Endocarditis
Gomes, Anna

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2018

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Diagnostic value of imaging in infective endocarditis: a systematic review

Department of Medical Microbiology (A Gomes MD, Prof B Sinha PhD), Department of Nuclear Medicine and Molecular Imaging (A W J M Glaudemans PhD, R J H Borra PhD, Prof R H J A Slart PhD), Department of Clinical Pharmacy and Pharmacology (Prof D J Touw PhD), Department of Cardiology (J P van Melle PhD, A H Maass PhD, P P van Geel PhD), Department of Radiology (T P Willems PhD, N H J Prakken PhD), Department of Thoracic Surgery (E Natour PhD), and Department of Internal Medicine, Division of Infectious Diseases (S van Assen PhD), University of Groningen, University Medical Center Groningen, Groningen, Netherlands; and Department of Biomedical Photonic Imaging, University of Twente, Enschede, Netherlands (R H J A Slart)

Summary

Sensitivity and specificity of the modified Duke criteria for native valve endocarditis are both suboptimal, at approximately 80%. Diagnostic accuracy for intracardiac prosthetic material-related infection is even lower. Non-invasive imaging modalities could potentially improve diagnosis of infective endocarditis; however, their diagnostic value is unclear. We did a systematic literature review to critically appraise the evidence for the diagnostic performance of these imaging modalities, according to PRISMA and GRADE criteria. We searched PubMed, Embase, and Cochrane databases. 31 studies were included that presented original data on the performance of electrocardiogram (ECG)-gated multidetector CT angiography (MDCTA), ECG-gated MRI, 18F-fluorodeoxyglucose (18F-FDG) PET/CT, and leucocyte scintigraphy in diagnosis of native valve endocarditis, intracardiac prosthetic material-related infection, and extracardiac foci in adults. We consistently found positive albeit weak evidence for the diagnostic benefit of 18F-FDG PET/CT and MDCTA. We conclude that additional imaging techniques should be considered if infective endocarditis is suspected. We propose an evidence-based diagnostic work-up for infective endocarditis including these non-invasive techniques.
Diagnostic value of imaging in infective endocarditis: a systematic review

Introduction

Infective endocarditis comprises native valve endocarditis and intracardiac prosthetic material-related infective endocarditis. The latter includes prosthetic valve endocarditis (covering all types of prosthetic valves, annuloplasty rings, intracardiac patches, and shunts),1 and infective endocarditis related to pacemakers, implantable cardioverter defibrillators (ICDs), and ventricular assist devices. As the number of procedures in which prosthetic material is introduced in the heart is rising,2, 3, 4, 5 the incidence of intracardiac material-related infective endocarditis is increasing.6

Infective endocarditis leads to substantial mortality (with in-hospital mortality of 14–22% and 1-year mortality of 40%)7, 8, 9 and morbidity,8 which can be the result of local spread of infection, metastatic infection, embolic infection, or immune-mediated damage.10 These numbers are probably an underestimation because they are based on registries from dedicated collaborating centers.

Early and accurate diagnosis of infective endocarditis is crucial because delayed treatment negatively affects outcome.11, 12 Clinical diagnosis of infective endocarditis is largely based on the modified Duke criteria,13 which are incorporated in the infective endocarditis guidelines.1, 4, 5, 14, 15 A cornerstone of the modified Duke criteria is echocardiography. However, both transthoracic echocardiography and transoesophageal echocardiography (TEE) miss infective endocarditis sequelae in 30% of patients—especially in patients with intracardiac prosthetic material, in whom the incidence of perivalvular complications (mycotic aneurysms and abscesses) is particularly high.4, 5, 16, 17, 18, 19 Therefore, the sensitivity and specificity of the modified Duke criteria are approximately 80% for native valve endocarditis (with autopsy as the gold standard)13 and even worse for intracardiac prosthetic material-related infective endocarditis, which leads to underdiagnosis and overdiagnosis of substantial proportions of patients.

Novel approaches to imaging of the heart and extracardiac complications are needed to improve and individualise the diagnostic work-up, therapy, prognosis, and financial expenses in patients with suspected infective endocarditis.4, 5, 12, 20, 21, 22, 23, 24, 25 Improved cardiac and extracardiac imaging is particularly warranted in a small subset of patients with relative contraindications for TEE, and in patients with intracardiac prosthetic material.26 Electrocardiogram (ECG)-gated multidetector CT angiography (MDCTA), ECG-gated MRI, 18F-fluoro-deoxyglucose (18F-FDG) PET/CT, and leucocyte scintigraphy (also called white blood cell imaging) are all promising imaging techniques.

The aim of this systematic review is to provide physicians with clear, evidence-based guidance on available imaging techniques to improve diagnostics in infective endocarditis. We summarise and discuss evidence regarding the added value of MDCTA, MRI, 18F-FDG PET/CT, and leucocyte scintigraphy in diagnosis of both cardiac and extracardiac foci of infective endocarditis in patients with native valves or intracardiac prosthetic material. On the basis of available evidence combined with multidisciplinary expert opinion, we provide a diagnostic flowchart for work-up of patients with suspected infective endocarditis.
Methods

Search strategy and selection criteria
The PRISMA statement\textsuperscript{27} and its accompanying Explanations and Elaboration paper\textsuperscript{28} were the basis for this systematic review. Two independent reviewers (AG, SvA) did a literature search in PubMed and Embase, including articles in any language published before or on Jan 11, 2016. Search terms were “positron emission tomography”, “computed tomography”, “magnetic resonance imaging”, “leucocyte radionuclide imaging”, “endocarditis”, “prosthesis related infection”, “prosthetic heart valve”, “pacemaker”, “implantable defibrillator”, “heart assist device”, “aortic root replacement”, and “septum occluding device”, as defined with the assistance of a library staff member (extensive overview of search terms in appendix). We included studies in adults that provided original data on the accuracy of MDCTA, MRI, \textsuperscript{18}F-FDG PET/CT, and leucocyte scintigraphy in diagnosis of infective endocarditis, and of \textsuperscript{18}F-FDG PET/CT and leucocyte scintigraphy in diagnosis of extracardiac complications. We excluded preclinical studies, case reports (fewer than five individuals), abstracts, and studies that did not meet our technical imaging criteria (appendix). Final decisions on the interpretation and inclusion of references were subsequently done in consensus with a third reviewer (BS). We checked references of included original articles and of relevant review articles, editorials, and commentaries for additional studies to be included, and searched the Cochrane Library for reviews on endocarditis. After removal of duplicates, we screened articles for eligibility based on title and abstract, and selected articles were evaluated based on full text. Exclusion was done stepwise: (1) study design, (2) topic, and (3) study population.

Both intracardiac infections related to the native heart and intracardiac prosthetic material (ICD or pacemaker leads, prosthetic valves with or without vascular graft of ascending aorta, ventricular assist devices, and atrial or ventricular septal defect patches) were included (appendix). In case of insufficient data in an article, we contacted the author to obtain the required information. The endpoints of analysis were infective endocarditis or extracardiac complications. We defined infective endocarditis as possible or definite diagnosis of endocarditis according to the modified Duke criteria,\textsuperscript{13} expert opinion, clinical follow-up, or autopsy data. We defined extracardiac complications as systemic embolism or metastatic infection.

Data extraction and quality assessment
After identification of all relevant articles, AG, SvA, and BS reached consensus regarding data to be extracted for analysis. AG extracted the data, in consensus with SvA and BS when needed.

AG assessed the methodological quality of the studies, in consensus with SvA and BS when needed. Risk of bias was separately assessed for different components for each study, as defined in the PRISMA guidelines. Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria were applied to assess included studies for possible bias, and for possible reasons to upgrade the quality of the provided evidence (appendix). Subsequently, a merged quality rate was assigned to each study, which was taken into account for the quality synthesis of results.
Results

In total, 31 studies were included (figure 1, table 1). 24 studies addressed the value of $^{18}$F-FDG PET/CT in the diagnosis of infective endocarditis or extracardiac complications. Three studies addressed the value of MDCTA in the diagnosis of infective endocarditis. Five studies addressed the value of $^{99m}$Tc-hexamethylpropylene amine oxime ($^{99m}$Tc-HMPAO; also known as $^{99m}$Tc-exametazime)-labelled leucocytes and single-photon emission CT (SPECT)/CT in the diagnosis of infective endocarditis or extracardiac complications. We did not include studies with leucocytes labelled other than with $^{99m}$Tc-HMPAO, because these studies did not fulfil inclusion criteria. All included studies met the GRADE criteria for, at best, low quality.

Figure 1
Study selection

One study was included for both $^{18}$F-FDG PET/CT and leucocyte scintigraphy. We excluded several articles because of multiple criteria—the most important exclusion criteria are noted in this figure. Based on technical criteria, only papers dealing with SPECT/CT have been retained for leucocyte scintigraphy. $^{18}$F-FDG=$^{18}$F-fluorodeoxyglucose. MDCTA=multidetector CT angiography. LS=leucocyte scintigraphy. SPECT=single-photon emission CT.
<table>
<thead>
<tr>
<th>Inclusion Number and type of cases</th>
<th>Gold standard</th>
<th>Diagnostic accuracy (sensitivity; specificity; PPV; NPV)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECG-gated MDCTA, n=92 (92 cases and 0 controls)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50% native valve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feuchtnern59 Prospective 37 suspected infective endocarditis (six prosthetic valves, two pacemakers)</td>
<td>Modified Duke criteria (surgery n=29)</td>
<td>Possible or definite infective endocarditis’ (37 of 37) vs TEE: 95% (97%; 88%; 97%; 88%); valve vegetation or definite infective endocarditis’ (27 of 29) vs surgery: 96% (96%; 97%; 96%; 97%)</td>
<td>Low</td>
</tr>
<tr>
<td>&gt;50% prosthetic valve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fagman60 Prospective 27 suspected infective endocarditis (27 prosthetic valves, three pacemakers)</td>
<td>Modified Duke criteria (surgery n=16)</td>
<td>Definite infective endocarditis’ (27 of 27): 93% sensitivity</td>
<td>Low</td>
</tr>
<tr>
<td>Habets69 Prospective 28 suspected infective endocarditis’ (28 prosthetic valves)</td>
<td>Expert team after follow-up</td>
<td>Infective endocarditis (24 of 28): (100%; 83%; ..); 20% major diagnostic change; 25% treatment change</td>
<td>Low</td>
</tr>
<tr>
<td>18F-FDG PET/CT, n=1402 (943 cases and 553 controls)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50% native valve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ozcan61 Retrospective 72 definite infective endocarditis’ (two ICDs or pacemakers, 12 prosthetic valves), 104 controls</td>
<td>Expert panel or imaging closest in time to PET, or both</td>
<td>Infective endocarditis’ and extracardiac complications (64 of 159 lesions): (40%; ..; 56%; ..); low uptake organs (33 of 38 lesions): (87%; 97%; 52%; ..)</td>
<td>Low</td>
</tr>
<tr>
<td>Asmar62 Retrospective 72 definite infective endocarditis’ (two ICDs or pacemakers, 12 prosthetic valves)</td>
<td>Standard work-up and succeeding examinations</td>
<td>Extracardiac complications (64 of 114 lesions): 56% PPV; new findings with clinical relevance (11 of 72): 15%; NNI=7</td>
<td>Low</td>
</tr>
<tr>
<td>Van Riet63 Prospective 25 definite infective endocarditis’ (ten prosthetic valves)</td>
<td>More than 6 months’ follow-up</td>
<td>Extracardiac complications (11 of 25): (100%; ..; ..; 100%); new findings (seven of 25): 28%; intracardiac signal (three of 25): 12% of definite infective endocarditis diagnosis</td>
<td>Low</td>
</tr>
<tr>
<td>Kestler64 Prospective 47 definite infective endocarditis’ (23 ICDs, prosthetic valves, or pacemakers), 94 controls</td>
<td>Expert team after follow-up</td>
<td>Extracardiac complications (35 of 47): (100%; 80%; 90%; 100%); new findings (15 of 47): 32%; relapse rate halved</td>
<td>Low</td>
</tr>
<tr>
<td>Kouijzer65 Prospective 72 Gram-positive bacteraemia and risk factor for extracardiac foci (six prosthetic valves [two with and four without ascending aorta], five pacemakers)</td>
<td>Modified Duke criteria</td>
<td>Definite infective endocarditis’ (18 of 72): (39%; 93%; 64%; 82%)</td>
<td>Low</td>
</tr>
<tr>
<td>Orvin66 Prospective 40 definite infective endocarditis’ (ten ICDs or pacemakers, 13 prosthetic valves, one left ventricular assist device)</td>
<td>Clinical outcome</td>
<td>Extracardiac complications (17 of 40): 43%, of which 20% asymptomatic; treatment modification (14 of 40): 35%; definite infective endocarditis’ (34 of 40): 6% sensitivity</td>
<td>Low</td>
</tr>
<tr>
<td>Salomäki67 Prospective Seven suspected infective endocarditis</td>
<td>Modified Duke criteria and follow-up in expert team</td>
<td>Infective endocarditis (one of seven suspected): 14% sensitivity overall; extracardiac complications (four of six definite infective endocarditis’): 67%</td>
<td>Low</td>
</tr>
</tbody>
</table>
### Diagnostic value of imaging in infective endocarditis: a systematic review

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion</th>
<th>Number and type of cases</th>
<th>Gold standard</th>
<th>Diagnostic accuracy (sensitivity; specificity; PPV; NPV)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonfiglioli</td>
<td>Prospective</td>
<td>71 suspected infective endocarditis (38 prosthetic valves)</td>
<td>Modified Duke criteria and expert opinion</td>
<td>Sensitivity; specificity; PPV; NPV</td>
<td>Low</td>
</tr>
<tr>
<td>Garcia-Navarro</td>
<td>Retrospective</td>
<td>27 suspected infective endocarditis (20 prosthetic valves)</td>
<td>Modified Duke criteria and TEE</td>
<td>Sensitivity; specificity</td>
<td>Medium</td>
</tr>
<tr>
<td>Ricciardi</td>
<td>Retrospective</td>
<td>27 suspected infective endocarditis (130 of 302)</td>
<td>Modified Duke criteria and expert opinion</td>
<td>Sensitivity; specificity; PPV; NPV</td>
<td>Low</td>
</tr>
<tr>
<td>Bartolo</td>
<td>Retrospective</td>
<td>27 suspected infective endocarditis (130 of 302)</td>
<td>Modified Duke criteria and expert opinion</td>
<td>Sensitivity; specificity; PPV; NPV</td>
<td>Low</td>
</tr>
<tr>
<td>Saby</td>
<td>Prospective</td>
<td>72 suspected infective endocarditis (72 prosthetic valves)</td>
<td>Expert team after follow-up</td>
<td>Sensitivity; specificity; PPV; NPV</td>
<td>Low</td>
</tr>
<tr>
<td>Bartolo</td>
<td>Retrospective</td>
<td>27 suspected infective endocarditis (130 of 302)</td>
<td>Modified Duke criteria and TEE</td>
<td>Sensitivity; specificity</td>
<td>Medium</td>
</tr>
<tr>
<td>Rouzet</td>
<td>Retrospective</td>
<td>39 suspected infective endocarditis (39 prosthetic valves)</td>
<td>Modified Duke criteria and follow-up in expert team</td>
<td>Sensitivity; specificity; PPV; NPV</td>
<td>Low</td>
</tr>
<tr>
<td>Sali A</td>
<td>Prospective</td>
<td>92 suspected infective endocarditis (92 prosthetic valves)</td>
<td>Modified Duke criteria and follow-up in expert team</td>
<td>Sensitivity; specificity; PPV; NPV</td>
<td>Low</td>
</tr>
<tr>
<td>Pizzi</td>
<td>Prospective</td>
<td>11 suspected endocarditis (11 aortic prosthetic valves)</td>
<td>Modified Duke criteria and follow-up in expert team</td>
<td>Sensitivity; specificity; PPV; NPV</td>
<td>Low</td>
</tr>
</tbody>
</table>

**Intracardiac signal:**
- Native or prosthetic valve endocarditis: (2.5 of 27); (55%); (20%); (85%); (100%); (100%); (50%)
- Prosthetic valve endocarditis: (six of 30); (100%); (100%)

**Extracardiac signal:**
- New findings: (24%) new findings
- Infective endocarditis diagnosis: (11 of 17); (65%); (6%)
- Other findings: (4 of 11); (36% of infective endocarditis diagnosis)
<table>
<thead>
<tr>
<th>Inclusion Number and type of cases</th>
<th>Gold standard</th>
<th>Diagnostic accuracy (sensitivity; specificity; PPV; NPV)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pacemaker or ICD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ahmed&quot;41 Prospective&quot; 46 suspected pocket infection (25 pacemakers, 21 ICDs), 40 controls (eight pacemakers, 12 ICDs)</td>
<td>More than 3 months clinical follow-up (n=14) or culture (n=32)</td>
<td>Pocket (32 of 46) (91%; 93%; 97%; 81%)</td>
<td>Low</td>
</tr>
<tr>
<td>Beck&quot;42 Retrospective&quot; 69 controls (69 ICDs)</td>
<td>Laboratory and clinical data</td>
<td>Device' (0 of 69) 100% specificity</td>
<td>Low</td>
</tr>
<tr>
<td>Bensimhon&quot;43 Prospective&quot; 21 suspected infection (18 pacemakers, three ICDs), 14 controls (14 pacemakers)</td>
<td>Device culture or 6-month follow-up with modified Duke criteria</td>
<td>Box or lead' (ten of 21): 90% (80%; 100%; 100%; 85%); boxes (five of 21): 100% (100%; 100%; 100%; 100%); leads (ten of 21): 81% (60%; 100%; 100%; 73%)</td>
<td>Low</td>
</tr>
<tr>
<td>Cautela&quot;44 Prospective&quot; 21 suspected infection (16 pacemakers, five ICDs)</td>
<td>Clinical criteria according to Le Dolley and colleagues&quot;55</td>
<td>Skin (one of 21): 100% sensitivity; pocket (13 of 21): (87%; 100%; ..; ..); device-related infective endocarditis' (13 of 21): (31%; 63%; ..; ..)</td>
<td>Low</td>
</tr>
<tr>
<td>Graziosi&quot;45 Prospective&quot; 27 suspected infective endocarditis' (12 pacemakers, 15 ICDs)</td>
<td>Expert team after follow-up</td>
<td>Lead' (13 of 27): (63%; 86%; 77%; 76%)</td>
<td>Low</td>
</tr>
<tr>
<td>Leccisotti&quot;46 Prospective&quot; 27 suspected infection (16 pacemakers, 11 ICDs), 15 controls (nine pacemakers, six ICDs)</td>
<td>Pocket or lead culture or follow-up</td>
<td>Device' (21 of 21): 93% at 1 h (86%; 100%; ..; ..), 95% at 3 h (91%; 100%; ..; ..); pocket (18 of 21): 94% at 1 h (89%; 100%; ..; ..), 97% at 3 h (94%; 100%; ..; ..); lead (13 of 21): 51% at 1 h (24%; 79%; ..; ..), 70% at 3 h (61%; 79%; ..; ..)</td>
<td>Low</td>
</tr>
<tr>
<td>Ploux&quot;47 Prospective&quot; Ten suspected infection (ten pacemakers), 40 controls (40 pacemakers)</td>
<td>Lead culture or follow-up</td>
<td>Lead' (six of ten): (100%; 93%; 66%; 100%)</td>
<td>Low</td>
</tr>
<tr>
<td>Sarrazin&quot;48 Prospective&quot; 42 suspected infection (25 pacemakers, 17 ICDs), 24 controls (24 at 4–8 weeks post-implant [six pacemakers, six ICDs], 12 at 6 months post-implant [ten pacemakers, two ICDs])</td>
<td>Surgery or follow-up</td>
<td>Device' (36 of 42): (89%; 86%; ..; ..); acute control (12 of 12): mild uptake; chronic control (12 of 12): no abnormal uptake</td>
<td>Low</td>
</tr>
<tr>
<td>Tili&quot;49 Retrospective&quot; 40 suspected infection (30 pacemakers, ten ICDs), 40 controls (37 pacemakers, three ICDs)</td>
<td>Device culture or at least 1-year clinical follow-up</td>
<td>Infection of box or lead' (18 of 40): 90% (83%; 95%; 94%; 88%); extracardiac complications (11 of 40): 28% identified; controls (40 of 40): 100% 18F-FDG-negative</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Ventricular assist device</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dell’Aquila&quot;50 Retrospective&quot; 40 suspected infection</td>
<td>Bacteriological cultures, surgery, and follow-up</td>
<td>Infection (30 of 40): (100%; 80%; 94%; 100%)</td>
<td>Low</td>
</tr>
<tr>
<td>Inclusion</td>
<td>Number and type of cases</td>
<td>Gold standard</td>
<td>Diagnostic accuracy (sensitivity; specificity; PPV; NPV)</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------------------</td>
<td>---------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Leucocyte scintigraphy with $^{99m}$Tc-HMPAO and SPECT/CT, n=283 (283 cases and 0 controls)</td>
<td>&gt;50% prosthetic valve</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Erba**$^{51}$  
Retrospective  
131 suspected infective endocarditis |  
Microbiology and 12-month follow-up |  
Infective endocarditis confirmed (51 of 131 and 35 of 51 prosthetic valves): (90%; 36%; 85%; 47%) |  
Low |
|  
**Hyafi**$^{52}$  
Retrospective  
42 suspected infective endocarditis' (42 prosthetic valves, TEE inconclusive) |  
Surgery (n=10) or follow-up (n=32) |  
Perivalvular abscess (6–12 of 43): (83–100%; 78–87%; 43–71%; 93–100%) |  
Low |
|  
**Rouzet**$^{53}$  
Retrospective  
39 suspected infective endocarditis (39 prosthetic valves) |  
Modified Duke criteria and 3-month follow-up |  
Definite infective endocarditis (nine of 39): 86% (64%; 100%; 81%) |  
Low |
|  
Pacemaker or ICD |  
**Erba**$^{53}$  
Retrospective  
63 suspected infection (49 pacemakers, 14 ICDs) |  
Microbiology and 12-month follow-up |  
Device-associated (32 of 63): 97% (94%; 100%; 100%; 94%) |  
Low |
|  
Ventricular assist device |  
**Litzler**$^{54}$  
Retrospective  
Eight suspected infection (eight left ventricular assist devices, of which five scanned twice) |  
Microbiology or follow-up |  
Left ventricular assist device (eight of 13 scans): (100%; 100%; 100%; 100%); extracardiac complications (three of 13 scans); unsuspected findings in 23% |  
Low |

**Table 1**

Clinical studies of imaging in infective endocarditis

Quality rated according to the GRADE approach. ECG=electrocardiogram. MDCTA=multidetector CT angiography. NPV=negative predictive value. PPV=positive predictive value. TEE=transesophageal echocardiography. $^{18}$F-FDG=$^{18}$F-fluorodeoxyglucose. ICD=implantable cardiac device. $^{99m}$Tc-HMPAO=$^{99m}$Tc-hexamethylpropylene-amino oxime. SPECT=single-photon emission CT. NNI=number needed to investigate.

*According to modified Duke criteria (for other studies, no clear indications were provided as to which criteria for clinical suspicion of infective endocarditis were used).
†Studies lacking adequate patient preparation of more than 6 h fasting and a low-carbohydrate, fat-allowed diet to suppress the physiological uptake of $^{18}$F-FDG in the heart.
‡Cases given as ranges between recalculation of values from original study based on definitions used in this Review and the numbers given in the original study.
Chapter 2

Native valve endocarditis

We included a prospective cohort study addressing the value of MDCTA in diagnosis of native valve endocarditis in patients suspected of infective endocarditis. Diagnosis of infective endocarditis overall had 97% sensitivity, 88% specificity, and 97% positive and 88% negative predictive values compared with TEE. Diagnosis of the presence of a vegetation had 96% sensitivity, 100% specificity, and 100% positive and 97% negative predictive values. For diagnosis of perivalvular infection, sensitivity, specificity, and positive and negative predictive values were all 100%. Because of the few patients included, the benefit of MDCTA in diagnosis of valvular dehiscence (n=1) and cusp perforation (n=1) could not be determined.

For 18F-FDG PET/CT, we included nine studies regarding patients with native valves. Seven studies included more than 50% of patients with suspected native valve endocarditis (two retrospective cohorts and four prospective cohorts, with one matched case-control study within a prospective cohort). Six studies included only patients with definite infective endocarditis according to the modified Duke criteria. The sensitivity of 18F-FDG PET/CT for diagnosis of native valve endocarditis was 14% (one of seven patients) with an appropriate pre-scan diet and 6% (two of 34 patients) without.

Overall, diagnosis of extracardiac complications had 14–100% sensitivity, 80% specificity, and 52–90% positive and 100% negative predictive values. Addition of 18F-FDG PET/CT to the standard work-up of infective endocarditis helped to detect 15–32% of additional potential infectious foci (number needed to investigate of seven), enough to modify treatment in 35% of patients and halve the relapse rate.

An additional study investigated patients with Gram-positive bacteraemia and at least one risk factor for a metastatic infection. Sensitivity for diagnosis of infective endocarditis in this study was 39%, suggesting that 18F-FDG PET/CT was not able to diagnose infective endocarditis reliably in patients with a relatively low risk for infective endocarditis.

Prosthetic valve endocarditis

We included three studies addressing the value of MDCTA in diagnosis of prosthetic valve endocarditis. Two studies included more than 50% of patients with suspected prosthetic valve endocarditis. The population of the prospective cohort consisted of patients suspected of infective endocarditis, and the population of the prospective cross-sectional study consisted of patients suspected of infective endocarditis based on the modified Duke criteria.

The sensitivity of MDCTA in diagnosis of prosthetic valve endocarditis overall was 93%. When added to standard diagnostic work-up of suspected infective endocarditis, an overall sensitivity of 100% and specificity of 83% for prosthetic valve endocarditis was obtained, with a change in treatment strategy in 25% of patients. Sensitivity was 100% for the diagnosis of perivalvular infection. For MDCTA in addition to the standard diagnostic work-up for suspected infective endocarditis, sensitivity was 100% and specificity 91%. The addition of MDCTA to standard work-up (including echocardiography) in patients suspected of endocarditis detected an additional three (37%) of eight patients with vegetations.
We included 13 studies11, 21, 24, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 addressing the value of 18F-FDG PET/CT in diagnosis of infective endocarditis, extracardiac complications, or both, in patients with prosthetic valves. Eight studies11, 34, 35, 36, 37, 38, 39, 40 included more than 50% of patients with suspected prosthetic valve endocarditis: these studies consisted of a case series,37 two retrospective cohorts,36, 38 one case-control study40 in a retrospective cohort, and four prospective cohorts.11, 34, 35, 39 All studies included patients with suspected infective endocarditis, which was on the basis of the modified Duke criteria in three studies.11, 35, 36 One study40 additionally included a control group, consisting of patients with a prosthetic valve in situ without suspicion of infective endocarditis.

For 18F-FDG PET/CT, diagnosis of infective endocarditis had 73–100% sensitivity, 71–100% specificity, and 67–100% positive and 50–100% negative predictive values.11, 34, 36, 37, 38, 39, 40 Addition of 18F-FDG PET/CT to the modified Duke criteria13 increased sensitivity from 52–70% to 91–97%.11, 39 18F-FDG PET/CT showed similar sensitivities for vegetations, perivalvular sequelae, and prosthetic valve dehiscence compared with echocardiography.11 Furthermore, both imaging modalities provided complementary information: seven (23%) of 30 patients had a positive 18F-FDG PET/CT and negative echocardiogram and eight (27%) of 30 had a negative 18F-FDG PET/CT and positive echocardiogram.11 In diagnosis of extracardiac complications, 18F-FDG PET/CT detected unexpected additional potential infectious foci in 11–24% of patients.35, 39 Controls had low 18F-FDG uptake.40

For 18F-FDG PET/CT angiography, diagnosis of infective endocarditis had 91% sensitivity, 91% specificity, and 93% positive and 88% negative predictive values.29

We included three studies38, 51, 52 addressing the value of 99mTc-HMPAO-labelled leucocyte scintigraphy with SPECT/CT in diagnosis of infective endocarditis or extracardiac complications in patients with prosthetic valves. These studies consisted of three retrospective cohorts.38, 51, 52 The populations studied included patients with definite infective endocarditis38, 51 or suspected infective endocarditis according to the modified Duke criteria but with inconclusive echocardiography results.52 Diagnosis of infective endocarditis overall had 64–90% sensitivity, 36–100% specificity, and 85–100% positive and 47–81% negative predictive values.38, 51 Diagnosis of abscess formation had 83–100% sensitivity, 78–87% specificity, and 43–71% positive and 93–100% negative predictive values.52

ICD or pacemaker-related infections
We included nine studies41, 42, 43, 44, 45, 46, 47, 48, 49 addressing the value of 18F-FDG PET/CT in diagnosis of ICD and pacemaker infections and related extracardiac complications. These studies consisted of two retrospective42, 49 and seven prospective41, 43, 44, 45, 46, 47, 48 cohort studies, and included patients with suspected device infection41, 43, 44, 46, 47, 48, 49 and patients with suspected infective endocarditis according to the modified Duke criteria.49 Five studies42, 43, 46, 47, 48 included controls. Diagnosis of cardiac device-related infection had 80–89% sensitivity, 86–100% specificity, and 94–100% positive and 85–88% negative predictive values.42, 43, 46, 48, 49 Diagnosis of cardiac device-related infective endocarditis had 31% sensitivity and 63% specificity in a study of 21 patients.44 Diagnosis of lead infection had 24–100% sensitivity, 79–100% specificity, and 66–100% positive and 73–100% negative predictive values,43, 45, 46 and diagnosis of pocket infection had 87–91% sensitivity, 93–100% specificity,
Chapter 2

and 97% positive and 81% negative predictive values. Controls showed only mild $^{18}$F-FDG uptake around the device in the acute phase less than 2 months after implantation, and no uptake more than 6 months after implantation. When patients were scanned 3 h after the $^{18}$F-FDG injection, sensitivity and specificity for the device were 91% and 100%, 61% and 79% for the leads, and 94% and 100% for the pocket, respectively, which was substantially higher (significantly so for the leads) than with the standard 1-h interval.

One retrospective cohort study addressed the value of $^{99m}$Tc-HMPAO-labelled leucocyte scintigraphy with SPECT/CT in diagnosis of ICD-related and pacemaker-related infections, which had 94% sensitivity, 100% specificity, and 100% positive and 94% negative predictive values.

**Ventricular assist device-related infections**

One retrospective cohort study addressed the value of $^{18}$F-FDG PET/CT in diagnosis of ventricular assist device-related infection in a population with clinical suspicion hereof. This study reported 100% sensitivity, 80% specificity, and 94% positive and 100% negative predictive values.

We included a study addressing the value of $^{99m}$Tc-HMPAO-labelled leucocyte scintigraphy with SPECT/CT in diagnosis of ventricular assist device-related infections and extracardiac complications. The population of this retrospective cohort study consisted of patients suspected of ventricular assist device-related infection. The sensitivity, specificity, and positive and negative predictive values for ventricular assist device-related infection were all 100%. Furthermore, in 23% of scans, scanning of the thorax and abdomen led to the detection of unsuspected extracardiac foci.

**Discussion**

**Imaging modalities**

Each imaging modality reviewed provides specific diagnostic information concerning sequelae of infective endocarditis. Both CT and MRI provide high-quality anatomical information, whereas $^{18}$F-FDG PET/CT and leucocyte scintigraphy provide functional data. In general, included studies were non-echo driven.

Imaging techniques vary in requirements, benefits, and limitations (table 2). MDCTA has consistently been shown to have added diagnostic value in the work-up of patients suspected of infective endocarditis. MDCTA offers high-resolution cardiac anatomical information in both native valve endocarditis and prosthetic valve endocarditis, and visualises infective endocarditis through identification of valve perforations, perivalvular extension of infection (abscesses, pseudo-aneurysms, fistulas, and valvular dehiscence with paravalvular leakage), and sometimes vegetations. MDCTA shows similar diagnostic value to TEE in the overall evaluation of infective endocarditis. However, it provides improved visualisation of perivalvular extension of infective endocarditis and less accurate visualisation of
Therefore, MDCTA together with TEE is advisable for optimal management of patients with infective endocarditis, especially for suspected perivalvular extension of infection. Moreover, coronary angiography can be omitted in preoperative planning if MDCTA is done. A native MDCTA (ie, without contrast) should be considered in patients with contraindications to contrast media (table 2).

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>TEE</th>
<th>ECG-gated MDCTA</th>
<th>ECG-gated MRI</th>
<th>¹⁸F-FDG PET/CT</th>
<th>Leucocyte scintigraphy with SPECT/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophageal pathology</td>
<td>Good</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Pregnancy, iodinated contrast allergy, renal insufficiency (eGFR &lt;60 mL/min per 1.73m²)</td>
<td>2 h fasting, intravenous contrast</td>
<td>Intravenous contrast</td>
<td>80 min (60 min preparation, 20 min scan time)</td>
<td>Moderate (4 mSv)</td>
<td>Moderate (4 mSv)</td>
</tr>
<tr>
<td>Pregnancy, most ICDs and pacemakers, gadolinium allergy, a renal insufficiency (eGFR &lt;30 mL/min per 1.73m²), claustrophobia</td>
<td>Intravenous contrast</td>
<td>26 h fasting, 24 h low-carbohydrate, fat-allowed diet</td>
<td>Functional data (molecular)</td>
<td>Functional data (molecular)</td>
<td></td>
</tr>
<tr>
<td>Pregnancy, uncontrolled diabetes</td>
<td>26 h fasting, 24 h low-carbohydrate, fat-allowed diet</td>
<td>Functional data (molecular)</td>
<td>Functional data (molecular)</td>
<td>Functional data (molecular)</td>
<td></td>
</tr>
<tr>
<td>Patient preparation</td>
<td>4–6 h fasting</td>
<td>2 h fasting, intravenous contrast</td>
<td>≥30 min</td>
<td>Moderate (4 mSv)</td>
<td>Moderate (4 mSv)</td>
</tr>
<tr>
<td>Monitoring of unstable patients possible</td>
<td>80 min (60 min preparation, 20 min scan time)</td>
<td>24 h (four visits, two scans)</td>
<td>24 h (four visits, two scans)</td>
<td>24 h (four visits, two scans)</td>
<td></td>
</tr>
<tr>
<td>Anatomical images</td>
<td>Good</td>
<td>Very good</td>
<td>Good</td>
<td>Good</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Functional images</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>ECG gating required</td>
<td>Not applicable</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Duration</td>
<td>30 min</td>
<td>15 min</td>
<td>≥30 min</td>
<td>80 min (60 min preparation, 20 min scan time)</td>
<td>24 h (four visits, two scans)</td>
</tr>
<tr>
<td>Radiation dose</td>
<td>None</td>
<td>High (10 mSv)</td>
<td>None</td>
<td>Moderate (4 mSv)</td>
<td>Moderate (4 mSv)</td>
</tr>
<tr>
<td>Quantification possibilities</td>
<td>Possible</td>
<td>Not possible</td>
<td>Excellent</td>
<td>Good</td>
<td>Possible</td>
</tr>
<tr>
<td>Diagnostic accuracy</td>
<td>Sensitive and specific</td>
<td>Sensitive and specific</td>
<td>Unclear</td>
<td>Sensitive</td>
<td>Specific</td>
</tr>
<tr>
<td>Susceptibility to artifacts</td>
<td>Metallic (very susceptible)</td>
<td>Metallic (moderately susceptible)</td>
<td>Metallic (moderately susceptible, cardiac and respiratory (moderately susceptible)</td>
<td>Cardiac and respiratory (slightly susceptible)</td>
<td>Metallic (slightly susceptible)</td>
</tr>
<tr>
<td>Suitability for therapy monitoring</td>
<td>Suitable</td>
<td>Not suitable</td>
<td>Unclear</td>
<td>Very suitable</td>
<td>Dependent on situation</td>
</tr>
<tr>
<td>Availability</td>
<td>Widely available</td>
<td>Widely available</td>
<td>Moderately available</td>
<td>Moderately available</td>
<td>Limited availability</td>
</tr>
<tr>
<td>Costs</td>
<td>Approximately €100</td>
<td>€300–400</td>
<td>€500–800</td>
<td>€800–1200</td>
<td>€600–800</td>
</tr>
</tbody>
</table>
Chapter 2

<table>
<thead>
<tr>
<th>TEE</th>
<th>ECG-gated MDCTA</th>
<th>ECG-gated MRI</th>
<th>$^{18}$F-FDG PET/CT</th>
<th>Leucocyte scintigraphy with SPECT/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limitations</td>
<td>Completely operator-dependent analysis</td>
<td>Frequent contraindications</td>
<td>Noisiness for patients</td>
<td>Pathological conditions mimicking pattern of focally increased uptake, difficulty to discriminate aseptic inflammation from infectious process (insufficient clear interpretation criteria)</td>
</tr>
</tbody>
</table>

**Table 2**
Requirements, benefits, and limitations of imaging techniques

TEE=transesophageal echocardiography. ECG=electrocardiogram. MDCTA=multidetector CT angiography. $^{18}$F-FDG=$^{18}$F-fluorodeoxyglucose. SPECT=single-photon emission CT. eGFR=estimated glomerular filtration rate. ICD=implantable cardioverter defibrillator.

$^{18}$F-FDG PET/CT is evolving as an important supplementary method in difficult-to-diagnose cases of suspected infective endocarditis, and is able to provide functional data on the extent of infective endocarditis before structural damage ensues using a single test.\(^{21, 24, 58}\) For cardiac infection, the added diagnostic value of $^{18}$F-FDG PET/CT has been demonstrated in patients suspected of prosthetic valve endocarditis or infections related to ICDs, pacemakers, or ventricular assist devices. Importantly, controls had low $^{18}$F-FDG uptake.\(^{40}\) For extracardiac infection, $^{18}$F-FDG PET/CT detects a significant number of clinically relevant foci in patients with known or suspected native valve endocarditis or prosthetic valve endocarditis.\(^{21, 39}\) Moreover, whole body imaging by $^{18}$F-FDG PET/CT can provide important clinical information concerning the presence of portal of entry and occult predisposing lesions such as primary tumours.\(^{59}\) This information can help to diagnose infective endocarditis or provide additional information about its devastating cardiac sequelae, improves the detection of abscesses that need to be drained, and can aid in the decision process to opt for cardiac surgery. Indeed, therapy was changed in 35% of cases when an $^{18}$F-FDG PET/CT was done.\(^{25}\) The addition of $^{18}$F-FDG PET/CT to the diagnostic work-up has been shown to be cost-effective for patients with Gram-positive bacteraemia with a high risk of development of metastatic infectious foci,\(^{12}\) and for patients with an ICD and suspected infective endocarditis.\(^{60}\)

Notwithstanding these results, uncertainty remains about the optimal use of $^{18}$F-FDG PET/CT in the diagnostic work-up of infective endocarditis. Both false negative and false positive results have been reported. False negative results might be due to prior administration of antimicrobial therapy,\(^{41, 44, 61, 62, 63}\) small size of vegetations,\(^{49}\) and elevated blood glucose concentration.\(^{58}\) False positive results might be a result of recent cardiac procedures,\(^{48, 58, 64, 65}\) recent thrombi,\(^{61, 66}\) and inadequate patient preparation (e.g., not enforcing a low-carbohydrate, fat-allowed diet). Additionally, interpretation of $^{18}$F-FDG PET/CT is not straightforward because the distribution and pattern of $^{18}$F-FDG uptake rather than the intensity...
only should be used as a diagnostic criterion of infection. Furthermore, accuracy might depend on the time of scanning.67

To further increase the accuracy of 18F-FDG PET/CT in infective endocarditis, CT angiography instead of low-dose CT could be applied for the cardiac segment in prosthetic valve endocarditis.39 Furthermore, preparation of patients with a fast of at least 6 h and a low-carbohydrate, fat-allowed diet appears to be crucial. In the study33 investigating patients with Gram-positive bacteraemia, insufficient patient preparation and the absence of ECG-triggered scanning might have contributed to its low sensitivity. Additionally, increased waiting time before scans—ie, more than 1 h post-infusion of 18F-FDG—might improve accuracy,44, 46, 68 although studies in other inflammatory and infectious diseases argue against this.69, 70 Dual-timepoint scanning with 18F-FDG PET/CT can probably not differentiate between malignant, inflammatory, and infectious processes, but can help to compensate for background uptake of 18F-FDG, increasing diagnostic accuracy of any abnormality. Insufficient evidence exists to support dual-timepoint imaging, nor to indicate the optimal timing. Altogether, development of interpretation criteria for positivity and negativity in the near future is important.

Leucocyte scintigraphy with SPECT/CT is highly specific for infection because granulocytes are recruited to the site of infection. Vegetations contain few granulocytes,71 which means a positive leucocyte scintigraphy probably visualises granulocytes in the inflamed tissue surrounding the valve involved in infective endocarditis, as well as those present during the resolving phase, and not specifically the granulocytes in the vegetations. The added value of this imaging technique has been demonstrated in cases with persisting diagnostic uncertainty for prosthetic valve endocarditis, ICD-related or pacemaker-related, and ventricular assist device-related infective endocarditis.38, 51, 52, 53, 54 Furthermore, leucocyte scintigraphy with SPECT/CT is able to detect extracardiac complications,51 excluding ophthalmitis and intracerebral infection.53 For infective endocarditis, a positive leucocyte scintigraphy with SPECT/CT correlates with high infectious activity and predicts poor prognosis.52 Additionally, a positive scan could point towards abscess and perivalvular infection and therefore indicates the requirement of surgical intervention.52, 72 By contrast, negative scans indicate the absence of infectious activity,72 and are consistently associated with a favourable clinical outcome once antimicrobial therapy alone is initiated.53, 72 Furthermore, negative scans seem to reliably exclude extensive perivalvular infection and the need for surgery in patients with definite infective endocarditis.52, 73 The specificity of leucocyte scintigraphy with SPECT/CT could be particularly useful when diagnostic uncertainty remains after 18F-FDG PET/CT.74, 75, 76 For patients with suspected prosthetic valve endocarditis, a sequential work-up strategy of 18F-FDG PET and leucocyte scintigraphy with SPECT/CT has been proposed if echocardiography is inconclusive.38 In this work-up, patients with negative 18F-FDG PET/CT as well as those showing an intense focal 18F-FDG PET/CT signal in the area of the cardiac valves do not need additional scanning. However, patients with low, diffuse 18F-FDG uptake around the cardiac prosthesis need leucocyte scintigraphy with SPECT/CT, particularly if scanned in the first 2 months after cardiac surgery.38 We also adopted this stepwise allocation of imaging techniques because use of imaging with high specificity in a patient group preselected by high-sensitivity imaging is clinically important. Leucocyte scintigraphy
has some limitations in clinical practice (laborious preparation, four patient visits required, and risk of missing small infectious foci), whereas $^{18}$F-FDG PET/CT provides better spatial resolution, improved opportunities for quantification, whole body imaging for identification of extracardiac complications, more feasible logistics, and increased comfort for patients (table 2).

Anecdotal data report the use of MRI to diagnose infective endocarditis, but no large studies have been done so far.\textsuperscript{77, 78, 79, 80} The data suggest that cardiac MRI might be a useful addition but not a substitute in the assessment of infective endocarditis.\textsuperscript{79, 80} However, existing data are insufficient to define a diagnostic role for MRI in the diagnostic work-up of patients suspected of infective endocarditis. The most substantial obstacle is artifacts by prosthetic material (table 2).

**Disease entities**

MDCTA is an important addition to the standard work-up based on the modified Duke criteria for diagnosis of native valve endocarditis. This imaging modality is especially accurate for detection of perivalvular infection, but less accurate for detection of vegetations. MDCTA is sensitive and therefore better able to exclude than to confirm native valve endocarditis.

Insufficient data are available for the ability of $^{18}$F-FDG PET/CT to detect native valve endocarditis. $^{18}$F-FDG PET/CT has added value for detection—and even more for exclusion—of extracardiac complications of native valve endocarditis, particularly in patients with high embolisation risk or clinical suspicion of an embolic event.

$^{18}$F-FDG PET/CT has added value for detection—and even more for exclusion—of extracardiac complications of native valve endocarditis, particularly in patients with high embolisation risk or clinical suspicion of an embolic event.

**Disease entities**

MDCTA, $^{18}$F-FDG PET/CT (with angiography), and leucocyte scintigraphy with SPECT/CT show added value to the standard work-up for diagnosis of prosthetic valve endocarditis. MDCTA is both sensitive and specific for detection of perivalvular infection mainly, but also of vegetations. Its addition to the standard work-up leads to a change of treatment strategy in 25% of patients\textsuperscript{18}—particularly when added to the standard work-up for infective endocarditis.

$^{18}$F-FDG PET/CT is less accurate for detection of prosthetic valve endocarditis than is MDCTA. However, the sensitivity of the combination of the modified Duke criteria and $^{18}$F-FDG PET/CT results is higher than is the sensitivity of the modified Duke criteria alone.\textsuperscript{11} Moreover, both MDCTA and $^{18}$F-FDG PET/CT provide complementary information: MDCTA contributes high-resolution anatomical information whereas $^{18}$F-FDG PET/CT contributes functional information and has the ability to detect extracardiac complications. Consequently, the combination of the two imaging modalities provides high diagnostic accuracy.\textsuperscript{19}

Leucocyte scintigraphy with SPECT/CT has added value in the diagnosis of prosthetic valve endocarditis because it is highly specific. However, leucocyte scintigraphy with SPECT/CT has insufficient sensitivity and has several limitations regarding preparation and patient comfort. Therefore, we believe leucocyte scintigraphy with SPECT/CT should be part of a sequential strategy for patients suspected of prosthetic valve endocarditis in whom echocardiography is inconclusive.\textsuperscript{38} In these patients, we recommend $^{18}$F-FDG PET as first-line imaging technique because of its high sensitivity for active infection. If $^{18}$F-FDG PET/CT findings are inconclusive, leucocyte scintigraphy with SPECT/CT should be considered because
of its high specificity. Leucocyte scintigraphy with SPECT/CT is preferred over \(^{18}\)F-FDG PET/CT for patients who have had cardiac surgery within the past month because of the high chance of false-positive results.

Both \(^{18}\)F-FDG PET/CT and leucocyte scintigraphy with SPECT/CT show added value for diagnosis of ICD-related or pacemaker-related infection. Leucocyte scintigraphy is specific for infection. By contrast, \(^{18}\)F-FDG PET/CT has high sensitivity and negative predictive value, and consequently can rule out infection. \(^{18}\)F-FDG PET/CT is especially useful for diagnosis of pocket infection, but is less reliable for diagnosis of lead infection or device-related infective endocarditis. Nevertheless, in the clinical context of suspected device-related infection, increased and heterogeneous \(^{18}\)F-FDG uptake along a lead appears to be a reliable sign of active infection.\(^{47}\) Furthermore, presence of a focal hotspot is considered the best criterion of lead infection.\(^{61}\) Accuracy of \(^{18}\)F-FDG PET/CT for detection of cardiac foci depends on patient preparation, scanning protocol used, and the interval post-implantation. Control patients with an ICD or pacemaker and without suspected infection had mild \(^{18}\)F-FDG uptake in the acute phase (≤2 months after cardiac surgery) but no uptake more than 6 months after cardiac surgery.\(^{48}\)

Both \(^{18}\)F-FDG PET/CT and leucocyte scintigraphy with SPECT/CT seem to be beneficial in the diagnosis of cardiac and extracardiac ventricular assist device-related infection.\(^{39, 54}\) \(^{18}\)F-FDG PET/CT is especially sensitive for device infection, and has a high negative predictive value.\(^{50}\) Leucocyte scintigraphy with SPECT/CT is reported to detect an extra 23% of otherwise unsuspected extracardiac complications when the thorax and abdomen are scanned, and when added to the standard clinical work-up.\(^{54}\)

**Limitations**

According to GRADE criteria, all studies included in this systematic review had to be classified as of low or very low quality. Reasons included the absence of random sequence generation, no masking for imaging technique or outcome assessment, mixed study populations, and no dose-response gradient addressed (appendix). Additional limitations came from the heterogeneity of the included studies, with regard to the study population, gold standard, and imaging protocol used (appendix).

**Proposed algorithm**

Despite the need for additional prospective comparative data for specific indications and optimal timing of the reviewed imaging modalities, existing evidence justifies the addition of these diagnostic tools to the modified Duke criteria to diagnose infective endocarditis reliably. We propose a diagnostic algorithm (figure 2) based on available evidence and multidisciplinary expert opinion of the authors. Imaging techniques with high sensitivity are required at the start of the diagnostic work-up, whereas high specificity is needed later on. The proposed algorithm is largely in line with existing published guidelines, but more detailed.\(^{5, 14, 81}\) Obviously, because of the overall low quality of included studies according to the GRADE criteria, and the fact that imaging modalities might be difficult to use in unstable patients, the proposed algorithm is meant to provide guidance for health-care professionals treating patients with suspected infective endocarditis, and should always be applied using good clinical reasoning and common sense.\(^{5, 81}\)
Laboratory tests include rheumatoid factor, urine sediment, blood culture, and molecular testing (for culture-negative organisms). TEE follows TTE standard in case of positive and non-diagnosis TTE, negative TTE but sustained clinical suspicion, Staphylococcus aureus, or intracardiac prosthetic material (e.g., prosthetic valve, pacemaker, ICD). Clinical suspicion is low when an alternative diagnosis has been found, performance of supplementary examination is negative, or suspicion of infective endocarditis is lowered. Clinical suspicion is sustained when suspicion of infective endocarditis remains, irrespective of negative supplementary examination, leading to additional examination. TEE and MDCTA are positive when results are good quality and show clear signs of infective endocarditis sequelae, negative when results are good quality and show no signs of infective endocarditis sequelae, and marked as non-diagnosis when results are poor quality and show no signs of infective endocarditis sequelae. 18F-FDG PET is positive in cases of high focal 18F-FDG uptake, negative in cases of no 18F-FDG uptake, and marked as non-diagnosis in cases of low diffuse 18F-FDG uptake. Yellow circles indicate the end of a diagnostic pathway, when efforts to diagnose (extracardiac complications of) infective endocarditis can be ceased. However, this decision should always be critically re-evaluated in patients without a satisfactory alternative diagnosis and remaining signs and symptoms. BSAC=British Society for Antimicrobial Chemotherapy. 18F-FDG=18F-fluorodeoxyglucose. MDCTA=electrocardiogram-gated multidetector CT angiography. TTE=transthoracic echocardiogram. TEE=transesophageal echocardiogram. *Allocation specifically for the detection of extracardiac foci.

For MDCTA we propose the following indications: (1) the presence of anatomic obstacles (jaws, neck, upper gastrointestinal tract) precluding TEE, and intolerance to or refusal of the TEE probe; (2) the presence of metallic material in the heart leading to poor visualisation of the endocardium by TEE.
(which can be better visualised by MDCTA); (3) an initial negative or inconclusive TEE and sustained suspicion of infective endocarditis;\textsuperscript{17, 29} (4) suspected perivalvular infection; and (5) planned cardiac surgery to optimise the surgeon’s insight in the local anatomy. We suggest MDCTA be done within 7 days of suspicion of infective endocarditis. Health-care professionals should keep in mind that MDCTA can show physiological post-surgical fluid collections, possibly interfering with infective endocarditis diagnosis.

We propose addition of 18F-FDG PET/CT to the diagnostic work-up of all cases with proven native valve endocarditis and intracardiac prosthetic material-related infective endocarditis to identify extracardiac complications. For this reason 18F-FDG PET/CT should be done after infective endocarditis has been proven by MDCTA. Even though the added value of 18F-FDG PET/CT for the detection of extracardiac complications has only been shown for native valve endocarditis and prosthetic valve endocarditis, this recommendation might be useful for all patients with infective endocarditis. Moreover, we suggest doing 18F-FDG PET/CT in patients with sustained suspicion of intracardiac prosthetic material-related infective endocarditis after negative or inconclusive standard work-up to detect cardiac foci.\textsuperscript{83, 84} An exception to this is patients who have had cardiac surgery within the past month, in accordance with the most widely accepted guideline for use of 18F-FDG in inflammation and infection.\textsuperscript{85} This limit is debatable, as other studies provide data in favour of extension of the interval to up to 2 months,\textsuperscript{38, 48} whereas in prosthetic vascular grafts the intensity of 18F-FDG uptake did not change over time.\textsuperscript{86, 87}

For native valve endocarditis, after negative or inconclusive work-up with TEE (and MDCTA) but sustained suspicion of infective endocarditis, repetition of TEE and MDCTA is advised. Although no existing evidence supports the use of 18F-FDG PET/CT in native valve endocarditis, its use can be considered in case of diagnostic difficulties and sustained suspicion of infective endocarditis after inconclusive TEE and MDCTA—analogous to its diagnostic value in intracardiac prosthetic material-related infective endocarditis. Clearly, echocardiography and MDCTA remain the first choice. We recommend that 18F-FDG PET/CT is done within 7 days of suspicion of infective endocarditis and that patients are prepared with a fast of at least 6 h and a low-carbohydrate, fat-allowed diet to limit physiological myocardial uptake of 18F-FDG.

In centers with access to a hybrid PET/CT camera system, 18F-FDG PET/CT should be done together with MDCTA. This one-stop approach increases convenience for the patient, and speeds up reporting of the scans, reducing imaging delay.

We propose specific use of leucocyte scintigraphy with SPECT/CT in high-risk patients with intracardiac prosthetic material after inconclusive standard work-up and inconclusive 18F-FDG PET/CT.\textsuperscript{72, 76} Furthermore, we propose the use of leucocyte scintigraphy with SPECT/CT less than 1 month after cardiac surgery after inconclusive MDCTA, instead of 18F-FDG PET/CT,\textsuperscript{5} because of the non-specific 18F-FDG uptake due to inflammation in this time period.
**Future perspectives**

Despite the overall low quality of the analysed studies, the presented results are promising in light of the devastating course of this disease and increasing incidence of infective endocarditis. Larger prospective studies are needed that directly compare different imaging techniques. Future studies should further define the exact role and position of MDCTA, MRI, $^{18}$F-FDG PET/CT, and leucocyte scintigraphy with SPECT/CT in the diagnostic work-up, but also in therapeutic follow-up of patients with known or suspected infective endocarditis (panel). Focus on diagnosis of infective endocarditis in patients with intracardiac prosthetic material—and more specifically on the different subgroups with respect to the type of implanted material—is warranted. Future studies could identify new indications for existing imaging techniques, and identify a role for novel imaging techniques. For example, three-dimensional TEE and novel hybrid imaging modalities such as simultaneous PET and MRI could prove valuable modalities in diagnosis of infective endocarditis.

**Panel: Specific questions for future research**

$^{18}$F-FDG = $^{18}$F-fluorodeoxyglucose. SPECT = single-photon emission CT. MDCTA = multidetector CT angiography.

- What is the range of normal and abnormal patterns of cardiac $^{18}$F-FDG uptake?²⁴⁰
- To what extent is $^{18}$F-FDG PET/CT useful for diagnosis of native valve endocarditis?²⁴⁰
- What is the optimal timeframe for $^{18}$F-FDG PET/CT scanning?²⁹⁵
- Could diagnostic accuracy of $^{18}$F-FDG PET/CT be improved by respiratory gated imaging?²⁰⁷
- What is the cutoff value for increased $^{18}$F-FDG uptake in the differentiation of infection from inflammation?²⁰⁷
- Could diagnostic differentiation between inflammatory and infectious processes be improved by allocation of dual-timepoint $^{18}$F-FDG PET/CT scanning? Which scanning protocol should therefore be used?²⁰⁷
- Can more specific tracers improve the diagnostic accuracy of PET/CT scanning?²⁰⁷
- What is the accuracy of $^{18}$F-FDG PET/CT versus leucocyte scintigraphy for ICD-related and pacemaker-related infection?²⁵⁷
- To what extent does antimicrobial therapy affect sensitivity of $^{18}$F-FDG PET/CT and leucocyte scintigraphy SPECT/CT?²⁵⁷
- Can $^{18}$F-FDG PET/CT,²⁵⁷ leucocyte scintigraphy SPECT/CT, and $^{18}$F-FDG PET/MRI be used to monitor the efficacy of antimicrobial treatment?²⁵⁷
- What is the optimal patient preparation and scanning protocol for myocardial visualisation of infection with $^{18}$F-FDG PET/CT and leucocyte scintigraphy SPECT/CT?²⁵⁷
- What is the sensitivity of $^{18}$F-FDG PET/CT and leucocyte scintigraphy SPECT/CT for specific pathogens?²⁵⁷
- Can leucocyte tracers be developed for PET/CT imaging?²⁵⁷
- Can simultaneously obtained contrast-enhanced $^{18}$F-FDG PET/MRI allow for an equal or better detection of infective endocarditis than $^{18}$F-FDG PET/CT at a significantly lower radiation dose? (However, this imaging modality is not always possible for patients with ICDs, pacemakers, or ventricular assist devices.)²⁵⁷
- Can further improvement in the use of state-of-the-art scanners, and dose reduction strategies such as iterative image reconstruction algorithms, further reduce radiation exposure of MDCTA?²⁵⁷
- Can innovative novel MRI sequences be developed for visualisation of infective endocarditis?²⁵⁷
- What are the the prognostic roles of imaging by MDCTA, $^{18}$F-FDG PET/CT, and leucocyte scintigraphy with SPECT/CT?²⁵⁷

**Conclusion**

Diagnosis of infective endocarditis remains difficult and will be a challenge in coming years because the number of patients with implanted prosthetic material is growing. Imaging has a pivotal role in the management of patients with infective endocarditis: to establish the diagnosis, evaluate the spread of infection, and guide heart surgery.⁹¹ In light of the difficulties encountered in the management of patients with infective endocarditis—especially in those with intracardiac prosthetic material—multimodal imaging can substantially improve diagnostic accuracy. Ongoing technical improvements (e.g., increase in resolution, reduction of scan times and radiation exposure, parallel multimodality, increased accessibility) provide multimodal imaging with high potential to improve quality of care.
MDCTA, ¹⁸F-FDG PET/CT, and leucocyte scintigraphy with SPECT/CT show benefits and added value when combined with the modified Duke criteria, alongside expert clinical judgment. Solid data on MRI are scarce. We emphasise that these imaging modalities should not be used as a substitute for clinical, microbiological, or echocardiographic evaluation, but should instead be integrated in the standard work-up and done together to improve the accuracy of infective endocarditis diagnosis.¹⁹, ²⁴, ³⁸, ⁵², ⁶⁵, ⁷³, ⁹² MDCTA is an exception, and might serve as a substitute for TEE in patients in whom this procedure is not feasible. Echocardiography remains the most important tool for detection of endocardial lesions (vegetations, abscesses, and perforations) and should be done rapidly and repeatedly if infective endocarditis is suspected.⁹³ Concomitant use of imaging techniques providing high-resolution anatomic and metabolic imaging of the heart next to clinical and microbiological data has the potential to increase sensitivity of diagnosis of infective endocarditis to almost 100%—while simultaneously optimising specificity. This improved accuracy is particularly important in patients with intracardiac prosthetic material because the modified Duke criteria are even less sensitive in this group than they are in patients with native valve endocarditis.¹⁹ As a result of the improved diagnosis of both infective endocarditis and extracardiac complications, rapid, accurate, tailor-made therapy can be initiated for more patients. Ultimately, this approach might improve prognosis, avoid unnecessary treatment, and reduce health-care costs for this group of patients.

Contributors
AG conceptualised the study, searched the literature, selected studies, critically appraised the literature, and composed and edited the report. SvA conceptualised the study, selected studies, critically appraised the literature, composed and edited the report, and supervised the report. BS conceptualised the study, selected studies in case of discussion, and composed and edited the report. AWJMG and RHJAS critically appraised the nuclear medicine studies; TPW, NHJP, and RJHB critically appraised the radiological studies. All authors critically reviewed the extracted data, contributed to writing and review of the manuscript, and approved the final version.

Declaration of interests
We declare no competing interests.

Acknowledgments
We thank Sjoukje van der Werf of the medical library of the University Medical Center Groningen (UMCG; Groningen, Netherlands) for helping us to set up the different strings of our literature searches. We thank Fons Klijn, application manager of the UMCG, for helping us with the design of the figures.
References


Chapter 2


58. Millar BC, Prendergast BD, Alavi A, Moore JE. ¹⁸FDG positron emission tomography (PET) has a role to play in the diagnosis and therapy of infective endocarditis and cardiac device infection. Int J Cardiol 2013; 167: 1724–36.


Chapter 2


88. Maurer AH, Burshteyn M, Adler LP, Steiner RM. How to differentiate benign versus malignant cardiac and paracardiac ¹⁸F FDG uptake at oncologic PET/CT. Radiographics 2011; 31: 1287–305.


Supplementary webappendix

Table 3: Extensive overview of search terms: search strategy PubMed and Embase

<table>
<thead>
<tr>
<th>Search Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>('positron emission tomography'/exp OR ('Positron' AND 'Emission' AND Tomograph*):ab,ti OR PET:ab,ti OR 'PET CT':ab,ti OR PETCT:ab,ti)</td>
</tr>
<tr>
<td>OR ('computer assisted tomography'/exp OR (compute* NEXT/3 tomograph*):ab,ti OR tomodensitometry*:ab,ti)</td>
</tr>
<tr>
<td>OR ('nuclear magnetic resonance imaging'/exp OR (magnetic:ab,ti AND resonance:ab,ti) OR MRI:ab,ti OR NMR:ab,ti OR MRA:ab,ti OR MRT:ab,ti OR (MR:ab,ti AND imaging:ab,ti) OR ('magnetization transfer contrast':ab,ti OR 'chemical shift':ab,ti) AND imag*:ab,ti) OR ((MR:ab,ti OR 'proton spin':ab,ti) AND tomograph*:ab,ti) OR zeugmatograph*:ab,ti)</td>
</tr>
<tr>
<td>OR ('leukocyte'/exp OR 'hexamethylpropylene amine oxime technetium tc 99m'/exp OR 'technetium 99m'/exp OR 'leukocyte in 111'/exp OR 'indium 111'/exp OR 'indium':ab,ti OR 111In*:ab,ti OR technetium:ab,ti OR 'white blood cell':ab,ti OR white blood cells:ab,ti OR leukocyte*:ab,ti OR leucocyte*:ab,ti OR 'monoclonal antibody'/exp OR monoclonal:ab,ti OR 'granulocyte antibody'/exp OR 'granulocyte antibodies':ab,ti OR 'granulocyte antibodies':ab,ti) AND ('scintillation camera'/exp OR 'single photon emission computer tomography'/exp OR scint*:ab,ti OR immunoscint*:ab,ti OR radioscan*:ab,ti OR SPECT:ab,ti) OR 'single photon emission computed tomography':ab,ti OR imaging:ab,ti OR scan*:ab,ti OR 'positron emission tomography'/exp OR ('Positron' AND 'Emission' AND Tomograph*):ab,ti OR PET:ab,ti OR 'PET CT':ab,ti OR PETCT:ab,ti)</td>
</tr>
<tr>
<td>AND ('endocarditis'/exp OR endocardit*:ab,ti OR (('infection'/exp OR infect*:ab,ti) AND ('heart valve prosthesis'/exp OR 'artificial heart pacemaker'/exp OR 'implantable cardioverter defibrillator'/exp OR 'heart assist device'/exp OR valve NEXT/3 prosthe*:ab,ti OR pacemaker*:ab,ti OR defibrillator*:ab,ti) OR (assist NEXT/1 device*:ab,ti) OR (cardiac:ab,ti OR cardiovascular:ab,ti) OR cied*:ab,ti OR 'artificial heart ventricle':ab,ti) OR vad*:ab,ti OR 'aortic grafts':ab,ti OR 'aortic root replacement':ab,ti OR (septal:ab,ti OR septum:ab,ti) AND (occlud*:ab,ti OR device*:ab,ti OR closure:ab,ti)) OR (bentall:ab,ti))</td>
</tr>
</tbody>
</table>

('positron emission tomography'/exp OR ('Positron' AND 'Emission' AND Tomograph*):ab,ti OR PET:ab,ti OR 'PET CT':ab,ti OR PETCT:ab,ti) |
| OR ('computer assisted tomography'/exp OR (compute* NEXT/3 tomograph*):ab,ti OR tomodensitometry*:ab,ti) |
| OR ('nuclear magnetic resonance imaging'/exp OR (magnetic:ab,ti AND resonance:ab,ti) OR MRI:ab,ti OR NMR:ab,ti OR MRA:ab,ti OR MRT:ab,ti OR (MR:ab,ti AND imaging:ab,ti) OR ('magnetization transfer contrast':ab,ti OR 'chemical shift':ab,ti) AND imag*:ab,ti) OR ((MR:ab,ti OR 'proton spin':ab,ti) AND tomograph*:ab,ti) OR zeugmatograph*:ab,ti) |
| OR ('leukocyte'/exp OR 'hexamethylpropylene amine oxime technetium tc 99m'/exp OR 'technetium 99m'/exp OR 'leukocyte in 111'/exp OR 'indium 111'/exp OR 'indium':ab,ti OR 111In*:ab,ti OR technetium:ab,ti OR 'white blood cell':ab,ti OR white blood cells:ab,ti OR leukocyte*:ab,ti OR leucocyte*:ab,ti OR 'monoclonal antibody'/exp OR monoclonal:ab,ti OR 'granulocyte antibody'/exp OR 'granulocyte antibodies':ab,ti OR 'granulocyte antibodies':ab,ti) AND ('scintillation camera'/exp OR 'single photon emission computer tomography'/exp OR scint*:ab,ti OR immunoscint*:ab,ti OR radioscan*:ab,ti OR SPECT:ab,ti) OR 'single photon emission computed tomography':ab,ti OR imaging:ab,ti OR scan*:ab,ti OR 'positron emission tomography'/exp OR ('Positron' AND 'Emission' AND Tomograph*):ab,ti OR PET:ab,ti OR 'PET CT':ab,ti OR PETCT:ab,ti) |
| AND ('endocarditis'/exp OR endocardit*:ab,ti OR (('infection'/exp OR infect*:ab,ti) AND ('heart valve prosthesis'/exp OR 'artificial heart pacemaker'/exp OR 'implantable cardioverter defibrillator'/exp OR 'heart assist device'/exp OR valve NEXT/3 prosthe*:ab,ti OR pacemaker*:ab,ti OR defibrillator*:ab,ti) OR (assist NEXT/1 device*:ab,ti) OR (cardiac:ab,ti OR cardiovascular:ab,ti) OR cied*:ab,ti OR 'artificial heart ventricle':ab,ti) OR vad*:ab,ti OR 'aortic grafts':ab,ti OR 'aortic root replacement':ab,ti OR (septal:ab,ti OR septum:ab,ti) AND (occlud*:ab,ti OR device*:ab,ti OR closure:ab,ti)) OR (bentall:ab,ti)) |
Table 4: Inclusion and exclusion criteria for selection of articles

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (≥18 year old)</td>
<td>Preclinical studies</td>
</tr>
<tr>
<td>Original data concerning the accuracy of MDCTA, MRI, FDG-PET/CT or leukocyte scintigraphy in diagnosing IE: both intracardiac infection related to the native heart as well as intracardiac prosthetic material (ICD or pacemaker leads, prosthetic valve with or without vascular graft of ascending aorta, ventricular assist device, atrial/ventricular septum defect patch), both in patients and in controls, both alone and in addition to the standard work-up</td>
<td>Case reports: automatically discarded by PubMed (NOT &quot;case reports&quot;[Filter]) and Embase (NOT 'case report'/de)</td>
</tr>
<tr>
<td>Studies investigating the accuracy of FDG-PET/CT or leukocyte scintigraphy in diagnosing extracardiac complications</td>
<td>Case series with less than five patients</td>
</tr>
<tr>
<td>Studies investigating the accuracy of MDCTA, MRI, FDG-PET/CT or leukocyte scintigraphy in the diagnosis of infections in general, and from which data concerning IE and extracardiac complications can be extracted and analysed separately</td>
<td>Abstracts / conference proceedings</td>
</tr>
<tr>
<td></td>
<td>Prosthetic aortic grafts without aortic valve</td>
</tr>
<tr>
<td></td>
<td>Minimum technical imaging criteria not met</td>
</tr>
<tr>
<td></td>
<td>-MDCTA: use of ECG-triggered 64-slice MDCT</td>
</tr>
<tr>
<td></td>
<td>-MRI: use of ECG-gated 1.5 Tesla scanner</td>
</tr>
<tr>
<td></td>
<td>-FDG-PET/CT: presence of low dose CT accompanying the FDG-PET</td>
</tr>
<tr>
<td></td>
<td>-Leukocyte scintigraphy: use of SPECT/CT</td>
</tr>
</tbody>
</table>

Table 5: GRADE criteria, items assessed to define the risk of bias of included studies

IE = infective endocarditis; CT = computed tomography; FDG-PET/CT = 18F-fluorodeoxyglucose positron emission tomography / computed tomography; TEE = transesophageal echocardiogram; TTE = transthoracic echocardiogram

<table>
<thead>
<tr>
<th>Items assessed to detect reasons to down- or upgrade the evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limitations in the design and implementation of available studies suggesting high likelihood of bias</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Indirectness of evidence</td>
</tr>
<tr>
<td>Unexplained heterogeneity or inconsistency of results</td>
</tr>
<tr>
<td>Imprecision of results</td>
</tr>
<tr>
<td>Large magnitude of effect, confounding factors reducing a demonstrated effect</td>
</tr>
<tr>
<td>Possible confounding factors</td>
</tr>
<tr>
<td>1 versus 2 observers</td>
</tr>
<tr>
<td>Independent observations</td>
</tr>
<tr>
<td>Gold standard</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Probability of IE diagnosis</td>
</tr>
<tr>
<td>TTE and/or TEE</td>
</tr>
<tr>
<td>Technical characteristics of imaging</td>
</tr>
<tr>
<td>Patient preparation</td>
</tr>
<tr>
<td>Time-frame after diagnosis and after start of antimicrobial therapy</td>
</tr>
<tr>
<td>Quality of the image</td>
</tr>
</tbody>
</table>
Panel 2: Limitations

1. No included study had random sequence generation, all studies carry high risk of bias on allocation concealment as the allocation to investigations was mostly based on patient characteristics and the clinically founded opinion of their treating physicians.

2. Participants and personnel could not be blinded for the performed intervention, as different imaging techniques are very characteristic and recognizable.

3. Blinding of outcome assessment was not possible, as different imaging techniques call for a unique assessment. However, outcome assessors could reliably be blinded for the outcome of other performed imaging. This issue is important since these imaging modalities are competitive. In addition, blinding of outcome assessors for the outcome of other clinical information is not important, as this information is needed for the interpretation of imaging. Furthermore, this matches clinical practice, thus increasing external validity.

4. Studies usually included a mixed population of patients. To assess whether a study investigated a well-defined population with respect to the main question of this systematic literature review we reasoned that studies focusing on one type of intracardiac prosthetic material present would answer the research question most reliably.

5. In none of the studies a dose-response gradient was addressed as a dichotomous variable, i.e. whether particular imaging adds to IE diagnosis or not.

6. Studies were heterogeneous concerning the following items:
   - study population included – varying degree of suspicion of IE, different exclusion criteria (e.g. time-point since implantation of intracardiac prosthetic material), presence of control group or not;
   - gold standard – echocardiography (TTE and/or TEE), pathological criteria, length of follow-up;
   - subgroup analyses according to the (kind of) intracardiac prosthetic material;
   - FDG-PET imaging protocol – patient preparation (low carbohydrate/high fat diet), cut-off blood glucose concentration, time-point of scanning after IE suspicion and after injection of FDG, allowance and report of the use of antimicrobial therapy before scanning, accompanying CT and its technical criteria and scanning protocol, quantitative analysis performed on attenuation-corrected (a-c) and/or non a-c images;
   - MDCTA imaging protocol – β-blocker use, 64/256-slice or dual source CT, contrast agent used;
   - Leukocyte scintigraphy imaging protocol – cut-off autologous radiolabeling of leukocyte efficiency, total activity injected, acquisition time.

References


Authors
Anna Gomes, MD¹
Peter Paul van Geel, MD PhD²
Michiel Santing, MD³
Niek H.J. Prakken, MD PhD⁴
Mathilde L. Ruis¹⁴
Sander van Assen, MD PhD⁵
Riemer H.J.A. Slart, MD PhD⁶⁷
Bhanu Sinha, MD PhD¹
Andor W.J.M. Glaudemans, MD PhD⁶

Under review.