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Challenges in cardiology: diagnosis of native and prosthetic valve endocarditis

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New cardiovascular imaging technologies have strongly influenced the diagnosis of bacterial endocarditis [infective endocarditis (IE)]. The clinical presentation of IE is polymorphic, which explains the difficulty of diagnosis and the delay in treatment. Symptoms such as fever, chills, loss of appetite and weight, and embolic phenomena strongly support the diagnosis of endocarditis, but are not always present, particularly in elderly or immuno-compromised patients. Moreover, subtle symptoms in patients at high risk for the development of IE, such as those with prosthetic valves or intracardiac devices, patients with congenital heart disease, and drug addicts should lead to the suspicion that a diagnosis of IE is highly probable. In this review, we will focus on the diagnosis of complex IE in native valves and prosthetic valves.

Infective endocarditis (IE) is a complex pathology that can present with different aspects depending on the organs involved, the underlying cardiac pathology, the microorganism involved, and the characteristics of the individual patient. The prognosis is often poor with high in-hospital mortality.

Diagnosis of IE is still based on the modified Duke criteria, which use a combination of microbiological and echocardiographic data (major criteria) and clinical (fever, predisposing conditions, immunological, and vascular phenomena) and more microbiological data, to stratify patients with endocarditis certain, possible, or unlikely.

The modified Duke criteria, used as a diagnostic algorithm since 2000, use a combination of microbiological and echocardiographic data (major criteria) and clinical and minor microbiological data to stratify patients with endocarditis certain, possible, improbable.[1]

Imaging, and especially echocardiography, plays a vital role in both the diagnosis and management of patients with IE. It is essential in the prognostic evaluation of the patient, in the initial evaluation of the embolic risk and therefore in subsequent therapeutic decisions, as well as having a fundamental role in the follow-up of medical and surgical therapy. Echocardiography has recently been joined by CAT, MRI, and nuclear medicine techniques, in particular PET/CT [positron emission tomography associated with computed tomography (CT)] with F-fluorodeoxyglucose (F-FDG) or with labelled leucocytes.[2]

However, it should be emphasised that among all imaging techniques, echocardiography [trans-thoracic (TTE) and trans-oesophageal (TEE)] is the widely available method capable of providing anatomical and functional data, with high sensitivity and specificity *Table 1*.

The endocardial lesion most frequently visualised on echocardiography is vegetation. The vegetation consists of a septic thrombus which is located on the low pressure surface of the valve structure and therefore on the atrial side of the atrioventricular valves and on the ventricular side of the semilunar valves. However, the diagnostic accuracy of echocardiography is not 100%. In particular, the sensitivity of the TTE in identifying vegetations is 70% on the native valve, but drops to 50% in the presence of prostheses or devices. On the other hand, the specificity of the method is 90% both on the native valve and on the valve prosthesis and/or device. Trans-oesophageal echocardiography reaches a sensitivity of 90% on a native valve and ∼85% on a prosthetic valve, while the specificity is >90%. This means that the negativity of a TEE must not exclude the disease a priori, especially if the examination is performed in the early stage of the disease when the vegetations are still too small to be detected. In the presence of a high clinical suspicion, the guidelines therefore recommend repeating the trans-oesophageal examination 7–10 days after the previous one.

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Table 1 Summary of the main echocardiographic data that identify the different anatomical-pathological conditions that characterise the diagnosis of infective endocarditis

	Anatomy	Echocardiography
Vegetation	Infected mass adhered to an endocardial structure or intracardiac protein material	Oscillating or non-oscillating intracardiac mass adherent to a valve, other endocardial structures, or cardiac intraprosthetic material
Abscess	Perivalvular cavity with necrosis and purulent material not communicating with the cardiovascular lumen	Thickened and inhomogeneous perivalvular area with an echo-dense appearance
Pseudoaneurysm	Perivalvular cavity communicating with the cardiovascular lumen	Perivalvular echo-free pulsatile space with presence of flow identified with Color Doppler
Perforation	Interruption of the continuity of the endocardial tissue	Interruption of the continuity of the endocardial tissue crossed by the Color Doppler flow
Fistula	Communication between two contiguous cavities through a perforation	Color Doppler flow through a perforation between two contiguous cavities
Valvular aneurism	Saccular expansion of valve tissue	Saccular expansion of valve tissue
Dehiscence of prosthesis	Dehiscence of a prosthesis	Paravalvular regurgitation with or without rocking motion of the prosthesis

Finally, a TEE specificity of <100% implies the possibility of false positives (tumours, thrombi, rupture of cord or fibrous strands of the valve or fibro-elastomas). This means that the test should always be interpreted in light of the clinical presentation and the likelihood of endocarditis.

Trans-oesophageal echocardiography is also mandatory in the presence of a cardiac prosthesis and/or intracardiac device, even when TTE has already confirmed the diagnosis of IE, because it provides further information on any perivalvular involvement. Furthermore, TEE must always be performed intraoperatively in all cases of IE requiring surgical treatment.[1,3-5]

Computed tomography is an additional fundamental modality for the study of abscesses/pseudoaneurysms in particular in the presence of valve prostheses with diagnostic accuracy equal if not superior to the TEE. It is especially useful in demonstrating the complications of perivalvular abscesses with possible fistulas and/or mycotic aneurysms, being less prone than TEE to prosthetic artefacts. Computed tomography also allows the evaluation of the coronary circulation in patients who cannot perform coronary angiography due to valve endocarditis and/or aortic valve prosthesis and can be advantageous in defining the degree of calcification of the valve, aortic root, and/or ascending aorta. It is also fundamental in the evaluation of embolic complications of extracardiac districts (cerebral, spinal, thoracic, and visceral) and therefore it must always be performed in patients with a diagnosis of endocarditis. Abdominal ultrasound is strongly recommended in the screening of embolic lesions and is particularly useful in critically ill patients as it can be performed at the bedside.

With the introduction of hybrid equipment for both conventional nuclear medicine [single photon emission CT (SPECT)/CT] and PET (PET/CT), nuclear and molecular imaging techniques are becoming an important additional tool for patients with suspected IE. However, the results of F-FDG PET/CT in patients who have recently undergone cardiac surgery should be interpreted with great caution, as a possible post-operative inflammatory reaction can result in a non-specific uptake of the tracer in the immediate post-operative period. Even with this limitation, F-FDG PET/CT in suspected IE on prosthetic valve (if performed in suspected endocarditis on implanted prostheses > 3 months before) increases the sensitivity of the Duke criteria from 70 to 95%.

Multimodality and 'Endocarditis Team'

For all the aspects described, two important clinical-organizational innovations have been suggested in recent years. On the one hand, the importance of a multimodal approach, on the other hand the indispensable nature, in centres with a large volume of cardiology and cardiac surgery, of a team of experts (Endocarditis Team) who, from the moment a suspected endocarditis is admitted, and subsequently in all diagnostic, clinical phases (both in pharmacological or surgical terms) collaborate in the best management of IE cases. In the team it is very important that the clinician is supported by the infectious disease specialist. The identification of the pathogen is in fact fundamental and the antibiotic therapy is strategically decisive in all the medical, surgical, and follow-up phases.

Various studies have validated the importance of a team of experts (clinician, infectious disease specialist, imaging specialist, anaesthesiologist, cardiac surgeon, neurologist, and possibly neurosurgeon) who lead to shared decisions especially in more complex cases. Among these, the treatment of IE of prostheses and devices is among the most difficult, even if the need for early surgery in patients with infected valve prostheses is increasingly gaining ground.

In particular, the role of the endocarditis team is to discuss the most fragile or extremely compromised patients, because if the indications for surgery (necessary in ~50% of IE cases) are well established by the guidelines, the surgical timing and follow-up of patients is still a matter of debate.

In fact, the surgical decision must take into consideration not only the location and extent of the infection but also the pre-operative state and the comorbidities of the patient and therefore the real feasibility of a very early surgery. The scores currently used in cardiac surgery [Euroscore II or STS (Society of Thoracic Surgery) score] are not specific and accurate for patients with IE. There is therefore a lack of tools that can help select the patients who can most benefit from surgery. For this purpose, new scores (e-risk Score and Endoval Score) have recently been validated which can perform this function and which could therefore be used in the discussions of the Endocarditis Team.

Some of the more complex and relevant questions that arise when faced with complex cases of IE.

When is cardiac surgery strongly recommended?

(1) In the presence of heart failure and haemodynamic instability.
(2) Absence of response to therapy (bacteraemia and hyperpyrexia) in the presence of resistant pathogens.
(3) AV block, abscesses, or lesions destroying the valve planes.
(4) Recurrent emboli or large vegetations unresponsive to therapy.
(5) Prosthetic endocarditis from staphylococcus or non-Hacek Gram-negative bacteria.

When to operate in the presence of mobile vegetations and in the absence of heart failure?

The European Society of Cardiology guidelines indicate the need to intervene (Class IIa) to prevent embolism in the presence of vegetations > 10 mm associated with severe regurgitation or valve stenosis. In the absence of severe valve disease but large vegetations (>15 mm), surgery may be considered.

Which echocardiographic techniques to use in the presence of a suspicion of endocarditis?

Both TTE and TEE have seen major technological improvements in recent years. Temporal and spatial resolution facilitates recognition of vegetations and complications of IE. Various new 3D tools such as transillumination, transparency effects, and various other technical devices proposed by the various companies further making the images more realistic and above all allow to simultaneously superimpose the jets in three-dimensional (3D) colour within the 3D images. In this way, the location and entity of regurgitation, perforation of the leaflets, fistulas can be identified with greater simplicity and accuracy.

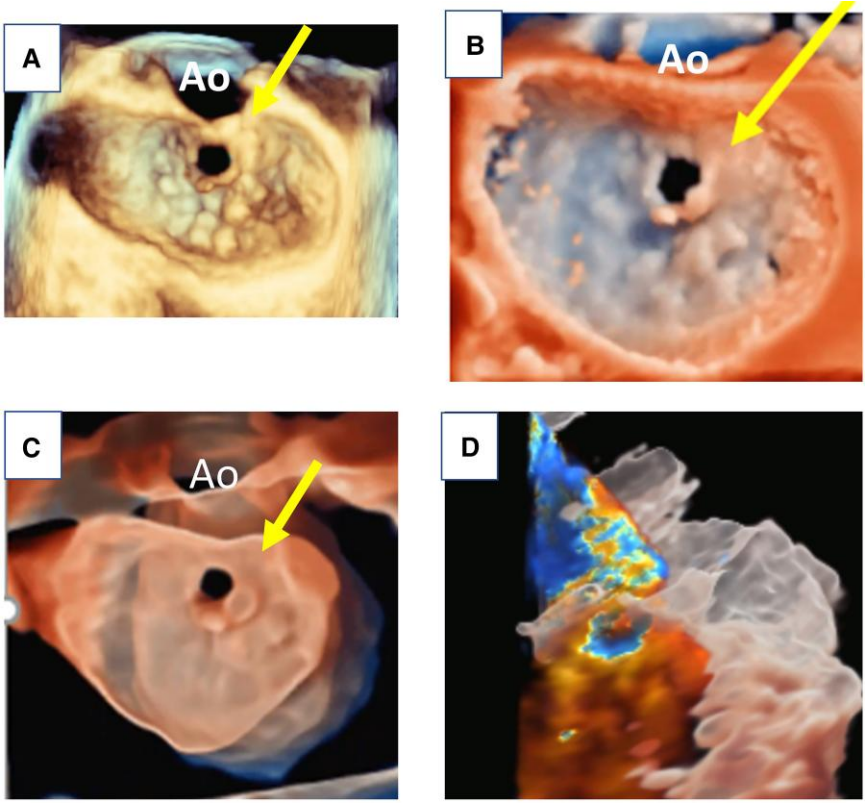

Figure 1 Case of endocarditis on native mitral valve. In the trans-oesophageal 3D exam, we observe: (*A*) conventional 3D trans esophageal echocardiography image showing an evident perforation of the anterior leaflet (arrow); (*B*) same image with trans-illumination effect and (*C*) with 'glass/transparency' effect; (*D*) the transparency effect in longitudinal view allows the superimposition of the colour which shows a severe regurgitation at the level of the perforation. Small vegetations are also visible on the posterior flap in the surgical view (*A*-*C*). Ao, aorta.

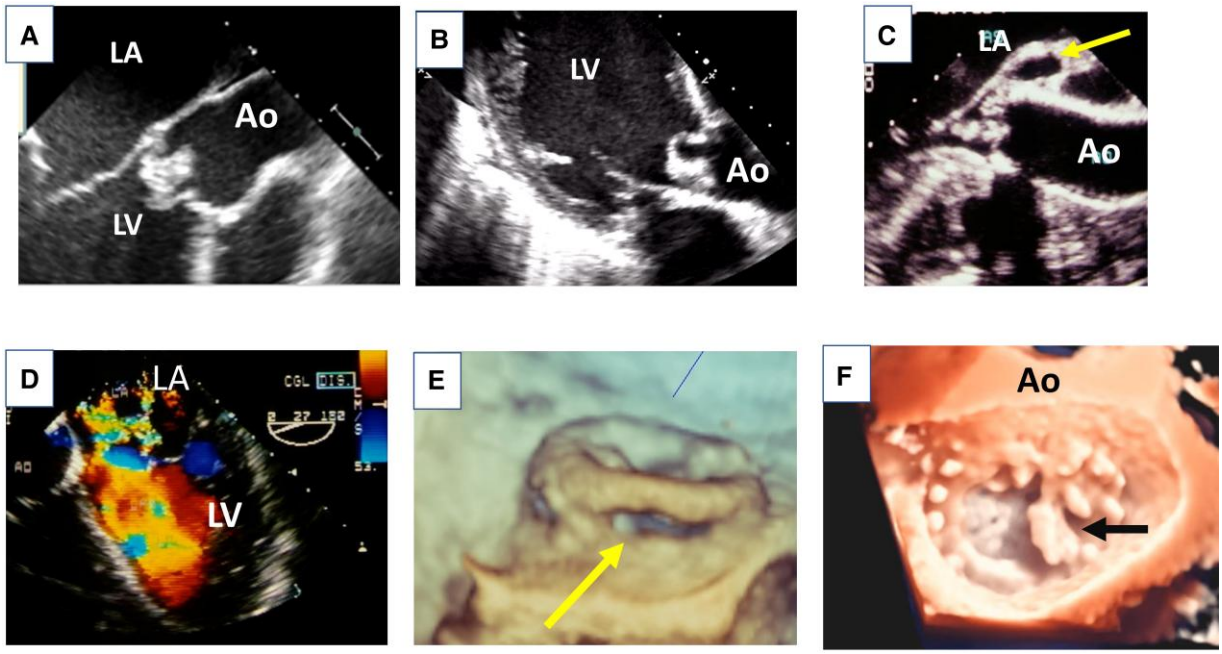

Figure 2 Various examples of cases of endocarditis. (*A*) Vegetation on native aortic valve (trans-oesophageal echocardiography long axis); (*B*) aneurysm of the right coronary cusp in the TTE long axis; (*C*) valvular tube—ascending aorta—Bentall in trans-oesophageal echocardiography long axis; evident vegetation on the valve plane and para-prosthetic abscess (arrow); (*D*) four trans-oesophageal echocardiography chambers with evidence of two perforations of the anterior mitral leaflet; (*E*) prosthetic detachment (arrow) of biologic mitral prosthesis in 3D trans esophageal echocardiography; (*F*) trans esophageal echocardiography image with trans-illumination effect with multiple vegetations (the arrow indicates the largest vegetation). Ao, aorta; LV, left ventricle; LA, left atrium.

Figures 1 and *2* show various examples of two-dimensional (2D), 3D, and 3D echocardiographic images with advanced tools.

Diagnosis of endocarditis in the presence of prosthetic valves and devices

Both in valve prostheses and in the presence of intracavitary catheters or devices (on the interatrial septum, interventricular, left auricle, etc.) the 2DTTE, 2DTEE, 3DTEE exams are complementary and the suggestion is to always perform a complete TTE and Doppler exam before TEE. ETT can be limited and less accurate in the search for specific vegetations or complications, but it is indispensable for characterizing haemodynamic data, biventricular function, the presence of multiple valvulopathies, pericardial and pleural effusions. In many cases, while not diagnosing IE with certainty, it suggests the presence of new pathological jets, dubious images at the level of the prosthetic structures, abscess cavities and, in the case of previous tests, it is possible to verify morphological or functional changes.[6,7]

However, as already underlined, TEE is essential to deepen the investigations and precisely define the pathology. Of great importance is the 2DETE and 3DETE technique to evaluate possible valve leaks or valve detachments and the presence of pseudoaneurysms, perforations, and abscesses. Trans-illumination is very useful to better identify the presence and location of leaks. The 'shadow' effect at the base of the trans-illumination allows in fact to have the 3D perception on a flat screen and in the case of leaks avoids confusing a real leak with a drop-out or artefact.[8]

Furthermore, the prostheses can now be investigated simultaneously with 3D images from the ventricular and atrial side in the case of mitral prostheses or from other planes based on the individual devices. Any vegetation may in fact not be visible from the atrial side, but identifiable from the ventricular side (especially when it is wedged into the prosthetic structure).

A sometimes very difficult diagnosis concerns the IE on pacemakers (PM) and intracavitary cables. The incidence can reach 1–3%, and still has a very high mortality rate (up to 25%). The medical or extraction therapeutic decision is therefore very relevant and the diagnosis often complex. The risk rises in the presence of revisions, post-implantation haematomas, age, and clinical conditions of the patient, and many other factors. The sensitivity of TTE is low and TEE in suspected PM or internal cardioverter defibrillator cable endocarditis is indicated. The images are similar to those of valve IE recognisable as mobile, low echogenicity and often multiple and irregular.[9]

The distinction between thrombus and vegetation on catheters is almost impossible and it is the clinic associated with haemo-culture and haematological data that directs the diagnosis. The 3D TEE and in some cases the intracardiac echo can further help not only in identifying the site and position of the vegetations but also the possibly associated valvular damage (tricuspid and pulmonary valve). The use of nuclear medicine can be useful, but it is not always easy to diagnose an infection on a catheter.

Endocarditis affecting the valvular structures of the right heart deserves a separate discussion. This form of endocarditis is generally associated with a better outcome

than left chamber endocarditis. This is due to multiple factors, first of all because younger patients are usually affected, because tricuspid valve dysfunction has a lower haemodynamic impact than mitral and/or aortic valves, and because embolization of vegetations is less frequent. Furthermore, abscess formation is less frequent and there is less resistance to antibiotics. Mortality is generally <5–10% even without surgery. The surgical indication for these forms consists in a non-eradicable infection (usually by fungi or staphylococcus), in repeated pulmonary embolizations (usually when the vegetations are >20 mm in size) or when there is right heart failure in the presence of severe pulmonary/tricuspid regurgitation. In the forms of endocarditis of the right heart, the new scores applied in the left heart forms are not applicable. Also the aetiology in addition to that similar to the IE of the other valves is peculiar and frequently related to the use of drugs.

Cases of extreme cardiac surgery complexity

In the presence of very advanced infection and tissue destruction, perforations, fistulas, abscesses, surgery assumes a very high risk and must be planned with extreme care (if deemed possible and indicated on the basis of the patient's condition and the risk–benefit discussed by the IE team). The various echocardiographic and CT techniques described above must be performed by integrating the diagnostic data of each of them and obtaining all the information required by the cardiac surgeon.

An example is the so-called Commando procedure which must be performed in the presence of the destruction of the mitro-aortic fibrous skeleton. Various proposed techniques consist of mitro-aortic replacement (only sometimes valve repairs are possible), reconstruction with patches of the destroyed tissue, reconstruction of the outflow tract.[10]

The pre-operative and intraoperative ultrasound (often also completed by CT data) aim at a precise assessment of the endocardial damage by defining every detail that can anticipate the planning of the surgical gesture which the cardiac surgeon will naturally then adapt to the anatomical situation he will have to face. Once the operation is completed and resumed after leaving the extra corporeal circulation, the execution of a perioperative TEE, careful to evaluate prosthetic functionality, possible residual fistulas/leaks, biventricular functionality, is essential.

Conclusions

Despite diagnostic, therapeutic, and surgical advances, IE remains a very severe pathology burdened by significant mortality. Organizational efforts that include the presence of all the most advanced diagnostic methodologies, the creation of an endocarditis team, cardiac surgical improvements, and data collection of cases observed in individual centres must be rigorously pursued to implement rapid procedures and reduce mortality of the IE.

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Data availability

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