

VALVULAR HEART DISEASES

New diagnostic approaches in infective endocarditis

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23 February 2016**CURRICULUM TOPIC: INFECTIVE ENDOCARDITIS**

Infective endocarditis (IE) has continued to be a serious cause of cardiac infection, associated with a poor prognosis and mortality.¹ The incidence of IE ranges between 3 and 10 episodes each year/100 000, depending on geographical area and has been noted to increase dramatically with age, for example, 14.5 episodes each year/100 000 in patients between 70 and 80 years of age.² Survival rates can be improved with an early and accurate diagnosis of this infection and its associated complications.¹ Over the years, a number of diagnostic guidelines and criteria have been proposed, most notably the Von Reyn Criteria (1981), the initial Duke Criteria (1994), the universally accepted Modified Duke Criteria (2000) and most recently the European Society of Cardiology (ESC) 2015 modified criteria.^{3–7}

Little is known about the historical epidemiology of IE >50 years ago; however, the relatively recent epidemiology of IE has changed in relation to the causative organisms, 'at-risk-populations' and the classification of the disease, most notably with the increased incidence of prosthetic valves and intracardiac devices.² Recently through enhanced surveillance of IE, the International Collaboration on Endocarditis reported on the shift in the current microbiology of IE, whereby *Staphylococcus aureus* is now the primary causative agent (31% of cases), followed by viridans group streptococci (17% of cases).⁸ The high incidence of *S. aureus* can be attributed to changing risk factors for its acquisition, including injection drug abuse, healthcare contact and invasive procedures.⁸ Most cases of IE due to *Bartonella* and *Coxiella* have been reported in European countries, possibly reflecting advances in diagnostic methodologies.⁸ As a result of these changes, the diagnosis of IE continues to remain a challenge, particularly when conventional, standard approaches such as microbiological culture and echocardiographic imaging are problematic. During the 15 years since the publication of the Modified Duke Criteria, there have been many developments within the field of molecular diagnostics and nuclear imaging, which could enhance the diagnosis of IE, particularly in the difficult-to-diagnose case. It is imperative to realise how essential the Modified Duke Criteria are in aiding in the diagnosis of the majority of cases of IE (80%) and also the important role that these new diagnostic approaches can play to aid in the diagnosis and monitoring of complications of IE, such as embolism (20–50% cases) and metastatic infection.²

Learning objectives

- ▶ To provide an overview of the current European Society of Cardiology guidelines and criteria, which are used in the diagnosis of infective endocarditis (IE), highlighting their advantages and limitations and to recognise the essential role played by a multidisciplinary team approach.
- ▶ To understand the role molecular microbiological techniques play in aiding in the diagnosis of IE.
- ▶ To appreciate the potential use and limitations of nuclear imaging, namely ¹⁸F-fluorodeoxyglucose-positron-emission tomography/CT, in diagnosing prosthetic valve IE, cardiac-device-associated IE and detection of secondary complications such as metastatic infection and embolic events.

CURRENT DIAGNOSIS**Multidisciplinary team approach**

The diagnosis of IE is challenging, as it can present differently according to a number of parameters, such as causative organism, clinical manifestation, underlying condition/risk factors and the absence/presence of complications associated with the infection, namely embolic events and metastatic infection. As such, the diagnosis and monitoring of a patient with IE requires a multidisciplinary team (MDT) approach involving primary care physicians, cardiologists, cardiac surgeons, electrophysiologists, microbiologists, histopathologists, infectious disease specialists, radiologists, specialists in imaging modalities such as echocardiography and in the case of complications on occasions other specialists such as CT and MRI specialists, neurologists, neurosurgeons, renal physicians, haematologists, rheumatologists and orthopaedic surgeons (figure 1).⁹

The most recent 2015 ESC guidelines for the management of IE endorse the MDT approach, for the management of IE patients in reference centres by a specialised team (the "Endocarditis Team").³

The Modified Duke Classification scheme

The international cornerstone diagnostic criteria, which are based on clinical, microbiological and echocardiographic findings, are the Modified Duke Criteria (box 1).^{6,7} The major criteria are predominantly focused on microbiological culture and positive endocardial involvement, as assessed by



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To cite: Millar BC, Habib G, Moore JE. *Heart* 2016;**102**:796–807.

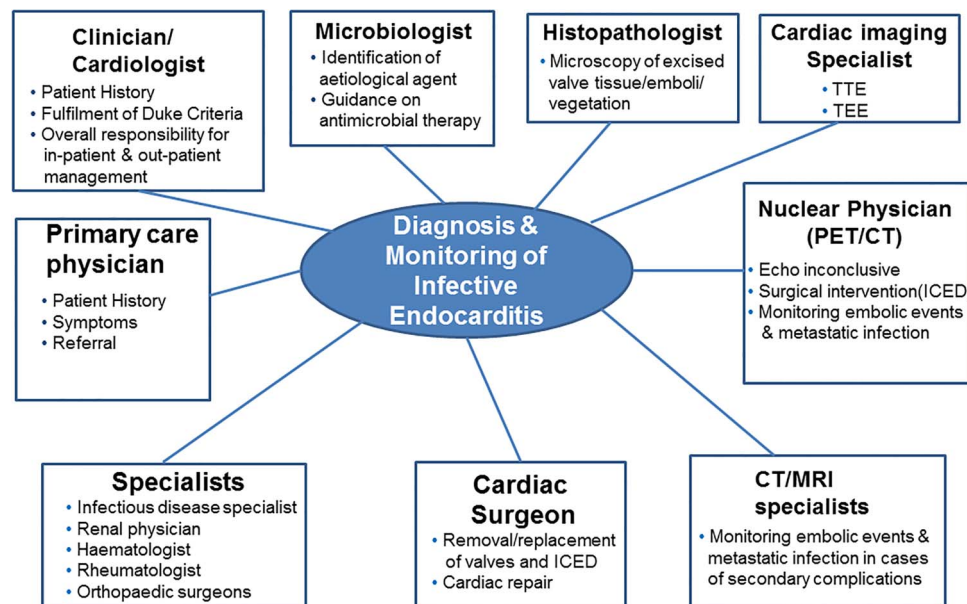


Figure 1 Multidisciplinary team approach to diagnosis and treatment of infective endocarditis (IE).

echocardiography either initially transthoracic echocardiography (TTE) or subsequently the more sensitive transoesophageal echocardiography (TEE) (approximately 75% vs 85–90%, respectively).¹⁰ Both TTE and TEE have been reported to have a specificity of more than 90%.¹⁰

Limitations of current diagnostic approaches

Although the Duke Criteria have been proven to be very specific and sensitive in the diagnosis of 80% of cases of IE, there are some situations which warrant caution, which the criteria do not consider and as such, the two major criteria are not fulfilled.²

In some cases, where there is a strong clinical suspicion of IE, microbiological blood culture remains negative. There are a number of reasons, which could contribute to this, such as commencement of antimicrobial therapy prior to blood cultures being taken, fastidious aetiological agents, for example, HACEK (*Haemophilus parainfluenzae*, *H. aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*) group of organisms, intracellular organisms, for example, *Coxiella burnetii*, *Tropheryma whippelii*, or the location of the vegetations could contribute to a lower level of bacteraemia (box 2).¹¹

Both TTE and TEE are the primary imaging tools used to aid in both the diagnosis of IE and the assessment of the severity of the disease, as well as the prediction of complications of IE, such as embolic events.¹⁰ Additionally, CT and MRI can be used to aid in the diagnosis of IE but are more commonly used to aid in the detection of embolic and metastatic complications.¹² One of the major Modified Duke Criteria is evidence of vegetation, abscess and new dehiscence of a prosthetic valve, as assessed by echocardiography.⁶ However, it must also be noted that there are situations, in the

clinically suggestive IE patient, where echocardiographical findings may be negative, inconclusive or difficult to interpret, particularly in the case of small vegetations, coexisting other cardiac changes, for example, degenerative lesions, pseudoaneurysms or in patients with prosthetic heart valves or intracardiac devices (box 2).¹⁰ Echocardiography should not be used as part of a routine fever screen but only if there is at least a moderate clinical suspicion of IE. Otherwise, Lambl's excrescences, ruptures chordae, myxomatous degeneration or any other non-infective finding can be mislabelled as a vegetation leading to potentially serious clinical confusion.

MOLECULAR DIAGNOSTICS

Over the last 20 years, molecular approaches have been used to identify the causal organisms of IE, and several groups internationally have suggested that molecular diagnosis should be included in the diagnostic workup and some groups have suggested to include a positive molecular finding as a major Duke Criterion.^{13–22} Molecular diagnostic approaches are varied depending on sample type, DNA extraction method, gene target(s) and molecular amplification process and subsequent analysis; however, a general workflow scheme is illustrated in figure 2.

Sample specimens

Molecular techniques have primarily been used to identify organisms in excised heart valve tissue and as such, provide a retrospective contribution to the diagnosis of IE. The majority of centres that have analysed heart valves by PCR amplification have directly analysed DNA extracted from fresh resected valve tissue; however, both frozen and paraffin-embedded valve tissue have also been used.^{13 23–25} However, it is also of importance to note that there have been further published studies,

Education in Heart

Box 1 Modified Duke criteria for the diagnosis of infective endocarditis (IE)*

Major criteria

Blood culture positive for IE

- ▶ Typical microorganisms consistent with IE from two separate blood cultures:
 - viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus* or
 - community-acquired enterococci, in the absence of a primary focus or
- ▶ Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:
 - at least two positive cultures of blood samples drawn >12 h apart or
 - all of 3 or a majority of >4 separate cultures of blood (with first and last sample drawn at least 1 h apart)
- ▶ Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titre 1 >800

Evidence of endocardial involvement

Echocardiogram positive for IE (*TEE recommended in patients with prosthetic valves, rated at least 'possible IE' by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients*), defined as follows:

- ▶ oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation or
- ▶ abscess or
- ▶ new partial dehiscence of prosthetic valve
- ▶ new valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)

Minor criteria

- ▶ predisposition, predisposing heart condition or injection drug use
- ▶ fever, temperature >38°C
- ▶ vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhages and Janeway's lesions
- ▶ immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots and rheumatoid factor
- ▶ Microbiological evidence:
 - positive blood culture but does not meet a major criterion as noted above† or
 - serological evidence of active infection with organism consistent with IE
- ▶ (*Echocardiographic minor criteria eliminated*)

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*Definite diagnosis of IE: (two major or one major and three minor or five minor criteria).

Possible diagnosis of IE: (one major and one minor or three minor criteria)

†Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.

TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

albeit limited to case studies or isolated original articles, which have used other sample specimens for DNA analysis, namely blood, serum and blood culture, which enables a more prospective diagnostic contribution.^{14 26 27} The use of such samples, particularly blood, warrants further investigation as positive findings from such a specimen could prove very useful in determining the antimicrobial

treatment regime in a blood culture negative patient. In addition, determination of the aetiological agent by DNA PCR diagnosis may also aid in determining if surgical intervention is warranted, including culture-negative IE due to fungal (*Aspergillus*), multidrug-resistant organisms, including pseudomonal IE and non-HACEK Gram negative bacteria.^{2 3} Other sample specimens such as vegetations, thrombi and embolic tissue have been investigated.^{28–30}

Box 2 Reasons of negative, inconclusive or false-positive echocardiographical findings in cases of infective endocarditis (IE)

- ▶ Very small vegetations (<3 mm)
- ▶ Identification of vegetations in the presence of pre-existent severe lesions, eg mitral valve prolapse, degenerative lesions, prosthetic valves
- ▶ A typical location of vegetations
- ▶ Non-oscillating vegetations
- ▶ The vegetation may not be seen because of shielding or blooming artefact
- ▶ Reduction in echogenicity by prosthetic valves or severe perivalvular calcifications
- ▶ Difficulties in differentiating between vegetations, thrombi, prolapsed cusp, cardiac tumours, myxomatous changes, Lambli's excrescences, strand or non-infective vegetations (Marantic endocarditis)

Gene targets

Molecular diagnostics have, predominately, focused on amplification of universal gene loci for the detection of microbial causal agents of IE, followed by subsequent sequence-base analysis of the resulting amplicon. In the case of bacterial organisms, broad-range primers used have targeted conserved bacterial rDNA sequences, namely either 16S rDNA or 23S rDNA and also the 16S–23S inter-spacer region.^{13–22 31–33}

In the case of yeasts and fungi, universal ribosomal DNA genes have been targeted, predominantly, the small ribosomal subunit 18S rDNA, the large ribosomal subunit 28S rDNA, and the long and

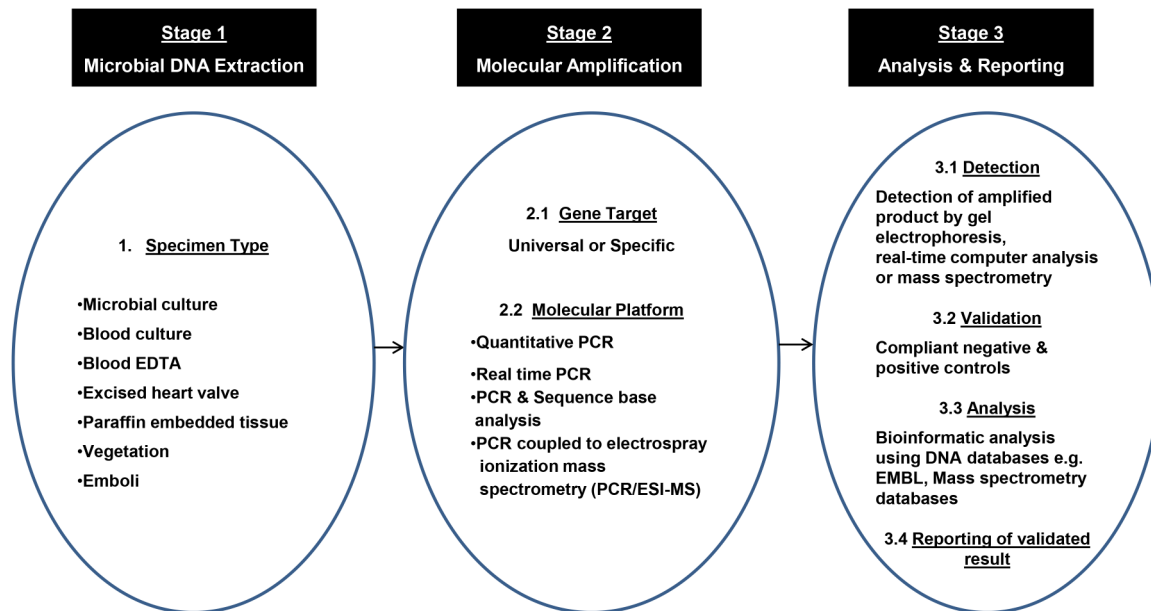


Figure 2 Molecular diagnostic workflow scheme.

short interspacer regions between the 18S, 5.8S and 28S rDNA genes.¹⁴

When there is a clinical suggestion of the causative agent, various specific genes may be targeted, for example, in the case of *C. burnetii*, *T. whipplei* and *Bartonella* sp., as well as detecting antibiotic resistance gene determinants.^{24 27 34–39}

Molecular platforms

For an informative overview on methodologies associated with molecular diagnostic methods in general, see Chandler and Colitz.⁴⁰ The predominant molecular platforms used to date, in relation to the diagnosis of IE, have focused on the use of PCR, which exponentially amplifies the target gene sequences to a detectable threshold. In addition, the sensitivity and specificity of PCR-related assays can be further augmented using seminested PCR or nested PCR.^{13 41–43} Increasingly, a real-time PCR amplification approach is being used to aid the diagnosis due to increased sensitivity, a reduction in contamination and the commercial availability of the SeptiFast real-time PCR system (Roche).^{44 45}

A novel molecular approach that involves universal 16S rDNA PCR followed by analysis of resultant amplicons by electrospray ionization–mass spectrometry (PCR–ESI–MS) has proven useful for the direct detection of pathogens and antimicrobial resistance from heart valves and offers potential in the future to be used to analyse biological specimens in cases of IE in an accurate and timely manner without the need for sequence-based analysis.^{46 47}

Indications for use

Molecular approaches have proven advantageous in a number of situations, particularly in both the detection and identification of organisms, in cases of culture-negative IE, particularly when the causative

organism is intracellular or fastidious in nature, for example, *C. burnetii*, *T. whipplei*, *Bartonella* sp., as well as due to characteristic organisms of IE, which have resulted in a negative blood culture or valve culture finding due to, for example, prior antimicrobial therapy.^{39 48–51} (table 1).

The 2015 ESC guidelines propose that in cases of culture-negative IE, serological diagnosis for *C. burnetii*, *Bartonella henselae*, *Bartonella quintana*, *Legionella pneumophila*, *Brucella* spp., *Mycoplasma* spp. and *Aspergillus* spp. should precede PCR approaches. Where serology is positive, a specific PCR approach should confirm the serological diagnosis. In cases of a negative serology result, a blood PCR should be performed to identify common aetiological organisms.³

Occasionally, some culture-positive isolates are difficult to identify, either to the genus or species level, by using conventional microbiological approaches and in such situations PCR analysis has provided an accurate identification ensuring valid epidemiological reporting and correct antimicrobial therapy.⁵²

Limited reports in the literature have used PCR analysis to characterise antibiotic-resistant organisms in cases of IE.³⁴ Of particular note is the molecular characterisation and discrimination of community-associated methicillin-resistant *S. aureus* (CA-MRSA) from hospital-acquired methicillin-resistant *S. aureus*, as cases of CA-MRSA are emerging in diabetic, intravenous drug misusers and previously healthy individuals with skin-associated infections.^{35–37}

However, molecular approaches have been used most extensively to retrospectively analyse heart valve material. Culture of valve tissue has demonstrated a sensitivity as low as 13% and a specificity of 71.6%, and contamination of such cultures has been noted as between 4% and 31%.^{38 41 42} It has

Table 1 Advantages and disadvantages of using molecular methods in the diagnosis of IE

Advantages (examples)	Disadvantages
<p><i>Aid in identifying aetiological agents that are difficult to culture</i></p> <ul style="list-style-type: none"> ▶ Negative cultures (<i>Tropheryma whipplei</i>) ▶ Slow-growing cultures (<i>Mycobacterium</i> spp.) ▶ Fastidious cultures (HACEK group) ▶ Cell-dependent cultures (<i>Chlamydia</i> spp.) ▶ Category 3 cultures for which a designated cell-culture laboratory is required (<i>Coxiella burnetii</i>) ▶ Difficult, specific culture requirements where limited serology testing exists (<i>Chlamydia</i> spp., fungi) <p><i>Rapid identification</i></p> <ul style="list-style-type: none"> ▶ Conventional culture methodologies may take 24–48 h to validate the presence of MRSA. Molecular-based technologies that amplify the <i>mecA</i> gene take approximately 4–5 h to make an identification from a clinical sample <p><i>Improved sensitivity</i></p> <ul style="list-style-type: none"> ▶ Blood culture detection systems rely on rates of change of various physiological and biochemical parameters in vitro, thereby requiring time to flag positive even when large numbers of organisms are present. The situation is further exacerbated in IE since there are a low number of organisms circulating in peripheral blood. PCR has the ability to enhance the signal from low numbers of existing organisms within a short time, usually 3 h 	<p><i>High cost</i></p> <ul style="list-style-type: none"> ▶ Cost must be balanced with the overall cost-benefits. An earlier diagnosis leading to specific and appropriate therapy results in lower hospitalisation costs <p><i>Questionable significance of results</i></p> <ul style="list-style-type: none"> ▶ PCR detects DNA and queries if the agent detected is viable or not and whether it is involved in the disease state ▶ The agent identified should be considered with respect to the patient's medical and social history <p><i>Labour intensive</i></p> <ul style="list-style-type: none"> ▶ Handling just one isolate is time-consuming due to the various stages of molecular analysis (eg, DNA extraction, PCR amplification, sequence confirmation). However, if molecular diagnosis was implemented in the routine processing of batched samples, efficiency would be increased <p><i>Contamination (false-positive results)</i></p> <ul style="list-style-type: none"> ▶ Various measures may be taken to prevent this (eg, separate reception, DNA isolation, PCR set-up, post-PCR handling rooms, dedicated equipment, internal assay controls) <p><i>Inhibition (false-negative results)</i></p> <ul style="list-style-type: none"> ▶ Assays must include internal standard controls <p><i>Non-specific artefacts</i></p> <ul style="list-style-type: none"> ▶ These are minimised under optimal conditions <p><i>Specialised equipment</i></p> <ul style="list-style-type: none"> ▶ Necessary to ensure accurate results <p><i>Space allocation</i></p> <ul style="list-style-type: none"> ▶ Necessary to ensure accurate results <p><i>Lack of education in modern molecular-based technologies</i></p> <ul style="list-style-type: none"> ▶ Laboratory personnel, clinicians, clinical scientists and nurses all must understand the principles of molecular-based technologies to ensure proper handling of the clinical specimens and appropriate interpretation and significance of results

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HACEK, *Haemophilus parainfluenzae*, *H. aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*; IE, infective endocarditis; MRSA, methicillin-resistant *Staphylococcus aureus*.

therefore been queried as to the true value that such valve culture has to the diagnosis of IE both due to its low sensitivity and to the fact that this is a time-consuming and costly process.⁴¹ PCR analysis of valve tissue has a sensitivity between 41.2% and 96% and a specificity between 95.3% and 100%, which has prompted many researchers to propose that PCR analysis resulting in a positive finding should be included as a major Duke criterion.^{14 18 41}

Concerns relating to molecular approaches

As with any laboratory assay, it is important to recognise and appreciate the limitations and concerns relating to molecular techniques (table 1).

In general, the incidence of detecting bacterial DNA in excised valves, during active infection and during initial antimicrobial treatment, is high but this diminishes with increasing time between successful antimicrobial treatment and subsequent valve surgery. However, caution should be taken when interpreting molecular results as DNA detection does not necessarily equate to viable organisms. This has been evident from several reports, which have shown the persistence of bacterial DNA, from organisms, months or even years, for example, 7 years in the case of *Streptococcus pneumoniae* and up to 16 years in the case of *C. burnetii*, following successful treatment of an episode of IE.^{53 54}

When conducting universal PCR amplification, the risk of contamination and therefore false-positive results must be realised and various steps must be taken to minimise these risks, such as segregation of preamplification and postamplification procedures, screening of assay reagents, staff training, inclusion of positive and negative controls at all stages of the assay.⁵⁵ Similarly, false-negative results can occur due to the presence of PCR-inhibiting substances, for example, haemoglobin in blood or the anticoagulant and anticomplementary agent, sodium polyanetholesulfonate in blood culture media, and as such controls should be included to enable a result to be reported accurately.^{56 57}

To validate the universal PCR result, it has been suggested that a positive result should be confirmed by serology, valve culture or blood culture and in the case of a negative PCR result that other genes are targeted before confirming a true negative result.³⁸

Due to the fact that molecular approaches are more expensive in terms of capital equipment, maintenance, reagents and specialised staff than conventional culture-based methods and that the majority of studies have used “in house” methods, which have not been universally standardised and validated, there may be some reluctance to include the use of this approach into the routine diagnosis of IE. However, with the commercial availability of the Real-Time SeptiFast Assay, a level of

Table 2 Advantages and limitations of ^{18}F -FDG-PET/CT in the diagnosis of IE and CIED-related infections

Advantages of PET/CT	Limitations of PET/CT
Non-invasive ^{18}F -FDG has a short half life (110 min) and is quickly removed	In patients exposed to radioactive tracer and in the case of PET/CT hybrid investigations, most of the radiation is caused by the CT
Images can be generated in a short turnaround time (approximately 2 h)	Cost
Excellent spatial and contrast resolution allowing the precise detection and delineation of infected sites	Lack of availability particularly within Europe. PET/CT scanners for cardiological purposes are generally limited to large centres Recent surgical procedures such as aortic root replacement may cause artefacts due to postsurgery inflammatory response and not infection
Allows the investigation of other sources of infection within the body should cardiac-related infection not be evident in the presence of fever/bacteraemia of unknown origin	Reduced uptake of ^{18}F -FDG tracer may be attributed to small vegetations below the detection threshold of PET (<4 mm), as well as any subsequent reduction in the inflammatory process, that is, resolution of the infection or the immunomodulatory effect of certain antibiotics, for example, azithromycin
Has proven useful in detecting cardiac-related infections particularly prosthetic valve and CIED infection in the absence of echocardiographic evidence	To date, there has not been a large-scale study on the clinical value of PET/CT in relation to the diagnosis and clinical management of patients with cardiac infection. Data from such a study would be required before there could be a general acceptance of the routine use of this technology in relation to cardiac infection
Has proven useful in indicating the need for surgical removal or sole antimicrobial therapy in patients with suspected CIED infection	Implantable cardioverter defibrillator leads frequently result in artefacts of sufficient magnitude to impact on clinical interpretation. Software-based corrections in CT-based attenuation correction algorithms are necessary for accurate cardiac imaging

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CIED, cardiac implantable electronic device; IE, infective endocarditis; ^{18}F -FDG, ^{18}F -fluorodeoxyglucose; PET, positron-emission tomography.

standardisation has been introduced. Due to cost implications, molecular assays may not be universally used as the standard approach for identification purposes. More recently, the use of alternative identification methods has been used widely in clinical microbiology, namely matrix-assisted laser desorption ionisation–time-of-flight mass spectrometry (MALDI–TOF MS), and this has been applied in a small number of isolated case reports relating to IE.^{38 58–60} This approach may be potentially more cost-effective in aiding in the identification of causal agents of IE directly from blood culture but warrants further investigation in this respect. The recent 2015 ESC guidelines, however, propose that blood-culture-positive isolates are identified by MALDI–TOF MS, to expedite microbial identification.³ The value of PCR amplification approaches, as extensively reported in the literature, however, should not be ignored, particularly in cases of culture-negative IE (table 1).

Adoption of molecular diagnosis in international guidelines

As a result of the extent of the published evidence of the usefulness of such PCR analyses of valve tissue material, the current British Society for Antimicrobial Chemotherapy (BSAC) and the ESC guidelines relating to the diagnosis of IE have included the PCR amplification of microbial DNA from heart valve tissue, albeit a retrospective contribution.^{3 61} However, such an approach has not been incorporated as yet into the American Heart Association guidelines.⁶² A more real-time approach has been proposed by the 2015 ESC guidelines, which include PCR analysis of blood samples in cases of culture-negative IE.³

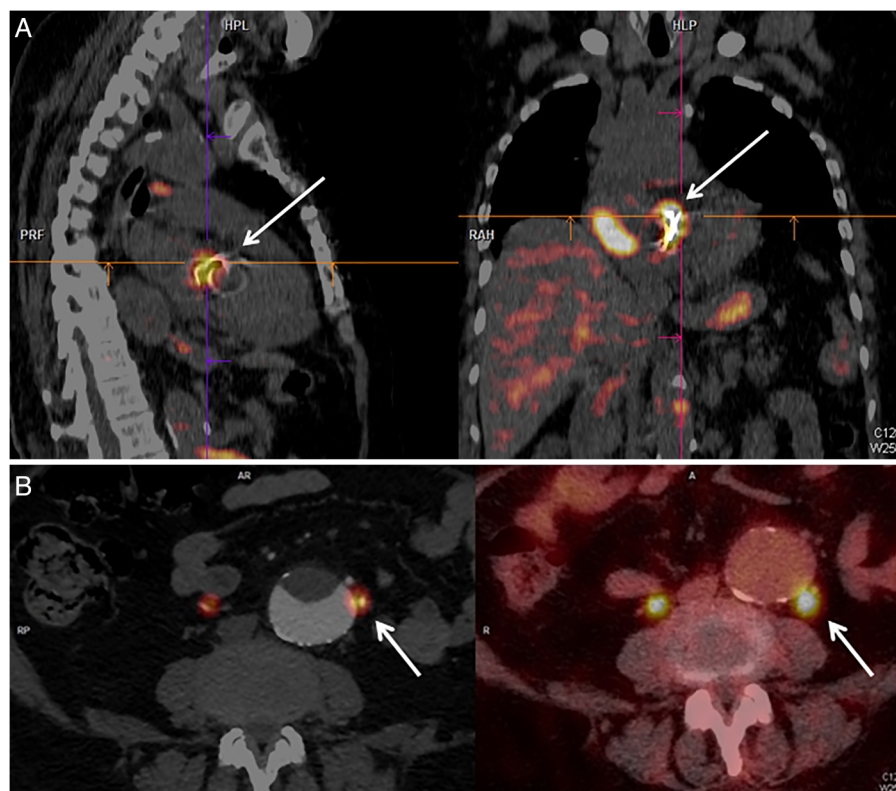
POSITRON-EMISSION TOMOGRAPHY

Positron-emission tomography (PET) using the radionuclide tracer, ^{18}F -fluorodeoxyglucose (^{18}F -FDG) enables the assessment of metabolic activity at a cellular level, as this tracer is taken up by any cell which is undergoing high glycolytic activity, as is the case in tumour cells, inflammation and infection.⁶³ To date, the primary clinical application of PET has been related to the field of oncology; however, increasingly other applications have been acknowledged.⁶⁴ The application of PET coupled with CT (PET/CT) has improved the accuracy of spatial awareness of the associated area of uptake. Recently, the usefulness of PET/CT in relation to IE was reviewed and it was concluded that although this application was in its infancy, the potential role it may have in aiding in the diagnosis and monitoring of complications of IE must be recognised.⁶⁵ The majority of publications to date have focused on case studies or retrospective original articles; however, such work has highlighted several indications where PET/CT could prove to be a useful addition to the current microbiological, echocardiographic and clinical criteria in diagnosing, as well as assessing complications of IE (table 2 and figure 3). Additionally, the use of whole body PET/CT could aid in determining the source of infection/fever of unknown origin, as well as occult tumours, in individuals where suspected IE is just one of many clinical suspicions.

Native and prosthetic valve IE

Due to the increased number of surgical interventions in an increasing ageing population, prosthetic valve endocarditis (PVE) continues to increase and represents up to 30% of IE cases in developed countries.⁶⁶ Most cases of PVE are

Figure 3 ^{18}F -FDG-PET/CT in a patient with bioprosthetic aortic valve infective endocarditis. (a) Uptake on the bioprosthesis (white arrows). (b) Partly thrombosed abdominal aortic aneurysm with uptake on the superior mesenteric artery (white arrow). Prosthetic endocarditis complicated by a mycotic aneurysm of the superior mesenteric artery was subsequently confirmed.



healthcare-associated early onset or late onset infections and due to the in-hospital mortality rate being as high as 41–63%, it is important that PVE is diagnosed quickly and accurately, so that it can be managed effectively.⁶⁷ The diagnosis of PVE can be problematic in that approximately 13–31% of cases are culture negative and echocardiography results are inconclusive in nearly 30% of cases, particularly PVE relating to the aortic valve. Several groups, have however, highlighted its potential in contributing to the diagnosis of PVE, albeit limited to predominately case studies and original articles.^{65 68–72} It has been reported that ^{18}F -FDG-PET/CT when used to aid in the diagnosis of PVE had a sensitivity (73%), specificity (80%), positive predictive value (85%) and negative predictive value (67%), and it increased the sensitivity of the modified Duke Criteria at admission from 70% to 97%; therefore, it has been advocated that the addition of the increase uptake of ^{18}F -FDG in prosthetic valves be included as a novel major Duke Criterion (figure 4).⁷⁰ In contrast, to date the published evidence relating to the use of PET in aiding in the diagnosis of native valve IE is limited and it has been suggested that such imaging is not beneficial in diagnosing cases of native valve IE.⁶⁸

Cardiac implantable electronic device

The number of cardiac implantable electronic devices (CIED) employed has increased twofold to threefold during the last 10–15 years.¹² This has been primarily due to an increasing ageing population and expanding indications for use. Infection of such devices results in a serious diagnostic

challenge and constitutes approximately 10% of cases of IE.⁸ The incidence of CIED infections is <2% or 4.82/1000 device days.⁷³ The diagnosis of CIED infection is difficult, often due to negative blood culture findings and inconclusive echocardiographic findings, due to technical difficulties in visualising all aspects of the leads, particularly in areas which are close to the vena cava, an area where vegetations are frequently encountered.¹² Care should be taken when interpreting echocardiographic findings as lead aggregations can be misinterpreted as vegetations. It is encouraged that TEE is used as its sensitivity is higher than TTE, namely 70–90% vs 20–30%, respectively.¹² Lead extraction is associated with significant morbidity (major complications 1.5–2%) and mortality (0.8%).⁷⁴

The recent guidelines, published by BSAC, for the diagnosis of CIEDs concluded that due to insufficient evidence of what ^{18}F -FDG-PET/CT adds to clinical diagnosis, it could not be recommended as a routine clinical test.⁷⁵ It was suggested, however, that such an investigation may be useful in selected cases, where there is a diagnostic uncertainty.⁷⁵ Limited studies have suggested that ^{18}F -FDG-PET/CT could aid in the diagnosis of CIED, particularly when echocardiographic findings are inconclusive, or in the early stages of pocket infection.^{65 76–78} Recently, ^{18}F -FDG-PET/CT has been shown to increase the diagnostic accuracy of the modified Duke criteria for IE, particularly in patients with possible IE, who present with a challenging clinical and surgical management situation.⁷⁹ However, although an algorithm has been suggested incorporating ^{18}F -FDG-PET/CT in the evaluation of such

Figure 4 Proposed algorithm for evaluating patients with suspected prosthetic valve endocarditis (PVE) using PET/CT. This algorithm integrates PET/CT in the diagnostic strategy of patients in whom the diagnosis of PVE remains uncertain after the initial evaluation using the modified Duke criteria. Thus, in case of *possible* PVE, or *rejected* PVE associated with high clinical suspicion, a new evaluation should be performed by using the PET/CT 2013 modified Duke criteria. These new criteria will allow the detection of more *definite* diagnoses, thanks to a higher sensitivity. 'Saby *et al*,⁷⁰ Copyright (2013), with permission from Elsevier'.

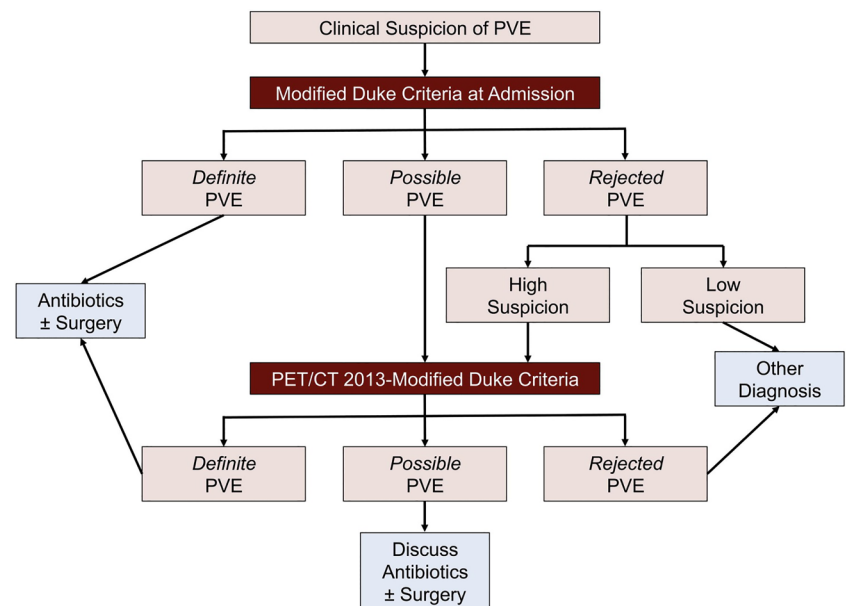


Table 3 Employment of cardiac imaging to aid in the diagnosis of IE

Imaging modality					
2D-Echo	3D-Echo	PET or PET/CT	CT	MRI	Leucocyte scintigraphy with SPECT or SPECT/CT
<i>Indications for use</i>					
<ul style="list-style-type: none"> ▶ Suspected IE ▶ Prognostic assessment ▶ Perioperative evaluation ▶ Follow-up under therapy ▶ Embolic risk assessment 	<ul style="list-style-type: none"> ▶ Suspected IE ▶ Assessment of definite IE and valvular complications ▶ Perioperative evaluation 	<ul style="list-style-type: none"> ▶ Suspected PVE ▶ Doubtful cases of IE ▶ Assessment of emboli 	<ul style="list-style-type: none"> ▶ Suspected IE ▶ Suspected perivalvular lesions ▶ Useful in cases involving calcified valves ▶ Detection of emboli/silent emboli ▶ Assessment of coronary arteries prior to surgery ▶ Multislice CT in assessment of complications 	<ul style="list-style-type: none"> ▶ Neurological complication ▶ Emboli ▶ Diagnosis of vertebral osteomyelitis 	<ul style="list-style-type: none"> ▶ Suspected PVE and CIED infection
<i>Advantages</i>					
<ul style="list-style-type: none"> ▶ Easy to use ▶ Highly validated ▶ Duke criteria ▶ Availability ▶ TEE 85–90% sensitivity 	<ul style="list-style-type: none"> ▶ Easy to use ▶ Anatomical assessment ▶ Detection of paravalvular abscesses, regurgitation and perforations 	<ul style="list-style-type: none"> ▶ Early diagnosis of PVE ▶ Aids with detection of embolic and metastatic complications 	<ul style="list-style-type: none"> ▶ Imaging emboli ▶ High temporal and spatial resolution ▶ Quick (min) ▶ Limited radiation (2–3 mSv) 	<ul style="list-style-type: none"> ▶ High sensitivity ▶ Accurate ▶ diagnosis of neurological involvement 	<ul style="list-style-type: none"> ▶ Higher specificity than PET ▶ Discrimination between infection and inflammation ▶ Can be used during the first 2 months following cardiac surgery
<i>Disadvantages</i>					
<ul style="list-style-type: none"> ▶ False-negative/positive ▶ TTE 50–75% sensitivity ▶ Lower sensitivity in cases of PVE IE ▶ Diagnosis and post-operative evaluation of CIED infection difficult ▶ Late diagnosis 	<ul style="list-style-type: none"> ▶ Limited data and centre experience ▶ Low frame rate may impair detection of smaller vegetations 	<ul style="list-style-type: none"> ▶ Limited data/ large-scale studies ▶ False positives during immediate/ early postoperative period ▶ Not advocated in cases of NVE ▶ Limited value in CIED infection ▶ Centre experience ▶ Availability ▶ Not advocated in unstable patients 	<ul style="list-style-type: none"> ▶ Routine CT screening not recommended ▶ Limited data ▶ Centre experience ▶ Availability ▶ Use of iodine contrast not advocated in some patients, eg decreased renal function, usable haemodynamics, allergy ▶ TEE superior in detecting small vegetations and valve perforations ▶ No significance difference in cases of NVE and PVE 	<ul style="list-style-type: none"> ▶ Lower spatial resolution than multislice CT ▶ Availability ▶ Time consuming ▶ Limited use in case of CIED infection 	<ul style="list-style-type: none"> ▶ Lower sensitivity than PET ▶ Longer acquisition times than PET ▶ Need for highly specialised equipment ▶ Safety risks associated with handling patients' blood ▶ Use heavy isotope tracers ▶ Availability ▶ Centre experience

CIED, cardiac implantable electronic device; IE, infective endocarditis; NVE, Native valve endocarditis; PET, positron-emission tomography; PVE, prosthetic valve endocarditis; SPECT, single positron-emission CT; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

CIED infections, the published data are still very limited and do not allow recommending the use of ^{18}F -FDG-PET/CT as a clinical tool in daily practice.⁸⁰

Embololic events and metastatic infection

Embololic events occur in 22–43% patients with IE, generally within the first 2 weeks of therapy, as a result of thrombi released from the vegetation, but many occur before treatment and may be the reason for presentation. Infarction of the spleen is most prevalent in left-sided IE (40%); however, other sites include limbs, kidneys, lungs and brain with the risk of minor embolic events evident in the skin and retina.⁸¹

Metastatic infection can lead to complications such as septic arthritis, spondylodiscitis, osteomyelitis,

pericarditis and metastatic soft tissue abscess. ^{18}F -FDG-PET/CT has been used to aid in detecting such complications associated with IE in cases both where clinical suspicion was evident and in cases before there was any clinical suggestion.^{65 81–85}

Concerns relating to the use of PET/CT

Although ^{18}F -FDG-PET/CT has some potential uses in diagnosing and monitoring IE, concerns relating to its uses should be acknowledged.⁶⁵ The procedure warrants exposure to the patient of radiation, both from intravenous injection of the ^{18}F -FDG tracer and the acquisition of the CT scan. This is of particular significance in cases of IE in children and as such ^{18}F -FDG-PET/CT analysis is not advised. The associated costs of the procedure are much higher than those of TTE and TEE; however, such costs must be assessed in terms of prevention of secondary complications and reduced costs due to shortened in-hospital stay.⁸⁶ Of significance is the technical aspects of the procedure, particularly relating to normal uptake of the tracer. Some groups have debated the limitations and difficulties associated with interpreting results in cases of IE, as cardiac tissue naturally uptakes the ^{18}F -FDG tracer. Other potential target tracers may have a future role in the detection and monitoring of IE, for example, the detection of *S. aureus* by pathogen-specific prothrombin activation has been investigated.^{87 88} Of recent interest has been the use of antimicrobial peptides such as ubiquicidin which are believed to differentiate between mammalian and bacterial or fungal cells, which when labelled with ^{68}Ga (^{68}Ga) can differentiate between sites of inflammation and infection.⁸⁹ Care must be taken when interpreting the ^{18}F -FDG-PET/CT findings as the uptake of the tracer could be a result from inflammation due to recent cardiac surgical procedures and implantation of cardiac valves or devices less than 1–2 months previously and not infection.^{65 80 90 91} CIED and leads may also result in artefacts on ^{18}F -FDG-PET/CT analysis; therefore, software-based corrections of the images are required in such situations.⁶⁵ In contrast, a false-negative finding could result from reduced uptake of tracer in small vegetations (<4 mm) and in cases of IE where there may be some resolution of infection or an immunomodulatory effect due to certain antibiotics.⁶⁵

To date, there has not been a large-scale study on the clinical value of ^{18}F -FDG-PET/CT in relation to cardiac infection, which in part could be due to a lack of availability of equipment for cardiological purposes and as such, there is a reluctance to include it routinely in any diagnostic guidelines, although its potential has been acknowledged in difficult cases (table 2).

OTHER IMAGING MODALITIES

Echocardiography has been and will continue to be the cornerstone imaging modality used to aid in the diagnosis of IE.¹⁰ While the current review has highlighted the potential role PET/CT imaging contributes to the detection and monitoring of IE, the

Key messages

Guidelines and diagnostic criteria

- ▶ The diagnosis and management of infective endocarditis (IE) involves the input from a multidisciplinary team.
- ▶ Microbiological culture of blood/valve tissue and echocardiography remain the cornerstone in the diagnosis of IE and identify approximately 80% of cases.
- ▶ Fulfilment of the Duke criteria is central to any diagnostic guidelines but should not overrule strong clinical suspicion.
- ▶ There are limitations associated both with culture and echocardiography which must be realised.

Molecular diagnosis

- ▶ In cases of suspected IE, which are culture-negative, particularly due to the causative agent being intracellular, molecular diagnostic approaches, particularly using heart valve tissue, may prove useful.
- ▶ Molecular diagnosis from valve tissue has been advocated in the European Society of Cardiology (ESC) and British Society for Antimicrobial Chemotherapy (BSAC) guidelines.
- ▶ Molecular diagnosis from blood samples in patients with culture-negative IE and serology-negative IE, has been advocated in the 2015 ESC guidelines.
- ▶ When using broad-range/universal PCR, care should be taken to minimise the risks associated with PCR inhibition and contamination, thereby ensuring a valid result.
- ▶ All molecular findings should be considered in concert with other laboratory markers, clinical findings and patient history.

^{18}F -FDG-PET/CT imaging

- ▶ Due to limited large-scale studies, ^{18}F -Fluorodeoxyglucose (^{18}F -FDG)-positron-emission tomography (PET)/CT has not been widely accepted into diagnostic guidelines for cardiac-related infections; however, the potential of such a method should not be overlooked in difficult to diagnose cases.
- ▶ ^{18}F -FDG-PET/CT has not proven valuable in diagnosing native valve IE.
- ▶ Numerous studies have advocated the use of ^{18}F -FDG-PET/CT in contributing to the diagnosis of prosthetic valve IE and have advocated that a positive finding be included as a major Duke Criterion.
- ▶ ^{18}F -FDG-PET/CT is a promising tool in aiding in detecting cardiac implantable electronic device (CIED) related infection but published data are still limited.
- ▶ ^{18}F -FDG-PET/CT is a useful tool in detecting secondary complications of IE, such as metastatic infection and peripheral embolic events, even before there is a clinical indication.

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role other imaging modalities have contributed must be recognised, along with their limitations (table 3). Such modalities include CT and leucocyte scintigraphy coupled to single positron emission CT (SPECT) or SPECT/CT to aid in the diagnosis of IE and PVE and CIED infection, respectively.^{12 92–94} Radiolabelled leucocytes scintigraphy is less sensitive but more specific than PET/CT (table 3). More recently, it has been documented that MRI can contribute to both the diagnosis and prognosis of IE.⁹⁵ CT and MRI are primarily useful in the detection of embolic events, including asymptomatic embolic events and secondary complications associated with IE and are used where there is a clinical indication.^{12 96–98}

A EUROPEAN PERSPECTIVE: IS IT TIME TO REFINES DIAGNOSTIC CRITERIA FOR IE?

Diagnosis of IE is frequently difficult in clinical practice. Although echocardiography and blood cultures are the cornerstone of diagnosis, they may be falsely negative in some situations, particularly when microorganism identification is masked by previous antibiotic therapy, and in patients with prosthetic valve or other intracardiac material. Published guidelines, including ESC guidelines, uniformly recommend the use of Modified Duke Criteria (box 1) for the diagnosis of IE. However, the sensitivity of those criteria is limited in some subgroups. It can be improved by using new microbiological diagnostic techniques, as well as new imaging modalities (MRI, CT, PET/CT and SPECT/CT). The latter nuclear imaging modalities are particularly helpful when echocardiographic studies are doubtful and may represent additional diagnostic criteria for IE. The 2015 ESC guidelines have specifically defined when such imaging modalities should be used to aid in the diagnosis of IE,

particularly in cases of IE which are possible/rejected but with a high clinical suspicion. The 2015 ESC Guidelines advocate in such cases, with regard to native valves, along with repeat echocardiography and microbiology, imaging (cerebral MRI, whole body CT and/or PET/CT) for embolic events and cardiac CT (for paravalvular lesions).³ In the case of prosthetic valves, the work up is the same as native valves with the addition of PET/CT or SPECT/CT.³

However, even if a refinement of diagnostic criteria may be warranted, those criteria will never replace the clinical judgement and the advice of the 'endocarditis team' (figure 1).

CONCLUSION

In conclusion, conventional diagnostic approaches such as microbiological culture, *C. burnetii* serology and echocardiography are successful in aiding in the diagnosis of the majority of cases of IE. When these methods are inconclusive, yet there is a strong clinical suspicion of IE and related infection, it is important to acknowledge the role molecular and ¹⁸F-FDG-PET/CT approaches may play in aiding in the diagnosis and management of these complicated cases.

Competing interests None declared.

Provenance and peer review Commissioned; externally peer reviewed.

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Heart 2016 102: 796-807 originally published online February 23, 2016
doi: 10.1136/heartjnl-2014-307021

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