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, $^{18}$F-fluorodeoxyglucose ($^{18}$F-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 $^{18}$F-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.
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**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), 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, the incidence of intracardiac material-related infective endocarditis is increasing.

Infective endocarditis leads to substantial mortality (with in-hospital mortality of 14–22% and 1-year mortality of 40%) and morbidity, which can be the result of local spread of infection, metastatic infection, embolic infection, or immune-mediated damage. 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. Clinical diagnosis of infective endocarditis is largely based on the modified Duke criteria, which are incorporated in the infective endocarditis guidelines. 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. Therefore, the sensitivity and specificity of the modified Duke criteria are approximately 80% for native valve endocarditis (with autopsy as the gold standard) 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. 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. Electrocardiogram (ECG)-gated multidetector CT angiography (MDCTA), ECG-gated MRI, $^{18}$F-fluoro-deoxyglucose ($^{18}$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, $^{18}$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.
Chapter 2

Methods

Search strategy and selection criteria
The PRISMA statement and its accompanying Explanations and Elaboration paper 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, F-FDG PET/CT, and leucocyte scintigraphy in diagnosis of infective endocarditis, and of 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, 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 studies11, 18, 21, 24, 25, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54 were included addressed the value of 18F-FDG PET/CT in the diagnosis of infective endocarditis or extracardiac complications. Three studies18, 29, 30 addressed the value of MDCTA in the diagnosis of infective endocarditis. Five studies38, 51, 52, 53, 54 addressed the value of 99mTc-hexamethylpropylene amine oxime (99mTc-HMPAO; also known as 99mTc-exametazine)-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 99mTc-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 study18 was included for both 18F-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. 18F-FDG=18F-fluorodeoxyglucose. MDCTA=multidetector CT angiography. LS=leucocyte scintigraphy. SPECT=single-photon emission CT.
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</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>
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</thead>
<tbody>
<tr>
<td>ECG-gated MDCTA, n=92 (92 cases and 0 controls)</td>
<td>&gt;50% native valve</td>
<td>Feuchtner</td>
<td>Prospective</td>
<td>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>
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<td>&gt;50% prosthetic valve</td>
<td>Fagman</td>
<td>Prospective</td>
<td>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>
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<td>Habets</td>
<td>Prospective</td>
<td>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>
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<tr>
<td>18F-FDG PET/CT, n=1402 (943 cases and 553 controls)</td>
<td>&gt;50% native valve</td>
<td>Ozcan</td>
<td>Retrospective</td>
<td>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>
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<td>Asmar</td>
<td>Retrospective</td>
<td>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>
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<td>Van Riet</td>
<td>Prospective</td>
<td>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>
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<td>Kestler</td>
<td>Prospective</td>
<td>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>
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<td>Kouijzer</td>
<td>Prospective</td>
<td>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>
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<td>Orvin</td>
<td>Prospective</td>
<td>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>
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<td>Salomäki</td>
<td>Prospective</td>
<td>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>
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<td>Inclusion</td>
<td>Number and type of cases</td>
<td>Gold standard</td>
<td>Diagnostic accuracy (sensitivity; specificity; PPV; NPV)</td>
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<td>[18]F-FDG PET/CT, n=1402 (943 cases and 553 controls)</td>
<td>&gt;50% prosthetic valve</td>
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<td>Bonfiglioli&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Prospective 71 suspected infective endocarditis (38 prosthetic valves)</td>
<td>Succeeding examinations</td>
<td>Extracardiac signal (17 of 71): 24% new findings; infective endocarditis diagnosis (11 of 17): 65% of extracardiac signal; intracardiac signal&lt;sup&gt;†&lt;/sup&gt; (four of 11): 36% of infective endocarditis diagnosis</td>
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<td>Ricciardi&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Retrospective 27 suspected infective endocarditis&lt;sup&gt;†&lt;/sup&gt; (20 prosthetic valves)</td>
<td>Modified Duke criteria and expert opinion</td>
<td>Native or prosthetic valve endocarditis (25 of 27): (55%; 100%; 100%; 18%); prosthetic valve endocarditis (18 of 20): (85%; 100%; 100%; 50%)</td>
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<td>Bartoletti&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Retrospective Six suspected infective endocarditis with negative TEE (six aortic prosthetic valves)</td>
<td>Histology (n=4) and TEE</td>
<td>Prosthetic valve endocarditis&lt;sup&gt;†&lt;/sup&gt; (six of six): 100% sensitivity</td>
<td>Very low</td>
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<td>Saby&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Prospective 72 suspected infective endocarditis (72 prosthetic valves)</td>
<td>Expert team after follow-up</td>
<td>Definite prosthetic valve endocarditis&lt;sup&gt;†&lt;/sup&gt; (30 of 72), for which PET (22 of 30): 76% (73%; 80%; 85%; 67%); modified Duke criteria (21 of 30): 70% sensitivity; PET and modified Duke criteria (29 of 30): 97% sensitivity</td>
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<td>Rouzet&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Retrospective 39 suspected infective endocarditis (39 prosthetic valves)</td>
<td>Modified Duke criteria and 3-month follow-up</td>
<td>Prosthetic valve endocarditis (nine of 39): 80% (93%; 71%; 68%; 94%)</td>
<td>Low</td>
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<td>Salomäki&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Prospective 16 suspected infective endocarditis (16 prosthetic valves)</td>
<td>Modified Duke criteria and follow-up in expert team</td>
<td>Prosthetic valve endocarditis (nine of 16): (100%; 71%; 82%; 100%); extracardiac complications (three of six definite infective endocarditis): 50%</td>
<td>Low</td>
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<td>Pizzi&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Prospective 92 suspected infective endocarditis: (36 ICDs or pacemakers, 61 prosthetic valves)</td>
<td>3-month follow-up in expert team (including PET)</td>
<td>Infective endocarditis&lt;sup&gt;†&lt;/sup&gt; (57 of 92), of which modified Duke criteria: (52%; 95%; 93%; 60%); PET/CT and modified Duke criteria: (91%; 90%; 92%; 88%); PET/CTA and modified Duke criteria: (91%; 88%; 91%; 88%); extracardiac complications (ten of 92): 11% new findings</td>
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<td>Fagman&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Retrospective 11 suspected endocarditis (11 aortic prosthetic valves), 19 controls (19 aortic prosthetic valves)</td>
<td>Modified Duke criteria and follow-up in expert team</td>
<td>Definite infective endocarditis&lt;sup&gt;†&lt;/sup&gt; (eight of 30): (75%; 84%; 67%; 89%); controls (19 of 19); low [18]F-FDG uptake</td>
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<td>Inclusion Number and type of cases</td>
<td>Gold standard</td>
<td>Diagnostic accuracy (sensitivity; specificity; PPV; NPV)</td>
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<td><strong>Pacemaker or ICD</strong></td>
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<td>Ahmed41 Prospective 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>
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<td>Beck62 Retrospective 69 controls (69 ICDS)</td>
<td>Laboratory and clinical data</td>
<td>Device¹ (0 of 69): 100% specificity</td>
<td>Low</td>
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<td>Bensimhon63 Prospective 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 lead¹ (ten of 21): 90% (80%; 100%; 100%; 85%); boxes (five of 21): 100% (100%; 100%; 100%); leads (ten of 21): 81% (60%; 100%; 100%; 73%)</td>
<td>Low</td>
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<td>Cautela44 Prospective 21 suspected infection (16 pacemakers, five ICDS)</td>
<td>Clinical criteria according to Le Dolley and colleagues55</td>
<td>Skin (one of 21): 100% sensitivity; pocket (13 of 21): (87%; 100%; ..; ..); device-related infective endocarditis¹ (13 of 21): (31%; 63%; ..; ..)</td>
<td>Low</td>
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<td>Graziosi45 Prospective 27 suspected infective endocarditis¹ (12 pacemakers, 15 ICDS)</td>
<td>Expert team after follow-up</td>
<td>Lead¹ (13 of 27): (63%; 86%; 77%; 76%)</td>
<td>Low</td>
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<td>Leccisotti46 Prospective 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>
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<td>Ploux77 Prospective Ten suspected infection (ten pacemakers), 40 controls (40 pacemakers)</td>
<td>Lead culture or follow-up</td>
<td>Lead¹ (six of ten): (100%; 93%; 66%; 100%)</td>
<td>Low</td>
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<td>Sarrazin88 Prospective 42 suspected infection (25 pacemakers, 17 ICDS), 24 controls (12 at 4–8 weeks post-implant [six pacemakers, six ICDS], 12 at &gt;6 months post-implant [ten pacemakers, two ICDS])</td>
<td>Surgery or follow-up</td>
<td>Device¹ (36 of 42): (89%; 86%; ..; ..); acute control (12 of 12): mild uptake; chronic control (12 of 12): no abnormal uptake</td>
<td>Low</td>
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<td>Tili89 Retrospective 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 lead¹ (18 of 40): 90% (83%; 95%; 94%; 88%); extracardiac complications (11 of 40): 28% identified; controls (40 of 40): 100% ¹H-F-FDG-negative</td>
<td>Low</td>
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<td><strong>Ventricular assist device</strong></td>
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<td>Dell’Aquila90 Retrospective 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>
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<td>Inclusion</td>
<td>Number and type of cases</td>
<td>Gold standard</td>
<td>Diagnostic accuracy (sensitivity; specificity; PPV; NPV)</td>
<td>Quality</td>
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<td>&gt;50% prosthetic valve</td>
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<tr>
<td><strong>Erba</strong>&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>131 suspected infective endocarditis</td>
<td>Microbiology and 12-month follow-up</td>
<td>Infective endocarditis confirmed (51 of 131 and 35 of 51 prosthetic valves): (90%; 36%; 85%; 47%)</td>
<td>Low</td>
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<tr>
<td><strong>Hyafi</strong>&lt;sup&gt;52&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>42 suspected infective endocarditis&lt;sup&gt;*&lt;/sup&gt; (42 prosthetic valves, TEE inconclusive)</td>
<td>Surgery (n=10) or follow-up (n=32)</td>
<td>³Perivalvular abscess (6–12 of 43): (83–100%; 78–87%; 43–71%; 93–100%)</td>
<td>Low</td>
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<td><strong>Rouzet</strong>&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>39 suspected infective endocarditis (39 prosthetic valves)</td>
<td>Modified Duke criteria and 3-month follow-up</td>
<td>Definite infective endocarditis (nine of 39): 86% (64%; 100%; 100%; 81%)</td>
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<td>Pacemaker or ICD</td>
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<td><strong>Erba</strong>&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>63 suspected infection (49 pacemakers, 14 ICDs)</td>
<td>Microbiology and 12-month follow-up</td>
<td>Device-associated (32 of 63): 9.7% (94%; 100%; 100%; 94%)</td>
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<td>Ventricular assist device</td>
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<td><strong>Litzler</strong>&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>Eight suspected infection (eight left ventricular assist devices, of which five scanned twice)</td>
<td>Microbiology or follow-up</td>
<td>Left ventricular assist device (eight of 13 scans): (100%; 100%; 100%; 100%); extracardiac complications (three of 13 scans): unsuspected findings in 23%</td>
<td>Low</td>
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**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. ¹⁸F-FDG = ¹⁸F-fluorodeoxyglucose. ICD = implantable cardiac device. ⁹⁹mTc-HMPAO = ⁹⁹mTc-hexamethylpropylene-amine 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 ¹⁸F-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.
Native valve endocarditis

We included a prospective cohort study\textsuperscript{29} 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 $^{18}$F-FDG PET/CT, we included nine studies\textsuperscript{21, 24, 25, 31, 32, 34, 35, 36} regarding patients with native valves. Seven studies\textsuperscript{21, 24, 25, 31, 32, 34} included more than 50% of patients with suspected native valve endocarditis (two retrospective cohorts\textsuperscript{24, 31} and four prospective cohorts,\textsuperscript{25, 32, 33, 34} with one matched case-control study\textsuperscript{21} within a prospective cohort). Six studies\textsuperscript{21, 24, 25, 31, 32, 34} included only patients with definite infective endocarditis according to the modified Duke criteria. The sensitivity of $^{18}$F-FDG PET/CT for diagnosis of native valve endocarditis was 14% (one of seven patients)\textsuperscript{34} with an appropriate pre-scan diet and 6% (two of 34 patients)\textsuperscript{25} without. Overall, diagnosis of extracardiac complications had 14–100% sensitivity, 80% specificity, and 52–90% positive and 100% negative predictive values.\textsuperscript{24, 31, 32, 33, 34} Addition of $^{18}$F-FDG PET/CT to the standard work-up of infective endocarditis helped to detect 15–32% of additional potential infectious foci\textsuperscript{21, 24, 25} (number needed to investigate of seven\textsuperscript{24}), enough to modify treatment in 35% of patients\textsuperscript{25} and halve the relapse rate.\textsuperscript{21} An additional study\textsuperscript{33} 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 $^{18}$F-FDG PET/CT was not able to diagnose infective endocarditis reliably in patients with a relatively low risk for infective endocarditis.\textsuperscript{33}

Prosthetic valve endocarditis

We included three studies\textsuperscript{18, 29, 30} addressing the value of MDCTA in diagnosis of prosthetic valve endocarditis. Two studies\textsuperscript{18, 30} included more than 50% of patients with suspected prosthetic valve endocarditis. The population of the prospective cohort\textsuperscript{30} consisted of patients suspected of infective endocarditis, and the population of the prospective cross-sectional study\textsuperscript{18} 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%.\textsuperscript{30} 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.\textsuperscript{18} Sensitivity was 100% for the diagnosis of perivalvular infection.\textsuperscript{39} For MDCTA in addition to the standard diagnostic work-up for suspected infective endocarditis, sensitivity was 100% and specificity 91%.\textsuperscript{18} 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.\textsuperscript{18}
Diagnostic value of imaging in infective endocarditis: a systematic review

We included 13 studies addressing the value of $^{18}$F-FDG PET/CT in diagnosis of infective endocarditis, extracardiac complications, or both, in patients with prosthetic valves. Eight studies included more than 50% of patients with suspected prosthetic valve endocarditis: these studies consisted of a case series, two retrospective cohorts, one case-control study in a retrospective cohort, and four prospective cohorts. All studies included patients with suspected infective endocarditis, which was on the basis of the modified Duke criteria in three studies. One study additionally included a control group, consisting of patients with a prosthetic valve in situ without suspicion of infective endocarditis.

For $^{18}$F-FDG PET/CT, diagnosis of infective endocarditis had 73–100% sensitivity, 71–100% specificity, and 67–100% positive and 50–100% negative predictive values. Addition of $^{18}$F-FDG PET/CT to the modified Duke criteria increased sensitivity from 52–70% to 91–97%. Furthermore, both imaging modalities provided complementary information: seven (23%) of 30 patients had a positive $^{18}$F-FDG PET/CT and negative echocardiogram and eight (27%) of 30 had a negative $^{18}$F-FDG PET/CT and positive echocardiogram. In diagnosis of extracardiac complications, $^{18}$F-FDG PET/CT detected unexpected additional potential infectious foci in 11–24% of patients. Controls had low $^{18}$F-FDG uptake.

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

We included three studies addressing the value of $^{99m}$Tc-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. The populations studied included patients with definite infective endocarditis or suspected infective endocarditis according to the modified Duke criteria but with inconclusive echocardiography results. Diagnosis of infective endocarditis overall had 64–90% sensitivity, 36–100% specificity, and 85–100% positive and 47–81% negative predictive values. Diagnosis of abscess formation had 83–100% sensitivity, 78–87% specificity, and 43–71% positive and 93–100% negative predictive values.

ICD or pacemaker-related infections

We included nine studies addressing the value of $^{18}$F-FDG PET/CT in diagnosis of ICD and pacemaker infections and related extracardiac complications. These studies consisted of two retrospective and seven prospective cohort studies, and included patients with suspected device infection and patients with suspected infective endocarditis according to the modified Duke criteria. Five studies 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. Diagnosis of cardiac device-related infective endocarditis had 31% sensitivity and 63% specificity in a study of 21 patients. Diagnosis of lead infection had 24–100% sensitivity, 79–100% specificity, and 66–100% positive and 73–100% negative predictive values, and diagnosis of pocket infection had 87–91% sensitivity, 93–100% specificity,
and 97% positive and 81% negative predictive values.\textsuperscript{41, 44, 46} Controls showed only mild \textsuperscript{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.\textsuperscript{41, 48, 49} When patients were scanned 3 h after the \textsuperscript{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,\textsuperscript{46} which was substantially higher (significantly so for the leads) than with the standard 1-h interval.

One retrospective cohort study addressed the value of \textsuperscript{99m}Tc-HMPAO-labelled leucocyte scintigraphy with SPECT/CT in diagnosis of ICD-related and pacemaker-related infections,\textsuperscript{51} which had 94% sensitivity, 100% specificity, and 100% positive and 94% negative predictive values.\textsuperscript{51}

**Ventricular assist device-related infections**

One retrospective cohort study\textsuperscript{50} addressed the value of \textsuperscript{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\textsuperscript{54} addressing the value of \textsuperscript{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.\textsuperscript{54}

**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 \textsuperscript{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.\textsuperscript{17, 29} 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>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><strong>Contraindications</strong></td>
<td>Oesophageal pathology</td>
<td>Pregnancy, iodinated contrast allergy, renal insufficiency (eGFR &lt;60 mL/min per 1.73 m$^3$)</td>
<td>Pregnancy, most ICDs and pacemakers, gadolinium allergy, a renal insufficiency (eGFR &lt;30 mL/min per 1.73 m$^3$), claustrophobia</td>
<td>Pregnancy, uncontrolled diabetes</td>
</tr>
<tr>
<td><strong>Patient preparation</strong></td>
<td>4–6 h fasting</td>
<td>2 h fasting, intravenous contrast</td>
<td>Intravenous contrast</td>
<td>26 h fasting, 24 h low-carbohydrate, fat-allowed diet</td>
</tr>
<tr>
<td><strong>Monitoring of unstable patients possible</strong></td>
<td>Good</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Anatomical vs functional</strong></td>
<td>Anatomical images, functional data (motion)</td>
<td>Detailed anatomical images</td>
<td>Functional data (molecular)</td>
<td>Functional data (molecular)</td>
</tr>
<tr>
<td><strong>Anatomical resolution</strong></td>
<td>Good</td>
<td>Very good</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td><strong>ECG gating required</strong></td>
<td>Not applicable</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>30 min</td>
<td>15 min</td>
<td>$\geq$30 min</td>
<td>80 min (60 min preparation, 20 min scan time)</td>
</tr>
<tr>
<td><strong>Radiation dose</strong></td>
<td>None</td>
<td>High (10 mSv)</td>
<td>None</td>
<td>Moderate (4 mSv)</td>
</tr>
<tr>
<td><strong>Quantification possibilities</strong></td>
<td>Possible</td>
<td>Not possible</td>
<td>Excellent</td>
<td>Good</td>
</tr>
<tr>
<td><strong>Diagnostic accuracy</strong></td>
<td>Sensitive and specific</td>
<td>Sensitive and specific</td>
<td>Unclear</td>
<td>Sensitive</td>
</tr>
<tr>
<td><strong>Susceptibility to artifacts</strong></td>
<td>Metallic (very susceptible)</td>
<td>Metallic (moderately susceptible)</td>
<td>Metallic (moderately susceptible), cardiac and respiratory (moderately susceptible)</td>
<td>Metallic (slightly susceptible)</td>
</tr>
<tr>
<td><strong>Suitability for therapy monitoring</strong></td>
<td>Suitable</td>
<td>Not suitable</td>
<td>Unclear</td>
<td>Very suitable</td>
</tr>
<tr>
<td><strong>Availability</strong></td>
<td>Widely available</td>
<td>Widely available</td>
<td>Moderately available</td>
<td>Moderately available</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td>Approximately €100</td>
<td>€300–400</td>
<td>€500–800</td>
<td>€800–1200</td>
</tr>
</tbody>
</table>
Table 2
Requirements, benefits, and limitations of imaging techniques

<table>
<thead>
<tr>
<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>Limitations</td>
<td>Completely operator-dependent analysis</td>
<td>Frequent contraindications</td>
<td>Noisiness for patients</td>
<td>Pathological conditions mimicking pattern of focially increased uptake, difficulty to discriminate aseptic inflammation from infectious process (insufficient clear interpretation criteria)</td>
</tr>
</tbody>
</table>

¹⁸F-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 ¹⁸F-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 ¹⁸F-FDG uptake.⁴⁰ For extracardiac infection, ¹⁸F-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 ¹⁸F-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 ¹⁸F-FDG PET/CT was done.²⁵ The addition of ¹⁸F-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 ¹⁸F-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 ¹⁸F-FDG PET/CT is not straightforward because the distribution and pattern of ¹⁸F-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.\textsuperscript{67}

To further increase the accuracy of \( {\text{\textsuperscript{18}}\text{F}} \)-FDG PET/CT in infective endocarditis, CT angiography instead of
low-dose CT could be applied for the cardiac segment in prosthetic valve endocarditis.\textsuperscript{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 study\textsuperscript{33} 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 \( {\text{\textsuperscript{18}}\text{F}} \)-FDG—
might improve accuracy,\textsuperscript{44, 46, 68} although studies in other inflammatory and infectious diseases argue
against this.\textsuperscript{69, 70} Dual-timepoint scanning with \( {\text{\textsuperscript{18}}\text{F}} \)-FDG PET/CT can probably not differentiate between
malignant, inflammatory, and infectious processes, but can help to compensate for background uptake
of \( {\text{\textsuperscript{18}}\text{F}} \)-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,\textsuperscript{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.\textsuperscript{38, 51, 52, 53, 54} Furthermore, leucocyte
scintigraphy with SPECT/CT is able to detect extracardiac complications,\textsuperscript{51} excluding ophthalmitis and
intracerebral infection.\textsuperscript{53} For infective endocarditis, a positive leucocyte scintigraphy with SPECT/CT correlates with high infectious activity and predicts poor prognosis.\textsuperscript{52} Additionally, a positive scan could
point towards abscess and perivalvular infection and therefore indicates the requirement of surgical
intervention.\textsuperscript{52, 72} By contrast, negative scans indicate the absence of infectious activity,\textsuperscript{72} and are
consistently associated with a favourable clinical outcome once antimicrobial therapy alone is initiated.\textsuperscript{53, 72}
Furthermore, negative scans seem to reliably exclude extensive perivalvular infection and the need
for surgery in patients with definite infective endocarditis.\textsuperscript{52, 72} The specificity of leucocyte scintigraphy
with SPECT/CT could be particularly useful when diagnostic uncertainty remains after \( {\text{\textsuperscript{18}}\text{F}} \)-FDG PET/
CT.\textsuperscript{74, 75, 76} For patients with suspected prosthetic valve endocarditis, a sequential work-up strategy
of \( {\text{\textsuperscript{18}}\text{F}} \)-FDG PET and leucocyte scintigraphy with SPECT/CT has been proposed if echocardiography is
inconclusive.\textsuperscript{38} In this work-up, patients with negative \( {\text{\textsuperscript{18}}\text{F}} \)-FDG PET/CT as well as those showing an
intense focal \( {\text{\textsuperscript{18}}\text{F}} \)-FDG PET/CT signal in the area of the cardiac valves do not need additional scanning.
However, patients with low, diffuse \( {\text{\textsuperscript{18}}\text{F}} \)-FDG uptake around the cardiac prosthesis need leucocyte
scintigraphy with SPECT/CT, particularly if scanned in the first 2 months after cardiac surgery.\textsuperscript{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
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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.$^{77, 78, 79, 80}$ The data suggest that cardiac MRI might be a useful addition but not a substitute in the assessment of infective endocarditis.$^{79, 80}$ 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.

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—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.$^{11}$ 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.$^{39}$

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.$^{38}$ 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. Furthermore, presence of a focal hotspot is considered the best criterion of lead infection. 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.

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. $^{18}$F-FDG PET/CT is especially sensitive for device infection, and has a high negative predictive value. 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.

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. 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.
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Figure 2
Flowcharts for the diagnostic imaging work-up of patients suspected of infective endocarditis

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=transsthoracic 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.
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which can be better visualised by MDCTA\(^2\)); (3) an initial negative or inconclusive TEE and sustained suspicion of infective endocarditis;\(^7\), \(^9\) (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 \(^{18}\)F-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 \(^{18}\)F-FDG PET/CT should be done after infective endocarditis has been proven by MDCTA. Even though the added value of \(^{18}\)F-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 \(^{18}\)F-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.\(^{53}, 54\) 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 \(^{18}\)F-FDG in inflammation and infection.\(^{55}\) This limit is debatable, as other studies provide data in favour of extension of the interval to up to 2 months,\(^{38}, 48\) whereas in prosthetic vascular grafts the intensity of \(^{18}\)F-FDG uptake did not change over time.\(^{86}, 87\)

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 \(^{18}\)F-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 \(^{18}\)F-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 \(^{18}\)F-FDG.

In centers with access to a hybrid PET/CT camera system, \(^{18}\)F-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 \(^{18}\)F-FDG PET/CT.\(^{72}, 76\) Furthermore, we propose the use of leucocyte scintigraphy with SPECT/CT less than 1 month after cardiac surgery after inconclusive MDCTA, instead of \(^{18}\)F-FDG PET/CT,\(^3\) because of the non-specific \(^{18}\)F-FDG uptake due to inflammation in this time period.
Chapter 2

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?
- To what extent is $^{18}$F-FDG PET/CT useful for diagnosis of native valve endocarditis?
- What is the optimal timeframe for $^{18}$F-FDG PET/CT scanning?
- Could diagnostic accuracy of $^{18}$F-FDG PET/CT be improved by respiratory gated imaging?
- What is the cutoff value for increased $^{18}$F-FDG uptake in the differentiation of infection from inflammation?
- 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?
- Can more specific tracers improve the diagnostic accuracy of PET/CT scanning?
- What is the accuracy of $^{18}$F-FDG PET/CT versus leucocyte scintigraphy for ICD-related and pacemaker-related infection?
- To what extent does antimicrobial therapy affect sensitivity of $^{18}$F-FDG PET/CT and leucocyte scintigraphy SPECT/CT?
- Can $^{18}$F-FDG PET/CT, $^{18}$F-FDG PET/MRI be used to monitor the efficacy of antimicrobial treatment?
- 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?
- What is the sensitivity of $^{18}$F-FDG PET/CT and leucocyte scintigraphy SPECT/CT for specific pathogens?
- Can leucocyte tracers be developed for PET/CT imaging?
- 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.)
- 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?
- Can innovative novel MRI sequences be developed for visualisation of infective endocarditis?
- What are the the prognostic roles of imaging by MDCTA, $^{18}$F-FDG PET/CT, and leucocyte scintigraphy with SPECT/CT?

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. 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.
Diagnostic value of imaging in infective endocarditis: a systematic review

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.

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. 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.

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.

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Supplementary webappendix

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

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<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>
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<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 'technecium':ab,ti OR 'white blood cell':ab,ti OR 'white blood cells':ab,ti OR leucocyte*:ab,ti OR leucocyte*:ab,ti OR 'monoclonal antibody'/exp OR monoclonal:ab,ti OR 'granulocyte antibody'/exp OR 'granulocyte antibody':ab,ti OR 'granulocyte antibodies':ab,ti AND ('scintiscanning'/exp OR '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>
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| 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 (assist NEXT/1 pump*):ab,ti OR (cardiac:ab,ti OR cardiovascular:ab,ti AND device*:ab,ti) OR cied*:ab,ti OR ('artificial heart ventricle':ab,ti OR vad:ab,ti OR 'aortic graft':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)))

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## Table 4: Inclusion and exclusion criteria for selection of articles

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<thead>
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<td>Adults (≥18 year old)</td>
<td>Preclinical studies</td>
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<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>
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<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 diagnosing 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>Prosthetic aortic grafts without aortic valve</td>
<td>Minimum technical imaging criteria not met</td>
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<tr>
<td>- MDCTA: use of ECG-triggered 64-slice MDCT</td>
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<tr>
<td>- MRI: use of ECG-gated 1.5 Tesla scanner</td>
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<tr>
<td>- FDG-PET/CT: presence of low dose CT accompanying the FDG-PET</td>
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<tr>
<td>- Leukocyte scintigraphy: use of SPECT/CT</td>
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## 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

### Items assessed to detect reasons to down- or upgrade the evidence

| Limitations in the design and implementation of available studies suggesting high likelihood of bias | patient sequence generation detection bias attrition bias reporting bias bias related to the time of imaging after diagnosis arrhythmias interfering with gating mode techniques start of antimicrobial therapy |

### Indirectness of evidence

Unexplained heterogeneity or inconsistency of results

Imprecision of results

Large magnitude of effect, confounding factors reducing a demonstrated effect

### Possible confounding factors

1 versus 2 observers

Independent observations

### Gold standard

surgery/pathology

expert team comprising of medical specialists: thoracic surgery, infectious diseases, medical microbiology, cardiology, imaging specialists

### Probability of IE diagnosis

according to the Duke criteria¹ from 1994 or the modified Duke criteria² from 2000

### TTE and/or TEE

real-time or recorded images

### Technical characteristics of imaging

duration of fasting, low-carbohydrate/fat-allowed diet, and/or administration of heparin pre-scanning for FDG-PET/CT; beta-blockade for cardiac CT

### Time-frame after diagnosis and after start of antimicrobial therapy

Quality of the image
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 prosthesis 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 prosthesis 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 prosthesis 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 PhD³
Andor W.J.M. Glaudemans, MD PhD⁶

Under review.