the site of implantation detected by ^{18}F-FDG PET/CT (only if the prosthesis was implanted for > 3 months) or WBC SPECT/CT should be considered as a major criterion; (3) The identification of recent embolic events or infectious aneurisms by imaging only (silent events) should be considered a minor criterion.

The use of multimodality imaging in IE has been addressed in detail in recent recommendations by the European Association of Nuclear Medicine.[8] The article described the technical and practical aspects of these techniques as well as reviewed the literature regarding diagnostic accuracy, advantages, limitations, and pitfalls. Several reports have shown promising results for ^{18}F-FDG PET/CT and WBC SPECT/CT imaging in IE.[8,10] When ^{18}F-FDG PET/CT is used to diagnose cardiac infection, patient preparation is very important in order to suppress physiological tracer uptake in the myocardium. These measures include high-fat low carbohydrate diet, prolonged fasting, and heparin injection prior to the scan.[8] A meta-analysis of published studies with adequate cardiac preparation including 407 patients found that the overall pooled sensitivity of ^{18}F-FDG PET/CT in patients with suspected IE is 81%, increasing to 85% when only PVE is considered. The overall pooled specificity was 90%, and 81% when only PVE was considered.[10] Notably, studies have included mainly patients with suspected PVE.[10] The same meta-analysis found that the diagnostic performance of WBC SPECT/CT was even better than that of ^{18}F-FDG PET/CT (sensitivity 86%, specificity 97%).[10] However, disadvantages of WBC SPECT/CT include the need for manipulation of blood products for labeling and a more time-consuming protocol.[8,10] Additional benefit of

nuclear imaging is that extracardiac complications, such as septic emboli and metastatic infection, are commonly detected by ^{18}F-FDG PET/CT or WBC SPECT/CT that can contribute to the diagnosis of IE and have therapeutic implications.[8,10] In one study, extracardiac findings were seen in 60% of patients, and in 15% these lesions were previously unknown and considered of clinical relevance.[11]

Advanced imaging tests should not be seen as a replacement for echocardiography in patients with suspected IE, but rather as an additional tool for patients in whom the diagnosis is complicated or uncertain. The European guideline suggests using these modalities when diagnosis is ''possible'' (or ''rejected'') according to the Duke criteria, but with a persisting high level of clinical suspicion.[2] In such cases, echocardiography and blood cultures should be repeated and multimodality imaging should be used, either for diagnosis of cardiac involvement in suspected PVE (cardiac CT, ^{18}F-FDG PET/CT or WBC SPECT/CT) or for imaging embolic events (cerebral MRI, whole-body CT and/or nuclear imaging).[2] The main added value of these techniques relies in the sensitivity of the modified Duke criteria that can be improved when initial TTE or TEE are negative or doubtful.[12,13] In one prospective study of 72 patients with suspected PVE, adding abnormal ^{18}F-FDG uptake around the prosthetic valve as a new major criterion increased the sensitivity of the Duke criteria at admission from 70% to 97% without significant impairment of specificity (50% vs. 40%).[12] Another study demonstrated in prospective cohort of 92 patients with suspected PVE that adding ^{18}F-FDG PET/CT as a major criterion to the modified Duke criteria at admission reduced the number of ''possible'' IE diagnoses by more than half.[13] A recent study reported that application of multimodality imaging was feasible in clinical practice and that both CT and nuclear imaging provided relevant complementary information in those patients in whom their application is suggested by the diagnostic flow charts, particularly in patients with intracardiac prosthetic material.[14] Thus, studies indicate that multimodality cardiac imaging may significantly improve early diagnosis of IE.

The cautious approach adopted by the American guidance is based on the limited data available till date on the diagnostic benefit of nuclear imaging. Also, the European guidelines also acknowledge several conditions in which caution must be exercised in the interpretation of ^{18}F-FDG PET results and that interpretation criteria need further refinement.[2,8,15] In patients who have undergone cardiac surgery, a postoperative inflammatory response may result in nonspecific tracer uptake particularly early after surgery.[8] The European guideline recommends the use of [18]F-

FDG PET after > 3 months after surgery, but more data are needed to define the period at which the risk of false-positive results is highest.[2,14] There may also be ^{18}F-FDG uptake associated with other cardiac structures and pathologic processes than IE, such as lipomatous inter-atrial septum, thrombi, atherosclerotic plaques, vasculitis, and tumors.[8] In patients with native valve endocarditis, the diagnostic value of ^{18}F-FDG PET/CT appears to be lower.[10] Only a small number of patients with suspected native valve IE have been included in the studies and the results suggest lower sensitivity than in PVE.[16,17] Antimicrobial treatment may also reduce tracer uptake. For these reasons, patient selection, patient preparation, imaging protocols, and image reading requires expertise and the results of the scan need to be interpreted in the clinical context.

The importance of a multidisciplinary approach for successful treatment of patients with complicated IE is highlighted in both the U.S. and European guidance.[2,3] Treatment decisions should be determined by a multi-specialty team (''The Endocarditis Team'') with expertise in cardiology, cardiothoracic surgery, infectious diseases, and imaging.[2] Immediate access to diagnostic procedures, including TTE, TEE, cardiac CT, and nuclear imaging should be available in a reference center.[2] When multimodality imaging is part of the guidelines, an imaging specialist with a high level of expertise needs to participate in the multidisciplinary endocarditis team who is responsible for interpretation of findings.

In summary, the most recent ESC and AHA guidance on the management of IE proposes new features concerning the use of imaging in diagnosis, including the need for collaborative approach (the ''Endocarditis team'') and the emergence of multimodality imaging techniques. The European guidelines have emphasized more new imaging modalities, including cardiac CT, of ^{18}F-FDG PET/CT and WBC SPECT/CT in the diagnostic criteria and flowchart of IE, particularly in suspected PVE. Current data indicate that multimodality imaging may contribute to early diagnosis of IE. However, the guidelines acknowledge that more data are needed on the diagnostic accuracy and the risks of false-positive and negative findings in different patient groups. Furthermore, studies should assess whether multimodality imaging results in a better prognosis for patients and is cost-effective.

Disclosures

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