The highly variable and nonspecific presentations of CIED infection, and can occur days to years after implantation.6,7 At the site of the device pocket to nonspecific signs of systemic infection vary significantly, ranging from simple local swelling or pain to nonspecific signs of systemic infection. Patient presentation can further classified into CIED pocket infection or CIED lead/ wire infection. Infection can involve any portion of the device and can be accompanied by a greater increase in the rate of CIED infection. These infections are associated with significant mortality and morbidity and warrant prompt medical treatment. Infection can involve any portion of the device and can be classified into CIED pocket infection or CIED lead/wire infection. Patient presentation can vary significantly, ranging from simple local swelling or pain at the site of the device pocket to nonspecific signs of systemic infection, and can occur days to years after implantation.6,7 The highly variable and nonspecific presentations of CIED infection make the diagnosis challenging. An accurate and timely diagnosis is paramount because therapy of all but the most superficial infections usually mandates device extraction and reimplantation, at considerable risk to the patient and cost to the payer.

See Editorial by Rouzet and Le Guludec
See Clinical Perspective

Investigation of patients with suspected CIED infection should include clinical information, physical examination, blood work and microbiological testing. Echocardiography is currently the first-line imaging technique in patients with suspected CIED infection, but is of limited value unless a more sensitive imaging modality is used. Furthermore, imaging is often negative in the early stages of infection, potentially delaying diagnosis.6,7 While echocardiography is the imaging modality of choice, other imaging modalities such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET) have demonstrated improved diagnostic accuracy in the diagnosis of CIED infection.8,9

Methods and Results—A systematic review of the literature and meta-analysis on the use of all 3 modalities in CIED infection were conducted. Pooled sensitivity, specificity, and summary receiver operating characteristic curves of each imaging methodologies were determined. The literature search identified 2493 articles. A total of 13 articles (11 studies for 18F-FDG PET-CT and 2 for LS), met the inclusion criteria. No studies for 67Ga citrate scintigraphy met the inclusion criteria. The pooled sensitivity of 18F-FDG PET-CT for the diagnosis of CIED infection was 87% (95% CI, 82%–91%) and pooled specificity was 94% (95% CI, 88%–98%). The summary receiver operating characteristic curve analysis demonstrated good overall accuracy, with an area under the curve of 0.935. There were insufficient data to do a meta-analysis for LS, but both studies reported sensitivity above 90% and specificity of 100%.

Conclusions—Both 18F-FDG PET-CT and LS yield high sensitivity, specificity, and accuracy, and thus seem to be useful for the diagnosis of CIED infection, based on robust data for 18F-FDG PET-CT but limited data for LS. When available, 18F-FDG PET-CT may be preferred. (Circ Cardiovasc Imaging. 2017;10:e005772. DOI: 10.1161/CIRCIMAGING.116.005772.)

Key Words: Fluor-18-fluorodeoxyglucose • gallium • leukocyte • positron emission tomography
vegetation is visualized along a lead. There is a need to identify a more accurate noninvasive test for the diagnosis of CIED infection, as well as a growing interest regarding the use of Fluor-18-fluorodeoxyglucose positron emission tomography and computed tomography (18F-FDG PET-CT) for infection and inflammatory conditions.6–10 Other tracers also exist with the potential to image infection; both 67Ga scintigraphy and labeled leukocytes scintigraphy (LS) have demonstrated their use in inflammatory and infectious disease.

We sought to perform a systematic review and meta-analysis to establish the accuracy of 18F-FDG PET-CT, 67Ga citrate scintigraphy, and LS for the diagnosis of CIED infection in adult patients.

Methods

Peer-reviewed studies investigating the accuracy of 18F-FDG PET-CT, 67Ga citrate scintigraphy, or LS for the diagnosis of CIED infection were included. Only studies where sufficient data were provided to calculate true positives, true negatives, false positives, and false negatives were considered. Animal studies and pediatric studies were excluded, as were abstracts, case reports, and case series. For 67Ga citrate and LS, only studies using single-photon emission computed tomography (SPECT) or SPECT-CT were included because planar imaging alone no longer reflects current practice.

The search strategy was developed and tested through an iterative process by an experienced medical information specialist in consultation with the review team. The database searches were executed on November 25 and 26, 2015. We searched Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, and Embase using the OVID platform and the CENTRAL database on Wiley. We searched PubMed for the most recent and unindexed citations only.

Strategies used a combination of controlled vocabulary (eg, “Endocarditis, Bacterial”, “Fluorodeoxyglucose F18”, and “Gallium Radioisotopes”) and keywords (eg, endocarditis, 18F-FDG, and GA-67). Vocabulary and syntax were adjusted across databases. When possible, animal-only and opinion-pieces were removed from the results. We performed a targeted gray literature of major health technology assessment organizations and Google Scholar on December 4, 2015. Specific details about the strategies appear in Appendix I in the Data Supplement.

Two independent reviewers assessed all abstracts for adherence to inclusion criteria. All abstracts accepted by either reviewers were selected for full-text review. Any disagreements were resolved through consensus at this stage. A third author was consulted in cases where consensus could not be reached. The reference lists of studies meeting the inclusion criteria were reviewed for missed articles.

Absolute numbers for true positives, true negatives, false positives, and false negatives on a per examination basis were extracted from the included papers by one of the reviewer, and the extracted data were verified by the second reviewer. Using the extracted values, estimates of sensitivity and specificity, as well as their 95% confidence intervals, were obtained for each study as were pooled estimates of sensitivity and specificity using weighted averages according to the patient population size. The Cochran Q test and the Inconsistency Index I² were calculated and used to assess heterogeneity between studies. Summary receiver operating characteristic curves were also computed with area under the curve (AUC) reported as a measure of diagnostic accuracy. The shape of the curve was calculated using Moses constant-of-linear model under the assumption of symmetry. The threshold effect was assessed using the Spearman correlation between sensitivity and specificity. The Moses–Shapiro–Littenberg model, a form of meta-regression that models the relationship between the diagnostic odds ratio and the diagnostic threshold of the test, was used to assess the ROC curve symmetry assumption. All analyses were performed using Meta-DiSc version 1.4 (Clinical Biostatistics Unit, Ramon y Cajal Hospital, Madrid, Spain). Positive predictive value and negative predictive value are dependent on the prevalence of the condition in the population and are most useful when it is known. For this reason, we decided to focus on sensitivity and specificity.

When sufficient data were provided to do so, subgroup analysis for pocket/generator infection and lead/IE were done. The same

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**Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.**
### Table 1. Review of the Literature

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Diagnostic Criteria</th>
<th>Reference Standard</th>
</tr>
</thead>
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<tr>
<td><strong>18F-FDG PET-CT</strong></td>
<td></td>
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<tr>
<td>Bensimhon et al¹³</td>
<td>21 patients with suspected CIED infection</td>
<td>Visual assessment</td>
<td>Microbiological analysis on extracted device (n=11) or clinical diagnosis/follow-up with modified Duke criteria (minimum 6 mo, n=10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quantitative measurement (SUV&lt;sub&gt;max&lt;/sub&gt;)</td>
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<tr>
<td>Ploux et al²²</td>
<td>10 patients with suspected CIED infection</td>
<td>Visual assessment</td>
<td>Microbiological analysis on extracted device (n=6) or clinical diagnosis/follow-up (minimum 3 mo)</td>
</tr>
<tr>
<td>Sarrazin et al²¹</td>
<td>42 patients with suspected CIED infection</td>
<td>Visual assessment</td>
<td>Microbiological analysis on extracted device (n=24) or clinical diagnosis/follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Semiquantitative ratio defined using maximum count rate around CIED and mean count rate of normal lungs parenchyma on non attenuation corrected images</td>
<td></td>
</tr>
<tr>
<td>Cautela et al¹⁴</td>
<td>21 patients admitted for CIED infection</td>
<td>Visual assessment</td>
<td>Clinical diagnosis and follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Semiquantitative assessment (SUV&lt;sub&gt;max&lt;/sub&gt; cut off on generator pocket or ratio using ROI on the liver or aorta)</td>
<td></td>
</tr>
<tr>
<td>Graziosi et al²⁰</td>
<td>26 patients with suspected CIED-IE</td>
<td>Visual assessment</td>
<td>Microbiological analysis on extracted device (n=14) and clinical diagnosis/follow-up with modified Duke criteria (minimum 6 mo)</td>
</tr>
<tr>
<td>Leccisotti et al²⁰</td>
<td>27 patients referred for CIED extraction because of suspicion of infection</td>
<td>Visual assessment (early and delayed acquisition); uptake greater than background along pocket or lead, visible on both AC and NAC images</td>
<td>Microbiological analysis on extracted device</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Semiquantitative assessment (target to background ratio calculated using SUV&lt;sub&gt;max&lt;/sub&gt; and ROI on left atrium)</td>
<td></td>
</tr>
<tr>
<td>Ahmed et al¹²</td>
<td>46 patients with suspected CIED pocket infection</td>
<td>Visual assessment; uptake was considered abnormal if higher than mediastinal blood pool</td>
<td>Clinical evolution and microbiological analysis on extracted device (n=32) or clinical diagnosis/follow-up (n=14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Semiquantitative ratio as per Sarrazin et al²¹</td>
<td></td>
</tr>
<tr>
<td>Pizzi et al¹⁹</td>
<td>28 patients admitted for suspicion of CIED-IE</td>
<td>Visual assessment</td>
<td>Combination of modified Duke criteria and clinical follow-up (minimum 3 mo)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Semiquantitative assessment (SUV&lt;sub&gt;max&lt;/sub&gt; and SUV ratio using SUV&lt;sub&gt;max&lt;/sub&gt; of abnormal area and mean SUV of blood pool)</td>
<td></td>
</tr>
<tr>
<td>Tili et al²²</td>
<td>40 patients with suspected CIED infection</td>
<td>Visual assessment</td>
<td>Microbiological analysis on extracted device (n=22) or clinical diagnosis/follow-up (minimum 12 mo)</td>
</tr>
<tr>
<td>Dell’Aquila et al¹⁵</td>
<td>40 scans in 31 patients with suspected LVAD infection</td>
<td>Visual assessment</td>
<td>Microbiological analysis on extracted or in-situ device or clinical diagnosis/follow-up</td>
</tr>
<tr>
<td>Memmott et al¹⁸</td>
<td>39 scans in 37 patients with suspected CIED infection</td>
<td>Visual assessment</td>
<td>Microbiological analysis on extracted device (n=24) or clinical diagnosis/follow-up (minimum 6 mo, n=13)</td>
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<td></td>
<td>Semiquantitative assessment; SUV&lt;sub&gt;max&lt;/sub&gt; cut off or ratio of SUV&lt;sub&gt;max&lt;/sub&gt; around leads and pocket to multiple reference points (lung [NAC], contralateral side [AC and NAC], hepatic blood pool, mediastinal blood pool)</td>
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<td><strong>Labeled leukocytes</strong></td>
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<tr>
<td>Litzler et al²⁴</td>
<td>13 scans in 8 patients with suspected LVAD infection</td>
<td>Visual assessment; at least one focus of abnormal uptake with time-dependent increase in activity between early and delayed images</td>
<td>Microbiological analysis on extracted device (n = 3) or clinical diagnosis/follow-up (n = 5)</td>
</tr>
<tr>
<td>Erba et al²³</td>
<td>63 patients with suspected CIED infection</td>
<td>Visual assessment; at least one focus of abnormal uptake with time-dependent increase in activity between early and delayed images</td>
<td>Microbiological analysis on extracted device (n = 35) or clinical diagnosis/follow-up (minimum 12 mo, n = 28)</td>
</tr>
</tbody>
</table>

¹⁸F-FDG indicates Fluor-18-fluorodeoxyglucose; ⁹⁹mTc-HMPAO, hexamethylpropyleneamine labeled with Technetium-99m; AC, attenuation corrected; CIED, cardiac implantable electronic device; CT, computed tomography; CTA, computed tomographic angiography; IE, infective endocarditis; LVAD, left ventricular assist device; NAC, nonattenuation corrected; PET, positron emission tomography; ROI, region of interest; SPECT, single-photon emission computed tomography; and SUV<sub>max</sub>, maximum standardized uptake value.
analysis and software as for the main analysis were used in these subgroup analyses.

Quality of Evidence
All included studies were assessed for risk of bias and applicability concerns using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool (Appendix II in the Data Supplement).11

Results
The literature search identified a total of 2493 abstracts, and 13 studies met the entry criteria (Figure 1); no additional eligible studies were identified from the reference lists of studies meeting the inclusion criteria. A total of 11 studies (331 patients, 340 examinations)12–22 and 2 studies (71 patients, 76 examinations)23,24 met the inclusion criteria for 18F-FDG PET-CT and LS, respectively. There were no studies for 67Ga citrate that met the criteria for inclusion. Pertinent study characteristics are summarized in Tables 1 and 2. All included studies were single-center and published between 2010 and 2016, and 8 of 13 were prospective studies.

Diagnostic Accuracy of 18F-FDG PET-CT
All 11 studies were included in the meta-analysis. The pooled sensitivity of 18F-FDG PET-CT for the diagnostic of CIED infection was 87% (95% CI, 82%–91%) and pooled specificity was 94% (95% CI, 88%–98%; Figure 2). The summary receiver operating characteristic curve analysis demonstrated good overall accuracy, with an AUC of 0.952 and a Q* of 0.89 (Figure 3).

I² value for sensitivity and specificity were 56.6% and 0%, respectively, indicating the absence of substantial heterogeneity in specificity, and moderate heterogeneity in sensitivity among the studies included in the meta-analysis.

Left ventricular assist device infection can present differently than pacemaker and implanted cardioverter defibrillator infection. For this reason, a subanalysis excluding the single left ventricular assist device infection study15 was performed. In the subanalysis, the results did not change significantly.

Location of Infection
A total of 4 studies12–14,17 provided sufficient information to calculate the operating characteristics of 18F-FDG PET-CT for pocket/generator related CIED infection. Pooled specificity and sensitivity in this subgroup analysis were 93% (95% CI, 84%–98%) and 98% (95% CI, 88%–100%), respectively, and AUC was 0.981 (Figure 4).

Six studies13,14,16,17,19,20 provided sufficient information to calculate the operating characteristics of 18F-FDG PET-CT for lead or IE-related CIED infection. Pooled specificity was 65% (95% CI, 53%–76%), specificity was 88% (95% CI, 77%–94%), and AUC was 0.861 (Figure 5).

Diagnostic Accuracy of LS
There were not enough studies to generate statistically meaningful pooled operating characteristics or a summary receiver
operating characteristic. The largest study (n=63) reported a sensitivity of 94% and a specificity of 100%, whereas a small study that enrolled 13 left ventricular assist device patients reported sensitivity and specificity of 100%.\textsuperscript{23,24}

Quality of Included Studies
The QUADAS-2 analysis (Figure 6) demonstrated that overall, there was low risk of bias and low concerns for applicability, except for risk of bias related to the reference standard. This is, in part, explained by the lack of a true, reliable “gold standard” in the diagnosis of CIED infection. In the majority of studies, the reference standard was either microbiological analysis on extracted device or clinical diagnosis and follow-up after a minimum length of time. In some studies, the examination results were either available to the team deciding on device extraction or making the final clinical diagnosis after follow-up, or it was unclear whether this information was made available to the medical team before treatment decision.

Discussion
This is the first systematic review and meta-analysis on the diagnostic accuracy of \textsuperscript{18}F-FDG PET-CT and LS using SPECT or SPECT-CT in CIED infection. Our meta-analysis on the use of \textsuperscript{18}F-FDG PET-CT demonstrated good accuracy, with a sensitivity of 87\%, a specificity of 94\%, and an AUC of 0.952. These data support the use of this modality in the investigation of suspected CIED infection. Although it is unclear whether it is cost-effective for all such patients to undergo \textsuperscript{18}F-FDG PET-CT, the high accuracy of the examination appears ideal to help clinicians in appropriately classifying and stratifying patient with “possible” CIED infection after standard work-up. In light of the significant cost, morbidity and mortality associated with these infections, combined with the significant risk associated with device extraction, the importance of a timely and accurate diagnosis cannot be overstated.\textsuperscript{25,26} The ability of \textsuperscript{18}F-FDG PET-CT to image all sites (pocket/generator, leads) of possible infection in one examination also

Figure 3. Summary receiver operating characteristic (SROC) curve for diagnostic accuracy of Fluor-18-fluorodeoxyglucose positron emission tomography and computed tomography in the diagnosis of cardiac implantable electronic device infection. SROC curves of pooled data (upper curve, upper 95\% confidence interval [CI]; middle curve, true SROC curve; lower curve, lower 95\% CI curve).\textsuperscript{12–20} AUC indicates area under the curve.

Figure 4. Forest plots of individual studies and pooled sensitivity and specificity of Fluor-18-fluorodeoxyglucose positron emission tomography and computed tomography for the diagnosis of cardiac implantable electronic device pocket/generator infection. 95\% confidence intervals (CIs) are included between parentheses.\textsuperscript{12–14,17}
represents a significant advantage, particularly when the extent of infection is uncertain (Figure 7). The possibility to image extracardiac complications at the same time (septic emboli and metastatic infection) is another advantage of this technology.27,28 A proposed algorithm incorporating the use of 18F-FDG PET-CT and LS in suspected CIED infection is presented in Figure 8.

A subgroup analysis demonstrated a large difference between the accuracy of the test in the investigation of pocket/generator infection and lead/IE. Both pooled sensitivity (93%) and specificity (98%) were excellent in the pocket/generator subanalysis. However, in the lead/IE subanalysis, although specificity was still good (88%), sensitivity was significantly lower at 65% (95% CI, 53%–76%). Although at first glance the results seem disappointing, it should be noted that most of the included studies were limited because they were not specifically designed to look for IE. Normal myocardium can demonstrate significant physiological uptake of FDG. Although this would be expected to have no impact on the diagnosis of pocket/generator or extracardiac lead infection, the absence of appropriate patient preparation to ensure myocardial suppression can certainly lower the test’s accuracy leading to either false-positive results (physiological uptake falsely interpreted as infection) or false-negative results (infectious uptake overshadowed by diffuse physiological uptake). This has been well demonstrated in the cardiac sarcoid literature, and is supported by a recent meta-analysis by Tang et al,29 who demonstrated that the accuracy of 18F-FDG PET-CT is significantly affected by adequate cardiac preparation. The most recent guidelines of the American Society of Nuclear Cardiology and Society of Nuclear Medicine and Molecular Imaging on cardiac PET recommend that a similar preparation should be used in patients with suspected IE or CIED infection, but only 2 of the 6 studies included in this subanalysis used an adequate cardiac preparation.10 The sensitivity for the detection of lead infection may also be lower because the limited spatial resolution of PET limits the detection of small vegetations (<1 cm) and can lead to false-negative results. Some authors have proposed the use of a delayed acquisition (3 hours after tracer injection), and contrast-enhanced CT may help offset this limitation.17,19

Two studies14,16 had lower sensitivity than the other cohorts. Neither of these studies used cardiac preparation to suppress physiological myocardial FDG uptake. Graziosi et al26 reported that 80% of the patients with false-negative results had received antibiotic therapy for at least 48 hours before undergoing 18F-FDG PET-CT, and that diffuse myocardial FDG uptake (likely a result of the lack of cardiac preparation) was present in 50% of false-positive and 20% of false-negative. Cautela et al14 also reported that 8 of 9 patients with false-negative examination had received previous antibiotic therapy.

Our systematic review could only identify 2 studies investigating LS in CIED infection using modern technology (SPECT alone or SPECT-CT) that met inclusion criteria. While this was not enough to do a meaningful meta-analysis or pooled analysis, it should still be noted that both studies reported excellent accuracy, with sensitivity of more than 90% and specificity of 100%. The specificity
thus appeared greater with LS (although direct statistical comparison with \textsuperscript{18}F-FDG PET-CT was not made). That LS seems to be potentially more specific is not surprising; one of the weaknesses of FDG is its lack of specificity because increased glucose utilization can be seen in numerous neoplastic, postoperative, inflammatory and infectious processes (Figure 9). However, the labeled leukocytes will only accumulate over time in leukocyte recruiting infections. In this context, which examination to perform becomes primarily a question of availability and practicality. Assuming the use of a Technetium-99m labeled agent for LS, the effective radiation dose of both examinations are comparable (0.017 mSv/MBq with a recommended dose of 185–370 MBq for LS versus 0.019 mSv/MBq with a recommended dose of 2.5–5.0 MBq/kg for \textsuperscript{18}F-FDG).\textsuperscript{30,31} The labeling process of LS is more cumbersome and requires the manipulation of blood product. LS is also lengthier; the examination requires the acquisition of images at 30 minutes, 4 to 6 hours and 20 to 24 hours after injection of the radiotracer. The entire \textsuperscript{18}F-FDG PET-CT examination, including the

![Figure 7](https://example.com/figure7.png)

**Figure 7.** Fluor-18-fluorodeoxyglucose positron emission tomography and computed tomography (\textsuperscript{18}F-FDG PET-CT; axial PET with attenuation correction [A], without attenuation correction [C], axial fused attenuation corrected and CT [D], and maximum intensity projection [B]) in an 89-year-old woman with suspicion of pacemaker infection. The patient presented with pain and swelling around the pacemaker box site on her upper left chest. Ultrasound (not shown) did not reveal any evidence of infection. \textsuperscript{18}F-FDG PET-CT images demonstrate a mild diffuse uptake around the pacemaker box, but with a clearly more intense and focal area of uptake along the medial side of the box (black arrow in A, B, and C, and white arrow in D). The pattern of uptake is unchanged on nonattenuation corrected images, confirming that this is not an attenuation correction artifact (C). There was no evidence of lead infection. Only the pacemaker box was removed. Cultures were positive for *Staphylococcus aureus*.

![Figure 8](https://example.com/figure8.png)

**Figure 8.** Proposed algorithm incorporating the use of Fluor-18-fluorodeoxyglucose positron emission tomography and computed tomography (\textsuperscript{18}F-FDG PET-CT) or labeled leukocytes scintigraphy in the investigation of suspected cardiac implantable electronic device (CIED) infection.
waiting period after FDG injection and image acquisition, can be performed in <3 hours. However, it should be noted that PET-CT cameras are still less widely available than SPECT equipment. In centers where both technologies are available, the ease of use, speed and practicality of FDG trumps the potentially slightly increased specificity of LS. Regardless, LS remains an excellent examination when it is the only or most easily available option.

Limitations
The lack of a reliable “gold standard” for the diagnosis of CIED infection is a limitation in our study. Studies used either microbiological analysis on extracted devices or long-term clinical diagnosis and follow-up as a gold standard which, while subject to criticism, does represent real-life practice. The fact that in some studies the medical team was aware of the test results, and used those results in deciding between device extraction and conservative therapy may have created a bias and is another limitation.

Interpretation criteria for 18F-FDG PET-CT are also still under investigation and development, as can be seen in the included studies. Nearly all studies reported good results with visual assessment, using both attenuation-corrected and non-attenuation-corrected images to account for attenuation correction artifacts commonly induced by the metallic portions of CIED. Criteria for quantitative and semiquantitative methods, however, are more heterogeneous and variable across studies. Some studies investigated the use of a standardized uptake value cut-off threshold or ratio; however, the methods used were too heterogeneous to permit a pooled analysis (Table 3).

The lack of adequate cardiac preparation to suppress physiological FDG myocardial uptake is also a limitation. This likely resulted in a lower sensitivity for 18F-FDG PET-CT, particularly in the subanalysis for lead/IE-related CIED.

Some authors have reported false-negative 18F-FDG PET-CT results in patients with extensive antibiotic therapy before imaging. As none of the studies were designed to assess the effects of previous antibiotic therapy on the accuracy of the tests, further studies will be required to determine the impact of antibiotics on 18F-FDG uptake.

Finally, it should be noted that there are no data available on the cost-effectiveness of these tests. Also, as a direct result of the included studies being designed to investigate the diagnostic performances of these tests, there are also no data on their impact on patient outcomes.

Conclusions
Both 18F-FDG PET-CT and LS are useful and accurate for the diagnosis of CIED infection, based on our meta-analysis for 18F-FDG PET-CT and limited data for LS. Prospective studies are warranted to further investigate the impact of these functional imaging tools on clinicians’ decision-making and patients’ outcome.

Figure 9. Fluor-18-fluorodeoxyglucose positron emission tomography and computed tomography (18F-FDG PET-CT; A–C) and labeled leukocytes scintigraphy (D–G) in a 43-year-old man with suspicion of left ventricular assist device (LVAD) infection. This 43-year-old man presented 2 months after LVAD implantation complaining of left upper quadrant pain. 18F-FDG PET-CT was ordered to rule out device infection. Images demonstrated a mild diffuse uptake along parts of the inflow and outflow cannulas, as well as most of the pump housing (black arrow, C). A more intense and focal area of uptake was also seen along the more medial aspect of the pump housing. This was interpreted as positive for infection, but considering the recent implantation, and the possibility that the FDG uptake might be related to postoperative inflammatory changes, labeled leukocytes scintigraphy (LS) with 99mTc-HMPAO was also ordered. Both examinations were obtained <48 hours apart. LS planar images at 1 hour (D) and 3 hours (E) post injection demonstrated an area of uptake along the medial aspect of the pump housing (black arrow in D and E), with increasing uptake over time. Single-photon emission computed tomography-CT images obtained at 3 hours confirmed that this corresponds to the area of more focal uptake previously seen on 18F-FDG PET-CT (white arrow in G and B, respectively). Cultures on explanted device were positive for Enterobacter and coagulase-negative Staphylococci, and confirmed that the infection was limited to the pump housing. This case illustrates the complimentary role of both modalities, particularly in the early postoperative setting, when diffuse inflammatory changes might make 18F-FDG PET-CT interpretation more difficult.
Table 3. Summary of Quantitative and Semiquantitative FDG Criteria Assessed

<table>
<thead>
<tr>
<th>Study</th>
<th>Semiquantitative methods assessed</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bensimhon et al13</td>
<td>SUVmax in 5-mm radius region of interest around the most intense uptake in the following areas: cutaneous side of the generator, muscle side of the generator and each hot spot along leads (up to a maximum of 5)</td>
<td>SUVmax cut off of 2.2 successfully discriminated between infected and noninfected generator box. SUV cut off of limited value for lead infection, with significant overlap between infected and noninfected leads. Visual assessment felt to be superior for lead infection</td>
</tr>
<tr>
<td>Sarrazin et al21</td>
<td>Semiquantitative ratio defined using maximum count rate around CIED and mean count rate of normal right and left lung parenchyma on NAC images</td>
<td>Post-hoc analysis demonstrates AUC on ROC curve of 0.887 for the diagnosis of patients with CIED infection. Using a ratio of 1.87 or higher achieved a specificity of 100%</td>
</tr>
<tr>
<td>Cautela et al14</td>
<td>SUVmax of the generator</td>
<td>SUVmax ≥1.21 was optimal to differentiate infected and noninfected generator (sensitivity of 93% and specificity of 83%)</td>
</tr>
<tr>
<td></td>
<td>SUV ratio using SUVmax of the generator and SUVmax of the contralateral noninfected prepectoral region.</td>
<td>Ratio &gt; 2.1 was optimal to differentiate infected and noninfected generator (sensitivity of 93% and specificity of 83%)</td>
</tr>
<tr>
<td></td>
<td>Ratio on NAC images using maximum count rate of the generator and maximum count rate of the contralateral noninfected prepectoral region</td>
<td>Ratio ≥1.06 correctly differentiated between all infected and noninfected generator</td>
</tr>
<tr>
<td>Leccisotti et al17</td>
<td>SUVmax of visually identified hot spot.</td>
<td>Significant difference observed between infected and noninfected generator (mean SUVmax 4.73±1.72 vs 3.51±1.92 respectively) and leads (3.25±0.93 vs 1.11±0.70 respectively, on delayed 3h images). No cut off proposed by the authors</td>
</tr>
<tr>
<td></td>
<td>SUV ratio using SUVmax of visually identified hot spot and SUVmax of the blood pool (measured in the left atrium)</td>
<td>Significant difference observed between infected and noninfected generator (mean SUV ratio 3.71±1.99 vs 1.61±1.14 respectively) and leads (3.01±1.31 vs 0.70±0.09, respectively, on delayed 3-h images). No cut-off proposed by the authors</td>
</tr>
<tr>
<td>Ahmed et al22</td>
<td>Semiquantitative ratio defined using maximum count rate around CIED and mean count rate of normal right and left lung parenchyma on NAC images</td>
<td>AUC on ROC curve of 0.98 for the identification of patients who go on to require device extraction, with an optimal cut off of 2.0 (sensitivity of 97% and specificity of 98%)</td>
</tr>
<tr>
<td>Memmott et al18</td>
<td>SUVmax of visually identified hot spot, at both 90 and 180 min post FDG injection.</td>
<td>AUC on ROC curve of 0.96 at 90 min and 0.92 at 180 min for the diagnosis of patients with CIED infection</td>
</tr>
<tr>
<td></td>
<td>Ratios using either SUVmax (AC) or maximum count rate (NAC) of visually identified hot spot over lung parenchyma (mean count rate on NAC images), contralateral reference region (SUVmax on AC and mean count rate on NAC images), mediastinal blood pool (SUVmax) and hepatic blood pool (SUVmax). Ratios calculated at both 90 and 180 min post FDG injection</td>
<td>The accuracy of these methods varied significantly, with AUC on ROC curve between 0.71 and 0.97. The ratio using the hepatic blood pool was found to be the most accurate parameter studied, with an AUC on ROC curve of 0.94 at 90 min and 0.97 at 180 min for the diagnosis of patients with CIED infection</td>
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<tr>
<td>Pizzi et al19</td>
<td>SUVmax of visually identified abnormal area</td>
<td>Cut-off values found to be similar to patients’ background value (1.21 for SUVmax and 1.06 for SUV ratio) and of limited value because of poor specificity of 50%</td>
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<td>SUV ratio using SUVmax of abnormal area and mean SUV of aortic blood pool</td>
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AC indicates attenuation corrected; AUC, area under the curve; CIED, cardiac implantable electronic device; NAC, nonattenuation corrected; ROC, receiver operating characteristic; SUVmax, maximum standardized uptake value; and SUVmean, mean standardized uptake value.

Acknowledgments

Dr Juneau is a Cardiac Imaging Fellow at the University of Ottawa Heart Institute supported by a grant from the Centre Hospitalier de l’Université de Montréal and its Foundation and the Vered-Beanlands Fellowship in Cardiology Research. Dr Beanlands is a career investigator supported by the Heart and Stroke Foundation of Ontario, a Tier 1 Research Chair supported by the University of Ottawa, and the University of Ottawa Heart Institute Vered Chair in Cardiology. Dr Chow holds the Saul and Edna Goldfarb Chair in Cardiac Imaging Research.

Disclosures

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References


18. Orvin K, Goldberg E, Bernstein H, Groshar D, Sage A, Kornowski R, Bishara J. The role of FDG-PET/CT imaging in early detection of

**CLINICAL PERSPECTIVE**

The diagnosis of cardiac implantable electronic device infection can be challenging. We performed a systematic review of the literature and meta-analysis on the use of Fluor-18-fluorodeoxyglucose positron emission tomography and computed tomography and leukocyte scintigraphy for the diagnosis of this condition. Our work shows that both modalities are accurate and can help in confirming or excluding the diagnosis, as well as help to more accurately define the extent of infection. On the basis of the currently available data, these imaging tests should not replace the standard work-up for patients with suspected cardiac implantable electronic device infection, but should rather be used as a complementary tool. Clinicians should consider their use in patients where the diagnosis is uncertain after initial work-up, when the extent of infection is uncertain, or when there is a marked difference between the clinical impression and the standard work-up results. The sensitivity of Fluor-18-fluorodeoxyglucose positron emission tomography and computed tomography seems to be lower for intracardiac lead/infective endocarditis infection than pocket/generator infection. This is potentially a result of the presence of physiological fluorodeoxyglucose uptake in the myocardium. Additional research is needed to determine whether adequate cardiac preparation can overcome this obstacle and to establish the cost-effectiveness of these imaging interventions and their impact on patient outcome.
Positron Emission Tomography and Single-Photon Emission Computed Tomography Imaging in the Diagnosis of Cardiac Implantable Electronic Device Infection: A Systematic Review and Meta-Analysis

Daniel Juneau, Mohammad Golfam, Samir Hazra, Lionel S. Zuckier, Shady Garas, Calum Redpath, Jordan Bernick, Eugene Leung, Sharon Chih, George Wells, Rob S.B. Beanlands and Benjamin J.W. Chow

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## Supplemental Material

### Supplemental Methods

#### Appendix 1. Complete search strategies.

FDG-PET-CT – Cardiovascular Infections/Inflammation

Final Strategies
2015 Nov 26-27

OVID Multifile

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1974 to 2015 Week 47>

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In

Dium Radioisotopes/ (9896)

Technetium/du (14140)

Technetium Tc 99m Exametazime/ (7586)

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Hexamethylpropyleneamine Oxime) adj3 (imaging or radioactiv* or radio-activ* or radioisotop* or radio-isotop* or radionuclide* or radio-nuclide* or scan* or scintigraph*)).tw,kw. (998)

((HMPAO-99m-Tc or HMPAO-99mTc or "HMPAO-(99m)Tc" or HMPAO Tc-99m or

Hexamethylpropyleneamine Oxime Tc-99m or Hexamethylpropylene-amine Oxime Technetium Tc 99m or Hexamethylpropyleneamine Oxime Technetium Tc 99m) adj3 (imaging or radioactiv* or radio-activ* or radioisotop* or radio-isotop* or radionuclide* or radio-nuclide* or scan* or scintigraph*)).tw,kw. (5)

exp Leukocytes/ri (558)

((label?ed or radiolabel?ed or radio-label?ed) adj1 (granulocyte? or leucocyte? or leukocyte? or WBC or WBCs or white blood cell? or white blood corpuscle?)).tw,kw. (3371)

((granulocyte? or leucocyte? or leukocyte? or WBC or WBCs or white blood cell? or white blood corpuscle?) adj3 (imaging or radioactiv* or radio-activ* or radioisotop* or radio-isotop* or radionuclide* or radio-nuclide* or scan* or scintigraph*)).tw,kw. (3346)

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((indium-111-label?ed or 111In-label?ed or ((111In)" adj label?ed) or In-111 label?ed or In111 label?ed) adj3 (granulocyte? or leucocyte? or leukocyte? or WBC or WBCs or white blood cell? or white blood corpuscle?)).tw,kw. (884)

or/64-74 (36239)

58 or 63 or 75 (118253)

71 51 and 76 (3542)

exp Animals/ not (exp Animals/ and Humans/) (9776432)

77 not 78 (3170)

80 (comment or editorial or interview or news).pt. (1640361)

81 (letter not (letter and randomized controlled trial)).pt. (1871051)

82 79 not (80 or 81) (2980)

83 82 use prnz (1142) [MEDLINE RECORDS]

84 endocarditis/ (23773)

85 bacterial endocarditis/ (40171)

86 exp fungal endocarditis/ (331)

87 prosthetic valve endocarditis/ (915)

88 subacute endocarditis/ (312)

89 endocardit*.tw,kw. (63581)

90 or/84-89 (78707)

91 exp heart valve prosthesis/ (61274)

92 exp infection/ (3470661)

93 inflammation/ (424482)

94 cardiovascular inflammation/ (555)

95 91 and (92 or 93 or 94) (8525)

96 (prosthe* adj3 valv* adj5 (infect* or inflam*)).tw,kw. (1251)

97 95 or 96 (9158)

98 exp valvular heart disease/ (229051)
99 98 and (92 or 93 or 94) (20012)
100 ((aort* or arter* or cardia* or cardio* or early valve* or heart? or mitral* or bicuspid* or bi-
- cuspid* or tricuspid* or tri-cuspid* or valve or valves or valvular or ventricle* or ventricular* or vessel
wall?) adj5 (infect* or inflam*)).tw,kw. (90136)
101 99 or 100 (106549)
102 exp blood vessel graft/ (175900)
103 exp blood vessel prosthesis/ (39615)
104 (102 or 103) and (92 or 93 or 94) (14361)
105 PVGI.tw,kw. (30)
106 ((blood vessel prosth* or vascular prosth* or vascular graft* or blood vessel graft*) adj5
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108 exp artificial heart pacemaker/ (69690)
109 exp heart assist device/ (33634)
110 (108 or 109) and (92 or 93 or 94) (10650)
111 ((cardia* or cardio* or heart$1 or heart-assist*) adj3 (device* or pump*) adj5 (infect* or
inflam*)).tw,kw. (889)
112 ((cardia* or cardio* or heart$1 or implantable) adj3 defibrillat* adj5 (infect* or inflam*)).tw,kw.
(361)
113 ((intravascular device* or intra-vascular device* or pacemaker* or artificial ventricle* or artificial
heart ventricle* or ventricle assist device* or ventricular assist device* or vascular assist device*) adj5
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114 ((CIED or CIEDs or ICD or ICDs or LVAD or LVADs or VAD or VADs) adj5 (infect* or inflam*)).tw,kw.
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115 or/110-114 (13697)
116 vasculitis/ (41488)
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118 exp arteritis/ (52655)
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122 pericarditis/ or constrictive pericarditis/ (26667)
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124 pericardium/ (24774)
125 124 and (92 or 93 or 94) (1932)
126 ((pericardi* or peri-cardi* or epicardi* or epi-cardi*) adj5 (infect* or inflam*)).tw,kw. (2575)
127 122 or 123 or 125 or 126 (34664)
128 exp myocarditis/ (32732)
129 (myocardit* or myo-cardit* or cardit*).tw,kw. (32018)
130 exp heart muscle/ (352462)
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137 positron emission tomography/ (136386)
138 and 137 (42181)
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146 indium 111/ (5977)
147 hexamethylpropylene amine oxime technetium tc 99m/ (4654)
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149 (HMPAO-99m-Tc or HMPAO-99mTc or "HMPAO-(99m)Tc" or HMPAO Tc-99m or Hexamethylpropyleneamine Oxime Tc-99m or Hexamethylpropylene-amine Oxime Technetium Tc 99m or Hexamethylpropyleneamine Oxime Technetium Tc 99m adj3 (imaging or radioactiv* or radio-activ* or radioisotop* or radio-isotop* or radionuclide* or radio-nuclide* or scan* or scintigraph*).tw,kw. (9)
150 leukocyte in 111/ (650)
151 ((label?ed or radiolabel?ed or radio-label?ed) adj1 (granulocyte? or leucocyte? or leukocyte? or WBC or WBCs or white blood cell? or white blood corpuscle?)).tw,kw. (3371)
152 ((granulocyte? or leucocyte? or leukocyte? or WBC or WBCs or white blood cell? or white blood corpuscle?) adj3 (imaging or radioactiv* or radio-activ* or radioisotop* or radio-isotop* or radionuclide* or radio-nuclide* or scan* or scintigraph*).tw,kw. (3346)
153 ((indium-111-label?ed or 111In-label?ed or ("(111In)" adj label?ed) or In-111 label?ed or In111 label?ed) adj3 (imaging or radioactiv* or radio-activ* or radioisotop* or radio-isotop* or radionuclide* or radio-nuclide* or scan* or scintigraph*).tw,kw. (911)
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156 141 or 145 or 155 (91995)
157 135 and 156 (3447)
158 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (40209729)
159 exp humans/ or exp human experimentation/ or exp human experiment/ (31154163)
160 158 not 159 (9057215)
161 157 not 160 (3314)
162 editorial.pt. (898431)
163 letter.pt. not (letter.pt. and randomized controlled trial/) (1866594)
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Date Run:  26/11/15 22:04:46.426
Description:  Ottawa Heart Institute - 2015 Nov 26

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((labeled or labelled or radiolabeled or radiolabelled or "radio-labeled" or "radio-labelled") near/1 (granulocyte* or leucocyte* or leukocyte* or WBC or WBCs or "white blood cell" or "white blood cells" or "white blood corpuscle" or "white blood corpuscles"):ti,ab,kw   26
((granulocyte* or leucocyte* or leukocyte* or WBC or WBCs or "white blood cell" or "white blood cells" or "white blood corpuscle" or "white blood corpuscles") near/3 (imaging or radioactiv* or (radio next activ*) or radioisotop* or (radio next isotop*) or radionuclide* or (radio next nuclide*) or scan* or scintigraph*)):ti,ab,kw   49
("indium-111-labeled" or "indium-111-labelled" or "111In-labeled" or "111In-labelled" or "(111In) labeled" or "(111In) labelled" or "In-111 labeled" or "In-111 labelled" or "In111 labeled" or "In111 labelled") near/3 (imaging or radioactiv* or (radio next activ*) or radioisotop* or (radio next isotop*) or radionuclide* or (radio next nuclide*) or scan* or scintigraph*)):ti,ab,kw   9
(or #64-#74)    414
#58 or #63 or #75    1517
#51 and #76    53

DSR – 1
DARE – 4
CENTRAL – 48

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Search Query                              Items
#84   Search #82 AND #83                   found
#82   Search #79 NOT (#80 OR #81)          2071
#81   Search letter[pt] NOT (letter[pt] AND randomized controlled trial[pt])    892018
Search Query | Items found
--- | ---
#79 Search #77 NOT #78 | 2182
#78 Search Animals[mesh] NOT (Animals[mesh] AND Humans[mesh]) | 4063250
#77 Search #51 AND #76 | 2520
#76 Search #58 OR #63 OR #75 | 72252
#75 Search #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 | 40393
#70 Search Leukocytes/ri [mesh] | 553


#67 Search Technetium Tc 99m Exametazime [mesh]

#66 Search Technetium/du [mesh]

#65 Search Indium Radioisotopes[mesh]

#64 Search Indium/du [mesh]

#63 Search #59 OR #60 OR #61 OR #62 Schema: syn


#60 Search Gallium Radioisotopes [mesh]

#59 Search Gallium/du [mesh]

#58 Search #52 OR #55 OR #56 OR #57
Search Query | Items found
--- | ---
#55 | Search #53 AND #54 | 14073
#54 | Search Positron-Emission Tomography [mesh] | 37035
#53 | Search Fluorodeoxyglucose F18 [mesh] | 21150
#52 | Search Fluorodeoxyglucose F18/du [mesh] | 17301
#51 | Search #4 OR #10 OR #15 OR #21 OR #30 OR #37 OR #43 OR #49 OR #50 | 276007
#49 | Search #44 OR #45 OR #47 OR #48 | 42817
#48 | Search ((myocardi*[tw] OR myo-cardi*[tw] OR cardiac muscle*[tw] OR heart muscle*[tw]) AND (infect*[tw] OR inflam*[tw])) OR ((myocardi*[ot] OR myo-cardi*[ot] OR cardiac muscle*[ot] OR heart muscle*[ot]) AND (infect*[ot] OR inflam*[ot])) | 31704
#47 | Search #46 AND (#7 OR #12) | 2684
#46 | Search Myocardium[mesh] | 163935
#45 | Search myocardit*[tw] OR myo-cardit*[tw] OR cardit*[tw] OR myocardit*[ot] OR myo-cardit*[ot] OR cardit*[ot] | 17755
#44 | Search Myocarditis[mesh] | 11917
#43 | Search #38 OR #39 OR #41 OR #42 | 17435
#41 | Search #40 AND (#7 OR #12) | 501
#40 | Search Pericardium[mesh] | 12889
#39 | Search pericardit*[tw] OR pericardit*[ot] | 13666
Search Query | Items found
--- | ---
#38 Search Pericarditis[mesh] | 10376
#37 Search #31 OR #32 OR #33 OR #34 OR #35 OR #36 | 53774
#35 Search Arteritis[mesh] | 18775
#33 Search Aortitis[mesh] | 1240
#31 Search Vasculitis[mesh:noexp] | 11345
#30 Search #25 OR #26 OR #27 OR #28 OR #29 | 9941
#25 Search (#22 OR #23 OR #24) AND (#7 OR #12) | 1608
#24 Search Heart-Assist Devices[mesh] | 9617
#23 Search Defibrillators, Implantable[mesh] | 12360
#22 Search Pacemaker, Artificial[mesh] | 23576
#21 Search #18 OR #19 OR #20 | 7115
#20 Search ((blood vessel prosthе*[tw] OR vascular prosthе*[tw] OR vascular graft*[tw] OR blood vessel graft*[tw]) AND (infect*[tw] OR inflam*[tw])) OR ((blood vessel prosthе*[ot] OR vascular prosthе*[ot] OR vascular graft*[ot] OR blood vessel graft*[ot]) AND (infect*[ot] OR inflam*[ot])) | 5214
Search Query | Items found
--- | ---
#19 Search PVGI[tw] OR PVGI[ot] | 17
#18 Search (#16 OR #17) AND (#7 OR #12) | 4530
#17 Search Blood Vessel Prosthesis[mesh] | 37053
#16 Search Vascular Grafting[mesh] | 85736
#15 Search #13 OR #14 | 177441
#13 Search #11 AND (#7 OR #12) | 5086
#12 Search Infection [mesh] | 651891
#11 Search Heart Valve Diseases [mesh] | 96621
#10 Search #8 OR #9 | 6525
#8 Search #5 AND (#6 OR #7) | 1036
#7 Search Inflammation [mesh:noexp] | 106657
#6 Search Prosthesis-Related Infections [mesh] | 8776
#5 Search Heart Valve Prosthesis [mesh] | 29457
#4 Search #1 OR #2 OR #3 | 33880
#3 Search endocardit*[tw] OR endocardit*[ot] | 33880
#2 Search Endocarditis, Bacterial [mesh] | 18680
#1 Search Endocarditis [mesh:noexp] | 6157
### Supplemental Tables

**Appendix 2. QUADAS-2**

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk of Bias</th>
<th>Applicability Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient Selection</td>
<td>Index Test</td>
</tr>
<tr>
<td>Ahmed 2015(^1)</td>
<td>L</td>
<td>U</td>
</tr>
<tr>
<td>Bensimhon 2011(^2)</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Cautela 2013(^3)</td>
<td>H</td>
<td>L</td>
</tr>
<tr>
<td>Dell’Aquilla 2016(^4)</td>
<td>U</td>
<td>L</td>
</tr>
<tr>
<td>Erba 2013(^5)</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Graziosi 2014(^6)</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Leccisotti 2014(^7)</td>
<td>H</td>
<td>L</td>
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<tr>
<td>Litzler 2010(^8)</td>
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<td>L</td>
</tr>
<tr>
<td>Memmott 2016(^9)</td>
<td>U</td>
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<td>Pizzi 2015(^10)</td>
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</tr>
<tr>
<td>Ploux 2011(^11)</td>
<td>U</td>
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</tr>
<tr>
<td>Sarrazin 2012(^12)</td>
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<td>U</td>
</tr>
<tr>
<td>Tili 2015(^13)</td>
<td>U</td>
<td>L</td>
</tr>
</tbody>
</table>

H : High risk       L : Low risk       U : Unclear risk
Supplemental Material References


