FDG-PET/CT in fever of unknown origin, bacteremia, and febrile neutropenia

Søren Hess\textsuperscript{1,2}

\textsuperscript{1}Department of Radiology and Nuclear Medicine, Hospital of Southwest Jutland, Denmark
\textsuperscript{2}Department of Regional Health Research, University of Southern Denmark, Odense, Denmark

\textit{Corresponding author}

Søren Hess, MD
Senior consultant, associate professor, head of section (Nuclear Medicine & PET)
Department of Radiology and Nuclear Medicine, Hospital of Southwest Jutland
Finsensgade 35, 6700 Esbjerg, Denmark, soeren.hess@rsyd.dk; +45 3036 1052
Orchid ID: 0000-0003-1249-133X

\textbf{DISCLOSURE STATEMENT}

Nothing to disclose

\textbf{KEYWORDS (4-8)}

FDG; PET; PET/CT; fever of unknown origin; bacteremia; febrile neutropenia; infection
KEYPOINTS (3-5 bullets)

- The literature on fever on unknown origin (FUO), bacteremia, and febrile neutropenia is generally heterogeneous and mainly based on retrospective series; in bacteremia and febrile neutropenia series are relatively small.
- FUO, bacteremia, and febrile neutropenia are diagnostic challenges; FDG-PET/CT is a well-established modality and should be considered early in the diagnostic work-up algorithm.
- In FUO, FDG-PET/CT is overall helpful in half the patients even after extensive workup and superior to gamma camera based radionuclide modalities – but diagnostic yield is highly dependent on patient selection (e.g. clear definition of FUO), and a mandatory presence of elevated inflammatory markers (e.g. C-reactive protein).
- FDG-PET/CT is cost-effective in establishing metastatic infection in bacteremia with impact on morbidity, mortality, and treatment strategy.

SYNOPSIS (100-150 words)

Fever of unknown origin (FUO), bacteremia and febrile neutropenia are diagnostic challenges; FDG-PET/CT is a well-established modality in infection imaging and the literature is increasingly supporting the use in these settings and it should be considered early in the diagnostic work up algorithm with the caveats in mind that studies are relatively small, heterogeneous, and mostly retrospective. In FUO, FDG-PET/CT is overall helpful in half the patients despite extensive workup prior to FDG-PET/CT, but diagnostic yield is still highly dependent on patient selection (e.g. clear definitions of FUO) and inflammatory markers. In bacteremia, FDG-PET/CT is cost-effective, reduces morbidity and mortality, and impacts treatment strategy. Thus, although the use of FDG-PET/CT in these domains is still not established as part of a definitive diagnostic strategy, but based on current knowledge, FDG-PET/CT may point clinicians in the right direction and help establish a final diagnosis in a difficult population and should be considered early in the diagnostic process.
INTRODUCTION

Fever of unknown origin (FUO), bacteremia, and febrile neutropenia share some common features, e.g. heterogeneous patient populations and potential systemic nature but often vague or non-specific symptoms unable to locate the origin of disease; imaging is pivotal to establish a final diagnosis, but despite the availability of multiple modalities, a significant proportion of patients remain underdiagnosed. FDG-PET/CT has potential in all three domains, but at present no definitive diagnostic strategy is established in either setting; this review summarizes the current evidence for the use of FDG-PET/CT with a focus on potential as well as challenges and caveats.

FEVER OF UNKNOWN ORIGIN

FUO remains a challenging clinical entity; patient populations are heterogeneous, diagnostic clues are often sparse, non-specific or non-existing. Although final diagnosis may overall be categorized as infection, non-infectious inflammatory disease, malignancy, or miscellaneous, more than 200 specific differential diagnoses are recognized [1], and despite extensive diagnostic workup a firm final diagnosis is never reached in a significant proportion of patients; in the papers included here the fraction of patients without a final diagnosis ranged 0-47% (Table 1). Since the first definition by Petersdorf et al. in 1961 [2], modifications have been implemented to reflect a health-care system increasingly based on out-patient activity [1] (Table 2).

In the past two decades, radionuclide imaging in FUO has shifted more and more from classic gamma camera-based imaging towards FDG-PET and FDG-PET/CT. This is supported not only by the increasing availability of PET/CT-scanners, better logistics with faster results and avoidance of handling patient blood, but also several comparative studies with results that generally favored FDG-PET or FDG-PET/CT over $^{67}$Gallium-citrate ($^{67}$Ga-citrate) or labelled white blood cells (WBC). An early prospective comparison of FDG-PET and the then gold-standard whole-body planar $^{67}$Ga-citrate in 58 patients yielded a final diagnosis in 64%; FDG-PET was helpful in 35%, $^{67}$Ga-citrate in 25%, and all $^{67}$Ga-positive findings were also FDG-avid. Thus, the authors concluded (based on better logistics and non-inferior results) that FDG-PET could replace $^{67}$Ga-citrate [3]. A very recent study prospectively compared FDG-PET/CT with $^{67}$Ga-citrate SPECT/CT in 58 patients and found the two helpful in 72% and 55%, respectively, with a false-positive rate of 44% in FDG-PET/CT and a false-negative rate of 55% with $^{67}$Ga-citrate [4].

An early prospective comparison of $^{111}$Indium-labelled WBC scintigraphy ($^{111}$In-WBC) and FDG-PET/CT at first glance strongly favored $^{111}$In-WBC, i.e. sensitivity and specificity was 71% and 92% versus 50% and 46%, respectively, but some caveats of potential selection and verification bias pertain to
this study [5, 6]. Thus, a later prospective study of 23 patients yielded opposite results, i.e. sensitivity and specificity of 86% and 78% (FDG-PET/CT) versus 20% and 100% (111In-WBC) [7].

A recent meta-analysis strongly favors FDG-PET/CT with sensitivities/specificities for FDG-PET/CT, FDG-PET, 67Ga-citrate, and WBC scintigraphy of 86%/52%, 76%/50%, 60%/63%, and 33%/83%, respectively, and an overall diagnostic yield in the four modalities of 58%, 44%, 35%, and 20%, respectively [8].

The studies with a focus on diagnostic accuracy of FDG-PET and FDG-PET/CT in FUO (Table 1) comprise the bulk of the available literature [9-36], although the list is not considered exhaustive as the literature search was not systematic; they also reflect the heterogeneous nature of the populations and methodologies, including variable reference standards, and the challenges related to this particular setting; definitions of FUO vary considerably (some also include inflammation of unknown origin (IUO), i.e. prolonged elevation of inflammatory markers without fever) which hampers direct comparison of study populations; most employ FDG-PET/CT, although a few of the older papers are based on stand-alone PET; only few series are prospective. Populations are generally relatively small, median 48 patients (range 12-376), and a final diagnosis is not reached in all patients, median 71% (range 50-100%).

How to assess the diagnostic value of FDG-PET/CT in the setting of FUO is controversial; instead of classic diagnostic parameters like sensitivity and specificity, which may be difficult to define and dichotomize with the abundance of potential differential diagnosis, most studies report the proportion of patients in whom FDG-PET/CT was considered helpful in the diagnostic process, median 54% (range 26-92%). However, how helpful is defined is also a matter of debate, e.g. only true positive findings that provide direct guidance to the clinician by establishing a diagnosis directly based on FDG-uptake, or if also true negative findings that may rule out focal infection, inflammation or malignancies with a high negative predictive value and generally holds favorable prognosis. For instance, Pelosi et al. defined only true positives as helpful, i.e. 46% (11 FDG-positive patients of 24), but if the 10 true negatives were also considered helpful the rate would increase to 88% [23]. Jaruskova et al. directly characterized 67 negative FDG-PET/CT scans as not-helpful. Conversely, e.g. Keidar et al. also considered true negatives as helpful and reported a negative predictive value (NPV) of 100% [16], like also Bleeker-Rovers et al. categorized 34 FDG-negative scans as true negative [37].

Another highly variable issue is the diagnostic pathways prior to FDG-PET/CT, which may contribute significantly to heterogeneity and potentially introduce selection bias. Some studies present comparative data on FDG-PET or FDG-PET/CT versus CT, e.g. Manohar et al. with sensitivity, specificity, and accuracy of FDG-PET/CT being 90%, 97%, and 92%, respectively, versus 44%, 67%, and 52%, respectively, for CT [28]. Bleeker-Rovers et al. found positive predictive value (PPV) and NPV for FDG-PET (65% and 90%) better than for CT (48% and 86%) [37], while Rosenbaum et al. found 100% PPV for FDG-PET compared to 39% for diagnostic CT [21].
Most studies employ several diagnostic modalities before referral to FDG-PET/CT, e.g. Buch-Olsen et al. reported that 57 patients underwent 126 examinations prior to FDG-PET/CT (not including chest x-ray and ultrasound of the abdomen which comprised the local initial routine workup in FUO) [30]. The earlier FDG-PET/CT is introduced the higher the potential impact as every imaging modality performed prior to FDG-PET/CT may potentially make a diagnosis and select patients to not undergo further modalities, thus leaving the harder cases to FDG-PET/CT. For instance, Ferda et al. reported the highest rate of helpfulness (92%), and they used FDG-PET/CT as entry method to the study [19].

Only limited data is available on cost-effectiveness, but according to Buch-Olsen et al. basic cost of FDG-PET/CT was covered if admission time was shortened by only 2.2 days which is not unrealistic when considering the potential for precisely guided therapy [30].

The relative abundance of studies on FUO is reflected in several systematic reviews and meta-analysis available. However, the abovementioned caveats and differences among studies are also reflected in the heterogeneity that is present in all of them including the variable outcome measures in the various papers. The two oldest [38, 39] and the newest [40] all focused on pooled sensitivity and specificity, i.e. 83-98% and 58-86%, respectively, with a tendency towards better sensitivity and specificity with FDG-PET/CT than stand-alone FDG-PET. It is worth mentioning that Hao et al. included and pooled values from several different settings of FUO including human immunodeficiency virus (HIV), intensive care unit (ICU) patients, and pediatric populations [39], while Kan et al. pooled both FUO and IUO [40]. Besson et al. found that abnormal FDG uptake was associated with a final diagnosis in 83% versus only 36% in patients with a normal FDG-PET/CT [41], whereas Bharucha et al. found an overall diagnostic yield of 56% which was reduced to 32% in patients who had undergone diagnostic CT prior to FDG-PET/CT [42]. Finally, Takeuchi et al. found that patients had a high likelihood of spontaneous remission with a normal FDG-PET/CT after a series of diagnostic procedures without final diagnosis [43].

FDG-PET/CT has also been explored in more specialized cases of FUO, e.g. as mentioned HIV: Two small series, one retrospective (n=10) and one prospective (n=20), found FDG-PET/CT helpful in 80-90% of patients [44, 45], and the prospective study found FDG-uptake in central lymph nodes to be associated with focal infection with 100% specificity, whereas absence of FDG in central lymph nodes had 100% NPV with regards to focal infection [45]. Also in critically ill ICU patients has FDG-PET/CT shown potential, i.e. sensitivity and specificity of 100% and 79%, respectively. The study included 33 patients with 17 being investigated for FUO, and in line with the conventional FUO patients mentioned above most patients had undergone extensive workup prior to FDG-PET/CT, e.g. either echocardiography or CT in two-thirds of the patients [46].

Studies in various pediatric settings have found similar results. Two retrospective studies examined children with FUO in 69 [47] and 31 patients [48], respectively: Final diagnosis was reached in 54% and 52%, respectively, and FDG PET or FDG-PET/CT was considered helpful in 32% and 45%,
respectively [47, 48]. Sturm et al. examined 11 children with FUO while waiting for liver transplantation; five were positive with intrahepatic FDG-uptake and based on these findings the patients underwent transplantation after continuous antibiotic treatment and images correlated with bacterial cultures from the excised livers in all patients [49].

In order to optimize the usage of FDG-PET/CT in FUO several of the abovementioned diagnostic studies have included some assessments of factors that may influence or predict the diagnostic yield, e.g. adenopathy and low hemoglobin levels [25], short disease course [31], and age >50 years [33], whereas others did not find inflammatory markers to predict positive findings [11]. A few studies have focused more directly on potential predictors of diagnostic success, and suspected malignancies, the number of positive inflammatory markers, and increasing values of CRP and ESR all seemed positively correlated with positive yield or greater likelihood of a beneficial result [50-52]. Overall, no firm conclusions or cut-offs can be established, but one study found FDG-PET/CT 100% negative in patients with CRP values < 5 mg/L [50], and Bleeker-Rovers et al. found that FDG-PET was not helpful if ESR/CRP was normal [13].

A few studies have assessed cost [53, 54], e.g. Balink et al. compared cost in two groups with IUO, one group underwent FDG-PET/CT (n=46), the other did not (n=46). A final diagnosis was reached in 70% of patients with FDG-PET/CT compared to only 30% of patients in the other group; costs from diagnostic procedures as well as hospitalization were lower in the group worked up with FDG-PET/CT due shorter duration [53]. The authors of both studies concluded that FDG-PET/CT has the potential to become cost-effective in FUO/IUO.

**BACTEREMIA**

Bacteremia is similar to FUO in that it is systemic in nature with possible infectious sites throughout the body. Nonetheless, several aspects of bacteria in the bloodstream are significantly different; it may lead to metastatic infections through secondary hematogenic spread, e.g. prosthetic infections, and spondylodiscitis. Thus, bacteremia can be classified as uncomplicated or metastatic, and morbidity is significantly higher in the latter cases, probably due to insufficient eradication; in uncomplicated bacteremia two weeks treatment is usually sufficient, while complicated bacteremia with metastatic foci requires several weeks longer. Thus, identification of metastatic infection may have significant clinical impact, but identifying such metastatic infections remains difficult since as many as 50% may be present without signs or symptoms pointing to the areas of interest [55].

In their landmark study, Vos et al. prospectively included 115 patients with gram-positive bacteremia to undergo FDG-PET/CT as part of workup and compared them to a matched historical control group of 230 bacteremia patients where FDG-PET/CT was not performed. Abnormal findings were verified using a composite reference standard including other imaging, microbiology, or pathology. Results were favorable in several respects, i.e. metastatic foci were diagnosed in significantly more cases than controls
(67.8% vs. 35.7%), FDG-PET/CT was the first modality to locate infectious foci in 30% of patients, relapse rate declined from 7.4% in controls to 2.6% in cases, and mortality decreased from 32.2% to 19.1% [56, 57]. Based on the same dataset, the same group also assessed cost-effectiveness, and concluded that the impact on morbidity and mortality by introduction of FDG-PET/CT to the routine diagnostic workup was indeed cost-effective in high-risk patients with gram-positive bacteremia [58].

Subsequent studies (Table 3) have all included some of these aspects while also adding further knowledge, albeit sometimes with different wording. For instance, some studies describe the number of metastatic foci whilst others present a detection rate for infectious foci, which is in essence just semantics – thus, despite different designation studies find comparable rates for the detection of infectious/metastatic foci, i.e. 45.8-73.7% [56, 57, 59-63]. It is noteworthy that Berrevoets et al. found 71.2% of the patients with metastatic foci (73.7% of all patients) to be without any signs or symptoms to suggest localization of such foci [59], and Brøndserud et al. [61] corroborated the finding that FDG-PET/CT is the incremental modality in a significant proportion, i.e. 41% (as compared to 30% in the study by Vos et al.[56]).

As a supplement to crude diagnostic rate, some studies also assessed the clinical impact on patient management, either changes in treatment or a combination of diagnostic and treatment related impact. Thus, Brøndserud et al. found “high clinical impact” in 47%, i.e. diagnostic findings only present or unequivocal on FDG-PET/CT, establishment of alternative diagnoses, or changes in treatment [61]. Berrevoets et al. [59] and Tsai et al. [60] only assessed treatment and found FDG-PET/CT to facilitate changes in 74% and 54.1%, respectively, whereas the fraction of treatment changes only constituted 14.7% of the high impact cases in the aforementioned study by Brøndserud et al. [61]. Another approach to personalized treatment based on FDG-PET/CT was presented in another study by the group of Berrevoets et al., i.e. 36 cases (bacteremia with high risk of metastatic spread, but negative echocardiography and FDG-PET/CT) treated with antibiotics for the same duration (ca. 15 days) as a control group of uncomplicated bacteremia patients: Relapse rate and mortality was similar in the two groups suggesting that a shorter course of antibiotics than recommended in complicated bacteremia is safe in cases without signs of metastatic infections [64].

Several studies have assessed if any parameters impact or predict the diagnostic yield. Tsai et al. found that CRP values higher than a cut-off of 54 mg/L resulted in positive findings in 86%, whereas this was the case in only 46% of patients with lower values. The proportion of patients with management changes based on FDG-PET/CT remained comparable (54%) [60]. Brøndserud et al. found no negative impact on diagnostic yield associated with duration of work-up period or antibiotics prior to FDG-PET/CT (which could have induced false negative findings), or underlying malignancies (which could have introduced either false negative or false positive findings) [61]. On the other hand, Pijls et al. established a significant negative association between duration of antibiotics prior to scan and diagnostic yield in both univariate and multivariate regression analysis; i.e. the overall detection rate was 64.5%, which increased to 71% in patients
with < 7 days antibiotics, whereas it decreased to 52%, 61%, and 38%, after 7-14 days, 15-21 days, and > 22 days, respectively.

Another important parameter is mortality, which Vos et al. found positively impacted by FDG-PET/CT, presumably due to higher diagnostic rate of metastatic infections leading to more specific treatment for prolonged periods. Similar results were encountered by Berrevoets et al.[59] and Yildiz et al. [63], i.e. mortality was reduced from 32.7% (controls) to 12.4% (cases), and from 44.4% (controls) to 16.6% (cases), respectively.

Limited data is available in pediatrics, but at least one retrospective study found FDG-PET/CT to have potential also in this clinical setting; 13 children with bacteremia and suspected metastatic infection underwent FDG-PET/CT resulting in 5 true positives, 6 true negatives, 2 false positives, and no false negatives to yield PPV of 71% and NPV of 100%. Thus, the authors concluded that 38% (5/13) was clinically helpful, but again this may be considered conservative as only true positive findings were considered helpful. If true negatives are also considered clinically important, FDG-PET/CT could actually be considered helpful in 85% (11/13) [65]. Nonetheless, further studies are needed in this particular setting.

**FEBRILE NEUTROPENIA**

Fever is a frequent finding during the cause of neutropenia in cancer patients, and as this is a potentially lethal condition, broad spectrum antibiotics are commonly administered to better patient outcome. However, febrile neutropenia is only caused by infections in 30-50% of cases and to avoid significant overtreatment with risk of side effects and resistance induction, it is important to accurately recognize infectious as well as non-infectious causes of febrile neutropenia [66]. FDG-PET was early suggested as an adjunct to conventional diagnostic workup [67], and basic diagnostic yield and clinical impact was the main focus of several studies from the same period (Table 4).

Koh et al. set up a retrospective case-control cohort based on comparable patients with hematologic malignancies, who developed fever during neutropenic periods and underwent either conventional investigations at the discretion of the managing physician which included cultures, serology, PCR-based investigations, chest x-ray and CT in various combinations (controls), or conventional investigations and FDG-PET/CT (cases). Final diagnosis was considered infection in two-thirds of patients in both groups, but only 5% of cases remained unclarified, whereas this was true for 30% of controls – thus detection rate for underlying disease was 94.6% of cases and 69.7% of controls. FDG-PET/CT had significant impact on treatment strategy in 1/3 cases compared to an impact of conventional imaging in 1/10 controls, and duration of systemic antifungal therapy was significantly shorter in cases than controls [68]. Comparable results were encountered by Guy et al. [69] and Gafter-Gvili et al. [70]. In the former, 20 patients underwent conventional imaging and FDG-PET/CT; FDG-PET/CT found infectious foci in seven
patients with negative conventional imaging, located eight additional infectious foci in other patients, and FDG-PET/CT were overall considered to have high clinical impact in 75% (i.e. location of additional foci or direct impact on therapy) [69]. In the latter, FDG-PET/CT generally performed comparably to whole-body CT, but still lead to changed diagnosis or treatment in 69% and 55%, respectively [70]. Similar results were found in a recent study in a pediatric setting, i.e. high clinical impact in 79%, and a positive contribution to final diagnosis in 60% of patients [71]. However, the most recent study from 2015 by Camus et al. found more equivocal results, i.e. a sensitivity of only 61%, albeit with high specificity and PPV, and with no discernable clinical impact on diagnosis or treatment, and the authors conclude that although FDG-PET/CT has potential, they found no advantage over CT [72]. Thus, despite the initial success and potential for lesion detection of FDG-PET/CT in the setting of febrile neutropenia, results remain equivocal and based on relatively small studies with methodological issues, e.g. ill-defined reference standards primarily based on post-hoc clinical adjudication often also based on results of FDG-PET/CT. Also, most studies included only hematological malignancies, whereas the potential value in patients with solid tumors is virtually unexplored.

Several additional features are worth considering; firstly, mucosal inflammation in the digestive tract also presents with fever and is an important differential diagnosis, but is also associated with certain pathogens (e.g. Streptococcus mitis). Secondly, bacteremia with coagulase-negative Staphylococci is commonly associated with central venous catheters but may also be secondary to mucosal inflammation. Thirdly, invasive pulmonary fungal infestation is an important differential cause of bacteremia in febrile neutropenia with high mortality. Thus, Vos et al. undertook a prospective observational/descriptive study to establish if FDG-PET/CT provided additional value when it was added to standard work-up in neutropenic patients with hematologic malignancies and a rise in CRP > 50 mg/L (thus, strictly not febrile neutropenia) [66]: They found several results with relevance to the abovementioned special features; i.e. FDG uptake in central venous catheters was associated with coagulase-negative Staphylococci and deep venous thrombosis, high esophageal FDG-uptake was associated with Streptococcus mitis, and pulmonary FDG uptake was associated with invasive fungal disease. The study was limited by relatively few patients, and a reference standard was not applied routinely.

Some limitations to the use of FDG-PET/CT have been broad forth in febrile neutropenia: Sensitivity could be hampered as FDG uptake in activated neutrophils is considered an essential pathophysiologic basis for positive FDG PET/CT findings in infectious settings, and specificity may be hampered due to the non-specific uptake in underlying malignancies and metastases. Nonetheless, in reality sensitivity is hardly a challenge; several of the abovementioned studies report high detection rates even in non-symptomatic patients [69, 66, 67]. Older studies have also shown autoradiographically that FDG uptake is present not only in neutrophils but also macrophages and constituents of granulation tissue, which may explain the uptake despite severe neutropenia [73, 74]. Regarding specificity, with the increasing use of
FDG-PET/CT in the diagnostic work up or staging of malignancies, the possibility of comparison in suspected infection may help interpretation, and data from several of the abovementioned studies did not point to specificity issues as they reported only few or no equivocal or false-positive findings [68, 69].
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Table 1. Selected papers on diagnostic efficacy of FDG-PET/CT in fever of unknown origin.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Modality</th>
<th>N</th>
<th>Design</th>
<th>Final diagnosis</th>
<th>Helpful (essential)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorenzen et al. (2001)</td>
<td>PET</td>
<td>16</td>
<td>Prospective</td>
<td>N.R.</td>
<td>69%*</td>
</tr>
<tr>
<td>Bleecker-Rovers et al. (2004)</td>
<td>PET</td>
<td>35</td>
<td>Retrospective</td>
<td>54%</td>
<td>37%</td>
</tr>
<tr>
<td>Buysschaert et al. (2004)</td>
<td>PET</td>
<td>110</td>
<td>Prospective</td>
<td>53%</td>
<td>26%</td>
</tr>
<tr>
<td>Jaruskova et al. (2006)</td>
<td>Mixed</td>
<td>118</td>
<td>Retrospective</td>
<td>N.R.</td>
<td>36%</td>
</tr>
<tr>
<td>Bleecker-Rovers et al. (2007)</td>
<td>PET</td>
<td>70</td>
<td>Prospective</td>
<td>50%</td>
<td>33%*</td>
</tr>
<tr>
<td>Vanderschueren et al. (2009)</td>
<td>PET</td>
<td>90</td>
<td>Prospective</td>
<td>58%</td>
<td>36%*</td>
</tr>
<tr>
<td>Kubota et al. (2011)</td>
<td>Mixed</td>
<td>81</td>
<td>Retrospective</td>
<td>67%</td>
<td>51%* 73%**</td>
</tr>
<tr>
<td>Keidar et al. (2008)</td>
<td>PET/CT</td>
<td>48</td>
<td>Retrospective</td>
<td>60%</td>
<td>46%*</td>
</tr>
<tr>
<td>Balink et al. (2009)</td>
<td>PET/CT</td>
<td>68</td>
<td>Retrospective</td>
<td>65%</td>
<td>56%*</td>
</tr>
<tr>
<td>Federici et al. (2010)</td>
<td>PET/CT</td>
<td>14</td>
<td>Retrospective</td>
<td>71%</td>
<td>50% (23%)</td>
</tr>
<tr>
<td>Ferda et al. (2010)</td>
<td>PET/CT</td>
<td>48</td>
<td>Retrospective</td>
<td>100%</td>
<td>92%</td>
</tr>
<tr>
<td>Kei et al. (2010)</td>
<td>PET/CT</td>
<td>12</td>
<td>Retrospective</td>
<td>58%</td>
<td>42%</td>
</tr>
<tr>
<td>Rosenbaum et al. (2011)</td>
<td>PET/CT</td>
<td>18</td>
<td>Retrospective</td>
<td>100%</td>
<td>N.R.</td>
</tr>
<tr>
<td>Sheng et al. (2011)</td>
<td>PET/CT</td>
<td>48</td>
<td>Retrospective</td>
<td>75%</td>
<td>N.R.</td>
</tr>
<tr>
<td>Pelosi et al. (2011)</td>
<td>PET/CT</td>
<td>24</td>
<td>Retrospective</td>
<td>71%</td>
<td>46%*</td>
</tr>
<tr>
<td>Ergül et al. (2011)</td>
<td>PET/CT</td>
<td>24</td>
<td>Retrospective</td>
<td>79%</td>
<td>50%*</td>
</tr>
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<td>Crouzet et al. (2012)</td>
<td>PET/CT</td>
<td>79</td>
<td>Retrospective</td>
<td>77%</td>
<td>57%</td>
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<tr>
<td>Kim et al. (2012)</td>
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<td>48</td>
<td>Retrospective</td>
<td>85%</td>
<td>66%**</td>
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<tr>
<td>Pedersen et al. (2012)</td>
<td>PET/CT</td>
<td>52</td>
<td>Retrospective</td>
<td>60%</td>
<td>45%</td>
</tr>
<tr>
<td>Manohar et al. (2013)</td>
<td>PET/CT</td>
<td>103</td>
<td>Retrospective</td>
<td>67%</td>
<td>61%*</td>
</tr>
<tr>
<td>Tokmak et al. (2014)</td>
<td>PET/CT</td>
<td>25</td>
<td>Retrospective</td>
<td>92%</td>
<td>60%*</td>
</tr>
<tr>
<td>Buch-Olsen et al. (2014)</td>
<td>PET/CT</td>
<td>57</td>
<td>Retrospective</td>
<td>86%</td>
<td>75%**</td>
</tr>
<tr>
<td>Gafter-Gvili et al. (2015)</td>
<td>PET/CT</td>
<td>112</td>
<td>Retrospective</td>
<td>74%</td>
<td>66%**</td>
</tr>
<tr>
<td>Singh et al. (2015)</td>
<td>PET/CT</td>
<td>47</td>
<td>Retrospective</td>
<td>54%</td>
<td>38% (6%)</td>
</tr>
<tr>
<td>Study</td>
<td>Modality</td>
<td>Sample Size</td>
<td>Study Design</td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
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</tr>
<tr>
<td>Bouter et al. (2016)</td>
<td>PET/CT</td>
<td>72</td>
<td>Retrospective</td>
<td>83%</td>
<td>65% (40%)*</td>
</tr>
<tr>
<td>Schönau et al. (2018)</td>
<td>PET/CT</td>
<td>240</td>
<td>Prospective</td>
<td>79%</td>
<td>57%</td>
</tr>
<tr>
<td>Abdelrahman et al. (2018)</td>
<td>PET/CT</td>
<td>27</td>
<td>Prospective</td>
<td>93%</td>
<td>85*</td>
</tr>
<tr>
<td>Wang et al. (2019)</td>
<td>PET/CT</td>
<td>376</td>
<td>Retrospective</td>
<td>91%</td>
<td>77%</td>
</tr>
</tbody>
</table>

N.R. = Not reported; * Only FDG-positive (true positive) findings were considered helpful; ** Both FDG-positive and FDG-negatives (true positive and true negative) findings were considered helpful
TABLE 2. Original and current definitions of fever of unknown origin (based on [1]).

<table>
<thead>
<tr>
<th>Original definition by Petersdorf et al.</th>
<th>Current definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temp. &gt; 38.3 C (101F) on 3 or more occasions</td>
<td>Temp. &gt; 38.3 C (101F) on 2 or more occasions</td>
</tr>
<tr>
<td>Duration of illness &gt; 3 weeks</td>
<td>Duration of illness &gt; 3 weeks</td>
</tr>
<tr>
<td>No diagnosis after 1 week admission (later revised to 3 days admission or 3 out-patient visits)</td>
<td>Not immunocompromised</td>
</tr>
<tr>
<td></td>
<td>No definitive diagnosis despite thorough history-taking, physical examination, and a series of predefined initial investigations including a multitude of inflammatory markers and basic serology, urinalysis, blood cultures, urine culture, chest x-ray, abdominal ultrasound, and tuberculin skin test</td>
</tr>
</tbody>
</table>
TABLE 3. Selected papers on bacteremia.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>N</th>
<th>Design</th>
<th>Diagnostic yield*</th>
<th>High clinical impact</th>
<th>Change of treatment</th>
<th>Relapse rates</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vos et al. (2010/2012)</td>
<td>115 (cases) 230 (controls)</td>
<td>Prospective</td>
<td>68% (cases) 36% (controls)</td>
<td>N.R.</td>
<td>N.R.</td>
<td>2.6% (cases) 7.4% (control)</td>
<td>19% (cases) 32% (control)</td>
</tr>
<tr>
<td>Berrevoets et al. (2017)</td>
<td>184</td>
<td>Retrospective</td>
<td>73.7% (DR)</td>
<td>N.R.</td>
<td>74%</td>
<td>74%</td>
<td>12.4% (cases) 32.7% (controls)</td>
</tr>
<tr>
<td>Tsai et al. (2018)</td>
<td>102</td>
<td>Retrospective</td>
<td>72.5% (DR)</td>
<td>N.R.</td>
<td>54.1%</td>
<td>N.R.</td>
<td>N.R.</td>
</tr>
<tr>
<td>Brøndserud et al. (2019)</td>
<td>157</td>
<td>Retrospective</td>
<td>56% (DR)</td>
<td>47%</td>
<td>14.7%</td>
<td>N.R.</td>
<td>N.R.</td>
</tr>
<tr>
<td>Pijl et al. (2019)</td>
<td>185</td>
<td>Retrospective</td>
<td>64.8% (DR)</td>
<td>N.R.</td>
<td>N.R.</td>
<td>N.R.</td>
<td>N.R.</td>
</tr>
<tr>
<td>Yildiz et al. (2019)</td>
<td>102</td>
<td>Retrospective</td>
<td>45.8%</td>
<td>N.R.</td>
<td>N.R.</td>
<td>N.R.</td>
<td>16.6% (cases) 44.4% (controls)</td>
</tr>
</tbody>
</table>

* Either proportion of patients with metastatic infections or overall detection rate (DR); N.R. = not reported; DR = Detection rate
<table>
<thead>
<tr>
<th><strong>Author (year)</strong></th>
<th><strong>N</strong></th>
<th><strong>Design</strong></th>
<th><strong>Underlying malignancy</strong></th>
<th><strong>Patient inclusion criteria</strong></th>
<th><strong>Diagnostic yield</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vos et al. (2012)</td>
<td>28</td>
<td>Prospective</td>
<td>Hematologic malignancies #</td>
<td>NC &lt; 0.1x10/L CRP &gt; 50 mg/L</td>
<td>N.R.</td>
</tr>
<tr>
<td>Koh et al. (2012)</td>
<td>37</td>
<td>Retrospective</td>
<td>Hematologic malignancies</td>
<td>&gt; 38.3 C NC &lt; 0.5x10⁹/L</td>
<td>94.6% (cases)* 69.7% (controls)*</td>
</tr>
<tr>
<td>Guy et al. (2012)</td>
<td>20</td>
<td>Prospective</td>
<td>Hematologic malignancies (n=19) Solid tumor (n=1)</td>
<td>&gt;38 C NC &lt; 500 cells/µL</td>
<td>N.R.</td>
</tr>
<tr>
<td>Gafter-Gvili et al. (2012)</td>
<td>79</td>
<td>Prospective</td>
<td>Hematologic malignancies</td>
<td>Fever NC &lt; 500 cells/mm³</td>
<td>80%/32% (FDG-PET/CT)** 73%/42% (whole-body CT)**</td>
</tr>
<tr>
<td>Camus et al. (2015)</td>
<td>48</td>
<td>Prospective</td>
<td>Hematologic malignancies</td>
<td>&gt;38 C NC &lt; 500 cells/µL</td>
<td>61% / 90%** PPV 96%</td>
</tr>
<tr>
<td>Wang et al. (2018)</td>
<td>14</td>
<td>Retrospective</td>
<td>Immunosuppressed children</td>
<td>&gt;38 C NC &lt; 0.47 cells/µL</td>
<td>N.R.</td>
</tr>
</tbody>
</table>

# Either intensive treatment chemotherapy or myeloablative therapy prior to hematopoietic stem cell transplantation

* Detection rate; ** Sensitivity/specificity

N.R. = not reported; NC = neutrophil count; PPV = positive predictive value