

REVIEW

The value of F-18-fluorodeoxyglucose positron emission tomography (FDG-PET/CT) in the intensive care unit: a review

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Abstract

Background: Despite intensive diagnostic testing, a septic focus might prove difficult to detect in intensive care unit (ICU) patients. Yet it is essential to identify the source of infection in order to consider all source control options. An advanced diagnostic procedure to establish the septic focus is a positron emission tomography / computed tomography (FDG-PET/CT) scan. The purpose of this review is to explore the diagnostic value of FDG-PET/CT in ICU patients.

Methods: A systematic search was performed to identify all relevant evidence. Titles and abstracts were screened using predefined criteria.

Results: Ten articles were included. No major multicentre prospective studies are available. The current evidence shows results with sensitivities between 85% and 100% and a specificity between 50% and 79% in finding a focus of infection. A change of therapy due to the results of a FDG-PET/CT scan is reported in 15-71% of all cases.

Conclusion: FDG-PET/CT could be a helpful examination to determine the focus in sepsis of unknown origin. However, several pitfalls and precautions should be taken into consideration.

Introduction

Sepsis is one of the most common causes of admission to the intensive care unit (ICU) with high reported mortality rates (25.8 to 38.9%) depending on the focus of the infection and number of organ failures.^[1-3]

Despite clinical examination, extensive microbiological and diagnostic testing such as computed tomography (CT), the septic focus cannot always be detected. Early source control with adequate antibiotic treatment is essential for the best clinical outcome in sepsis patients.^[4]

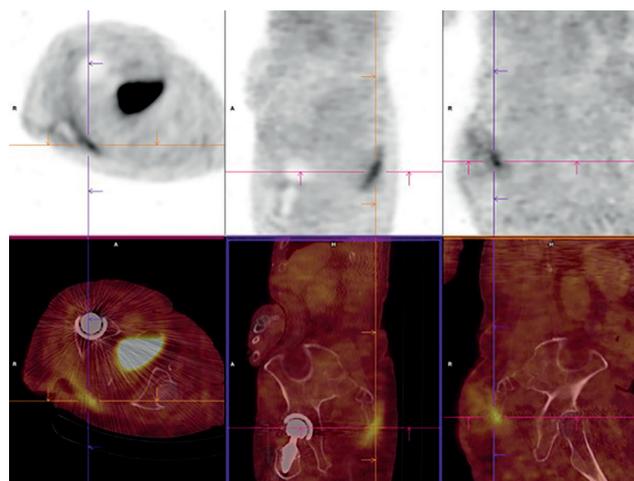


Figure 1. A positive FDG-PET/CT scan in an ICU sepsis patient

A 71-year-old male patient was admitted to the ICU with respiratory failure. He developed septicaemia with *Enterococcus faecium* which was treated with vancomycin. A transoesophageal echocardiogram (TEE) showed a vegetation on the posterior mitral leaflet. He underwent cardiac surgery with a mitral valve bioprosthesis. Postoperative course was complicated and prolonged due to cardiac tamponade, acute renal failure, delirium and ICU acquired weakness. He also developed a sacral ulcer. After 45 days in the ICU he developed a new sepsis episode with *E. faecium* positive blood cultures. Repeat TEE did not reveal any signs of prosthetic vegetations. CT body did not identify a focus of infection and sacral wound cultures were negative. FDG-PET/CT (CT without contrast) revealed a hot spot in the sacral area and the diagnosis of osteomyelitis was confirmed with MRI. A debridement of the infected area was performed and the patient was treated with intensive antibiotic therapy for 8 weeks. He was discharged from ICU after more than 50 days

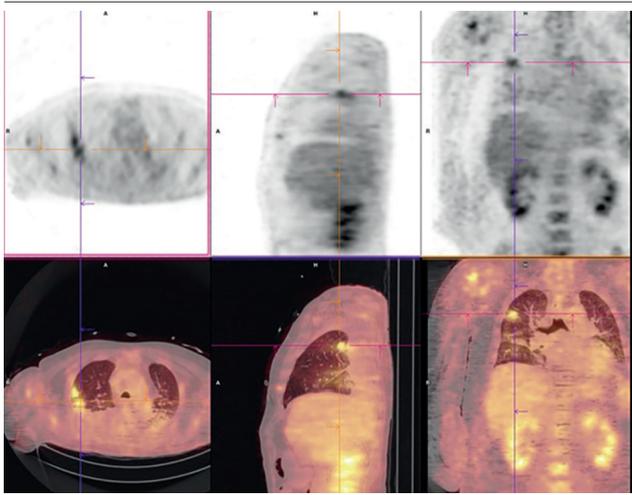


Figure 2. A negative FDG-PET/CT scan in an ICU sepsis patient

A 66-year-old patient was admitted to the ICU with septic shock three weeks after pacemaker (PM) implantation. The insertion was complicated due to bleeding and a large haematoma which was surgically evacuated. Blood cultures became positive for *Staphylococcus aureus*. Under clinical suspicion of an infected PM, the PM was surgically explanted and a pus pocket evacuated. Patient was treated with flucloxacillin and gentamycin. Pacemaker lead cultures grew *S. aureus*. Under antibiotics blood cultures remained positive with *S. aureus*. An echocardiogram and CT body did not reveal a focus of infection. A FDG-PET/CT (CT without contrast) was performed showing FDG uptake in the right upper lung and left gluteal muscle. The FDG uptake in the lung was attributed to pneumonia. An ultrasound of the gluteal muscle did not reveal an abscess. The patient was treated for 6 weeks with flucloxacillin and improved slowly. Follow-up blood cultures remained negative and he was discharged from ICU after 2 weeks.

Fluorodeoxyglucose-positron emission tomography (FDG-PET) can detect areas with enhanced glucose cell metabolism. In general, infection and inflammation foci have an increased FDG uptake as do many malignancies or metastases.^[5-7] FDG-PET has also proven to be of value as a diagnostic tool in patients with fever of unknown origin.^[8] PET technology has been combined with CT scanning (FDG-PET/CT), providing attenuation correction as well as anatomical mapping. Despite the growing use of FDG-PET/CT, there are limited data on FDG-PET/CT and no current guidelines for its use in ICU patients. Clinical experience teaches us that FDG-PET/CT can be both true positive and false negative in this sometimes challenging patient population (*figures 1 and 2*), giving rise to questions as to when and how to make use of this diagnostic tool. In this article we will give an overview of the best available evidence on the use of FDG-PET/CT in ICU patients through a systematic review.

Methods

Search description

We searched the electronic databases PubMed, Embase and the Cochrane Library Database. The last search was performed on 3 July 2018. We searched all terms related to intensive care,

sepsis and positron emission tomography and included MeSH/Emtree terms. No publication dates or age restrictions were used. Humans and English or Dutch were used as restrictions. The reference list of other relevant papers and reviews was searched as well.

Study selection

The title and abstract of the studies were screened and selected papers that met our inclusion criteria were selected for full text screening (*figure 3*). We excluded studies in patients with malignancies, animal studies and studies without original data. We included both case reports and larger studies. Articles that did not provide an abstract were included for full text screening. Abstracts that did not result in original papers (e.g. poster presentations) were excluded. The reference list of all eligible articles was evaluated.

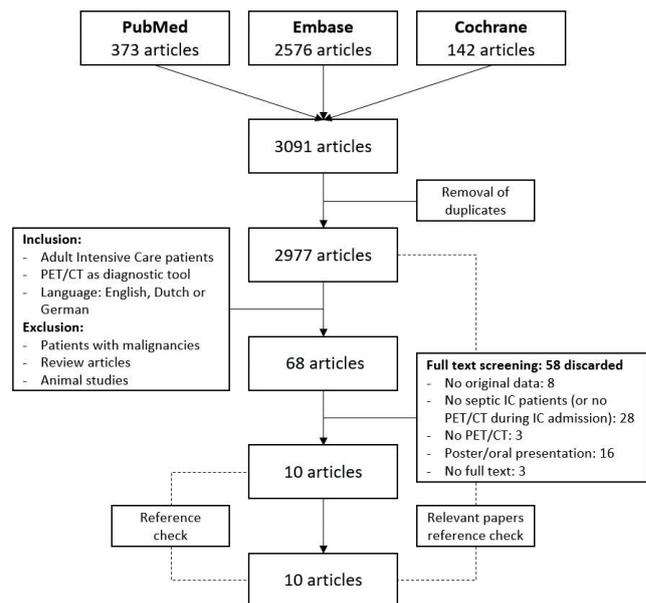


Figure 3. Flowchart for selection of studies (date last search: 03 July 2018)

Data extraction

The data were extracted from each paper using a standardised format (*table 1*). The study details that were documented include general demographics, sample size, time till FDG-PET/CT, previous examinations, results, sensitivity/specificity, and positive and negative predictive value when possible.

Data synthesis

Studies were grouped by publication type (i.e. case report or observational study) and arranged according to the publication date. A narrative synthesis was used in this review due to the limited number of available studies.

Table 1. Articles included in the systematic review and outcomes

Study	Year	Study type	n	Sex	Type of PET and CT	Time till PET/CT	Other examinations	Result	Type of change	Sens	Spec	PPV	NPV
Prospective / observational studies													
Mandry et al ^[9]	2014	Prospective	17	-	¹⁸ F-FDG PET CT with iodinated contrast	3 days	Chest X-ray, BAL, echocardiography, abdominal echography, whole body CT-scan	71% change of therapy	Antibiotics modification (n=10) Surgery (n=2)	85%	50%	85%	50%
Tseng et al ^[12]	2013	Retrospective observational	53	-	¹⁸ F-FDG PET CT (contrast not stated)	Within 2 weeks	Chest X-ray, abdominal echography, CT-scan	25% change of therapy	Surgery (n=9) Drainage (n=4) Antibiotics modifications not mentioned	-	-	-	-
Kluge et al ^[10]	2012	Retrospective observational	18	-	¹⁸ F-FDG PET CT with contrast	1-42 days	Chest X-ray, CT scan, TEE	33% change of therapy	Surgery (n=2) Pacemaker removal (n=2) Initiation antibiotic therapy (n=1) Prolongation antibiotic therapy (n=1)	100%	57%	79%	100%
Simons et al ^[11]	2010	Retrospective observational	33	-	¹⁸ F-FDG PET CT (contrast not stated)	Not stated	Chest X-ray, CT scan, abdominal echography, echocardiography	15% immediate change of therapy	Surgery (n=3) Removal of i.v. cannula (n=1) Start antibiotic therapy (n=1)	100%	79%	88%	100%
Case reports													
Colombo et al ^[15]	2018	Case report	1	M	¹⁸ F-FDG PET CT (contrast not stated)	Not stated	Thoraco-abdominal CT scan TEE	Infected pacemaker lead	Removal of pacemaker lead Continuation of antibiotics	-	-	-	-
Fort et al ^[18]	2018	Case series	2	M	¹⁸ F-FDG PET CT (contrast not stated)	Not stated	CT scan	Septic thrombosis CVC Pneumonia	Removal CVC, antifungal therapy Antibiotic therapy	-	-	-	-
Muckart et al ^[16]	2016	Case series	4	3 M 1 F	¹⁸ F-FDG PET CT (without contrast)	29, 33, 30, 46 days	Liver echography, facial X-rays, CT scan,	Osteomyelitis, scapular osteitis, pulmonary TBC, inter-loop abscess	Surgery or drainage (n=3) TBC treatment (n=1)	-	-	-	-
Akin et al ^[14]	2016	Case report	1	M	¹⁸ F-FDG PET CT (contrast not stated)	2 weeks	Vessel echography	Infected thrombus right atrium	Prolonged antibiotic therapy and therapeutic anticoagulation	-	-	-	-
Treglia et al ^[17]	2015	Case report	1	M	¹⁸ F-FDG PET CT (contrast not stated)	Not stated	Whole body CT scan	Periurethral abscess	Drainage and subsequent antibiotic modification	-	-	-	-
Adjtoutah et al ^[13]	2014	Case report	1	M	¹⁸ F-FDG PET CT (contrast not stated)	3 weeks	Thoraco-abdominal CT scan	Infected vascular prosthesis	Removal of catheters and antibiotic modification	-	-	-	-

N = number of patients, PET/CT= positron emission tomography / computed tomography, Sens = sensitivity, Spec = specificity PPV= positive predictive value, NPV = negative predictive value, BAL = bronchoalveolar lavage, TEE = transoesophageal echo, TBC = tuberculosis, CVC = central venous catheter

Results

Search results

The search resulted in 3091 articles (figure 3). After deduplication and applying inclusion and exclusion criteria during both abstract and full text screening, ten articles remained. Reference screening did not result in more articles matching our criteria. One paper was a prospective pilot study,^[9] three articles were retrospective observational studies^[10-12] and six articles consisted of case reports.^[13-18]

Available evidence

Mandry et al. (2014) included 17 patients with severe sepsis in whom a septic focus was not established 48 hours after initial presentation despite extensive clinical, biological and imaging investigations.^[9] FDG-PET/CT (with intravenous contrast) was performed within 24 hours of inclusion. The patients were followed until ICU discharge. The most probable diagnosis was established including all previous and subsequent diagnostic

procedures. This diagnosis was compared with the results of the FDG-PET/CT. They found a sensitivity and positive predictive value of 85% and a specificity and negative predictive value of 50% comparing PET diagnosis with the definite diagnosis. In 12 patients (71%) the FDG-PET/CT resulted in a change of therapy. Two patients experienced a minor adverse event during the imaging (desaturation and drop in systolic arterial pressure). Tseng et al. (2013) performed a retrospective observational study in patients with sepsis of unknown origin who underwent FDG-PET/CT within two weeks of admission.^[12] In this study 53 patients were included of which 35 (66%) showed a positive FDG-PET/CT; 13 patients (25%) had their treatment modified because of the FDG-PET/CT results. No sensitivity or specificity was described because of the lack of a gold standard.

A retrospective observational study by Kluge et al. included 18 patients admitted to the ICU with severe sepsis without an identified source of infection who underwent FDG-PET/CT.^[10] The final clinical diagnosis was made retrospectively taking all available information into consideration. Fourteen FDG-PET/CT scans proved to be positive, of which 11 were true positives. No false negatives were found. They calculated a sensitivity and negative predictive value of 100%. The specificity was 57% and positive predictive value 79%. In five patients (28%) the FDG-PET/CT was essential for the final diagnosis and in six patients (33%) the treatment was modified because of the results.

Simons et al. (2010) performed a retrospective observational study where they evaluated all FDG-PET/CT scans performed in ICU patients with a clinical suspicion of infection.^[11] The final diagnosis was made with all available clinical evidence. They evaluated 33 patients and found 24 positive FDG-PET/CT scans; 21 scans proved to be true positives and in five patients the result led to a direct therapeutic intervention. A sensitivity and negative predictive value of 100%, a specificity of 79% and a positive predictive value of 88% were found.

Several case reports have been published regarding the use of FDG-PET/CT in ICU patients with an unexplained positive blood culture or sepsis of unknown origin (*table 1*).^[13-18] All reported a new focus for the bacteraemia, and patients were treated accordingly. Furthermore, Kampe et al. studied neurologically critically ill patients who underwent FDG-PET/CT.^[19] Besides septic foci they also searched for malignancy or large vessel vasculitis. In 66.7% of the patients with a suspected infectious focus they found a relevant imaging finding. Because of the heterogeneity of the studied group and the different outcomes this paper was not included in our table.

Discussion

No major multicentre prospective studies or systematic reviews are available in the literature which investigate the relevance of FDG-PET/CT in septic ICU patients. The current evidence shows results with sensitivities between 85% and 100% and a specificity between 50% and 79% in finding a focus of infection. In 15-71% of all cases the FDG-PET/CT led to a change in

therapy, usually surgery and/or modification of the antibiotics (*table 1*). There are several pitfalls which can impede reliable interpretation of FDG-PET/CT scans in septic patients.

First of all, to investigate the usefulness of FDG-PET/CT there should be a gold standard, which is not available. In all reviewed studies the definite diagnosis was made retrospectively taking all available evidence into account. This could have caused an underestimation or overestimation of the value of a FDG-PET/CT. Furthermore, as shown by Kluge et al., a FDG-PET/CT scan can also yield false-positive results.^[10] They found three false-positive results. The first was a sterile haematoma. A possible explanation could be that in a timeframe between scan and surgical exploration, bacteria could have been eradicated by antibiotics. In the second case the FDG-PET/CT suggested an abscess in the chest wall. Due to lack of focal inflammation and a negative ultrasound, no exploration was performed. However, focal inflammation could have been undetectable in an oedematous patient and an ultrasonography is strongly operator dependent and can be falsely negative. The last patient appeared to have an abscess in her tongue; exploration was negative. This might be due to the fact that the physiological FDG uptake in the head and neck area is quite high, making a FDG-PET/CT difficult to interpret.

A true false-positive scan could result in unnecessary interventions, surgical or otherwise, which may be an additional risk for patients. A false-negative result is equally disconcerting. After all, a patient with sepsis of unknown origin is certain to have an infection or inflammation. A negative result, therefore, could be caused by a technical issue, or the use of co-medication; both of these topics which will be discussed later.

Secondly, a FDG-PET/CT scan is usually taken from skull base to proximal femora, as was the case in two studies.^[11,12] In our opinion, a whole body scan should be performed since an infection of the legs, arms, ear-nose-throat or skull base will otherwise be missed. Mandry et al. found a patient with tibial osteitis as a cause of sepsis, a diagnosis which would have been missed if the patient had not undergone a whole body scan.^[9]

Thirdly, proper patient preparation for PET scanning is essential. Since FDG-PET/CT depends on the uptake of radioactively labelled fluorodeoxyglucose (FDG), patients should fast for at least four hours, but preferably six hours, before scanning and infusions containing glucose should be discontinued during that period. A 2014 review recommends a fasting period of at least six hours.^[20] The timing and management of refraining from nutrients should be accurate and closely monitored, otherwise a poor quality scan which is less reliable could be the result. The three observational studies all followed a protocol where the glucose levels had to be less than 11 mmol/l before scanning.^[10-12] Two studies used a six-hour fasting period^[11,12] whereas in one study patients fasted for four hours.^[10] Mandry et al. required an even lower blood glucose level of 9 mmol/l and state that the patients had been fasted overnight.^[9]

Table 2. Suspected and confirmed (i.e. true positive) infectious sites per organ system detected by FDG-PET/CT in the included studies

Study	Respiratory system	Musculoskeletal system	Musculoskeletal system Cardiovascular system	Gastro-intestinal system	Genitourinary system	Other
Mandry et al (2014) ^[9]	6 pneumonia 1 pulmonary abscess	2 osteitis	1 abscess abdominal aortic stent graft	1 abdominal parietal abscess	1 pyelonephritis	
Tseng et al* (2013) ^[12]	8 pneumonia 3 septic emboli 1 lung empyema	13 spondylodiscitis 2 septic arthritis 2 psoas muscle abscess 1 pyogenic myositis 1 infectious hematoma	1 infective endocarditis	1 liver abscess 1 biliary tract infection	1 lobar nephronia	
Kluge et al (2012) ^[10]	2 pneumonia	1 cervical abscess 1 spondylodiscitis	1 infected VC thrombosis 1 infected vascular graft 2 pacemaker infections	1 pseudomembranous colitis 1 necrotizing pancreatitis		1 nocardiosis
Simons et al (2010) ^[11]	1 mediastinitis 4 pneumonia	1 arthritis 1 osteomyelitis 1 infected hip prosthesis 1 leg abscess	1 phlebitis 1 infected thrombus	1 peritonitis	1 prostatitis	3 candida abscess 1 dental abscess 1 thyroid abscess 2 sinusitis 1 lymphoma
Colombo et al (2018) ^[15]			1 infected pacemaker lead			
Fort et al (2018) ^[18]	1 pneumonia					1 CVC infection
Muckart et al (2016) ^[16]	1 pulmonary TBC	1 osteomyelitis 1 scapular osteitis		1 inter-loop abscess		
Akin et al (2016) ^[14]			1 infected thrombus right atrium			
Treglia et al (2015) ^[17]					1 periurethral abscess	
Adjoutah et al (2014) ^[13]			1 infected vascular prosthesis			

VC = vena cava, TBC = tuberculosis, CVC = central venous catheter

* No true positives were reported, numbers depicted are positive findings on FDG-PET/CT

To evaluate the heart valves in order to diagnose or exclude endocarditis, the left ventricular muscle should have a low to absent FDG uptake. This is established by a 24-hour carbohydrate-free diet prior to the scan.^[21] In practice this means cessation of parenteral nutrition as there are no carbohydrate-free formulas. None of the studies reported to have taken this into account. Medication may interfere with the accuracy of the FDG-PET/CT scan as well. Many patients with septic shock in the ICU are treated with corticosteroids according to sepsis guidelines. Imaging infection and inflammation sites with FDG-PET/CT is based on accumulation of FDG in activated granulocytes. Corticosteroids may suppress the activated granulocytes and hence diminish the FDG uptake.^[22] In addition corticosteroids may increase glucose blood levels and this may lead to a poor quality scan which can be the cause of a false-negative result. Another known medicine which can cause an abnormal result is metformin. Due to metformin-induced FDG uptake in the bowel, the FDG-PET/CT scan will show an elevated uptake of the bowel if metformin was used up to 72 hours prior to the investigation.^[23] In these patients, an intestinal infection (e.g. diverticulitis) could be missed as diagnosis. The above-mentioned studies did not specify their protocols with regards to these confounders.^[9-12]

ICU-specific indications

There are several indications in which an FDG-PET/CT scan can be a useful tool in patients admitted in the ICU. First, in patients with *Staphylococcus aureus* bacteraemia, an early FDG-PET/CT has proven to be valuable for detection of metastatic infectious foci which can lead to treatment modification. This is also associated with a significantly reduced mortality.^[5] Therefore, if a patient with *S. aureus* bacteraemia can be transported, early FDG-PET/CT is recommended. Secondly, if osteomyelitis or spondylodiscitis is suspected FDG-PET/CT has proven to be one of the best imaging techniques.^[24,25] Usually magnetic resonance imaging (MRI) is performed when osteomyelitis or spondylodiscitis is suspected. However, this investigation is not always available or possible in patients with metal implants, or due to lack of MRI compatible monitoring or ventilators in ventilated patients. Thirdly, in patients with grafts, e.g. endovascular grafts, infection of this graft can be present. Since an endovascular graft infection usually needs surgical intervention or extended antimicrobial therapy and has a high mortality of between 25 and 88%, it is important to obtain an early diagnosis.^[25] An FDG-PET/CT scan has a high accuracy in diagnosing endovascular graft infection, with a sensitivity and specificity of over 90%.^[24,25] Finally, FDG-PET/CT can be of use

in diagnosing and managing infectious endocarditis, both in native valve endocarditis as well as when a prosthetic valve or implantable electronic device is present.^[26]

In the studies included in this review, the foci detected by FDG-PET/CT were very heterogeneous, as is depicted in *table 2*. Overall, infections of the respiratory system, especially pneumonia, and the musculoskeletal system appear to be most common. Pneumonia could be missed by conventional investigations due to the changes in lung composition which are usually seen in ventilated and septic patients. Infections of the musculoskeletal system are clinically easily missed in sedated patients, and as stated before, FDG-PET/CT is one of the best imaging techniques to establish this diagnosis.

Situations in which FDG-PET/CT is less helpful are, for instance, suspected prosthetic joint infection. FDG-PET/CT is not reliable in the first year of implantation, due to postoperative inflammation.^[27] However, if inflammation of the surrounding tissue is visible on FDG-PET/CT, an infection could still be suspected. Organs which have a high physiological uptake of glucose are also difficult to evaluate with FDG-PET/CT. Intracerebral pathology is often not detectable with FDG-PET/CT, specifically in infectious diseases such as meningitis.^[28] The urinary tract is another example of a site with high physiological FDG uptake, which leads to a less reliable interpretation of an FDG-PET/CT scan.^[29]

For several patient groups there are evidence-based indications for the use of PET/CT, especially in oncology and fever of unknown origin.^[30] For the critically ill, no such evidence exists. Tseng et al. tried to develop a scoring system to identify those patients with sepsis of unknown origin who would have a positive FDG-PET/CT scan. They found that patients with a normal aspartate transaminase and an elevated alkaline phosphatase had the highest chance of a positive scan (89%).^[12] However, this study took place in an area where liver cirrhosis is endemic. It is probable that this scoring system will not apply to the general population. Another interesting study investigated the predictive value of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) for FDG-PET/CT outcome in patients with fever and inflammation of unknown origin.^[31] They found that in patients with a CRP level less than 5 mg/l the FDG-PET/CT scan was 100% true negative. Besides, the percentage of established diagnoses increases with higher CRP levels. An elevated ESR (>20 mm/h) can indicate the presence of inflammation and predict a positive FDG-PET/CT, but in a lesser degree compared with CRP.^[31] Other biomarkers for diagnosing sepsis have been investigated, but without very promising results.^[32]

Besides selecting the right patients, the question of timing is important. The studies included in our review show a spread from mere days^[9,10] to weeks^[10,12-14] or even more than a month^[10,16] after admission. Some do not describe the timing of the scan at all.^[11,15,17,18] The timing of FDG-PET/CT scanning depends on the clinical state of the patient, the previous

investigations and the available resources. In the Netherlands, there are no protocols regarding timing and patient selection for critically ill patients admitted to the ICU and the decision to perform FDG-PET/CT is usually made at the discretion of the medical specialist [personal communication with academic hospitals]. The same is true for other investigations, such as CT or transthoracic /transoesophageal echocardiograms.

Finally, the costs should be taken into account. The cost of an FDG-PET/CT scan vary per country and hospital. In the Netherlands a PET scan costs around € 500. If FDG-PET/CT could prevent other investigations (such as CT or MRI) or reduce the time a patient spends in hospital, it will be cost beneficial. For high-risk patients with a gram positive bacteraemia, a cost-effectiveness analysis has been made.^[33] They found that the cost increase in these patients was not due to the FDG-PET/CT itself but to the in-hospital treatment of metastatic foci that were found. They did find a decrease in mortality and morbidity, and an acceptable cost-effectiveness ratio per prevented death. Since the costs of a day in the ICU are rather high, it sounds likely that early FDG-PET/CT in septic patients can contribute to a more targeted therapy which could reduce the time in the ICU and therefore result in a reduction of the overall costs. Another problem can arise if the hospital does not have a FDG-PET/CT scanner. The potential benefit of the FDG-PET/CT should be weighed against the potential risks of transportation of the ICU patient and its cost. On the other hand, delaying a FDG-PET/CT scan might prove dangerous as well.

Conclusion and recommendation

FDG-PET/CT could be a helpful examination to determine the focus in sepsis of unknown origin. The available evidence is scarce but shows promising results, with sensitivities between 85% and 100% and specificities between 50% and 79% in finding a focus of infection. However, several pitfalls and precautions should be taken into consideration.

Based on the available literature, a strong evidence-based recommendation cannot be made. However, we will try to generate some advice regarding indication, timing, preparation and results of FDG-PET/CT in ICU patients.

1. **Indication:** In patients admitted to the ICU with sepsis or bacteraemia of unknown origin in which conventional investigations do not yield a definite result, an FDG-PET/CT should be considered. In special cases, such as *S. aureus* bacteraemia or suspected osteomyelitis/spondylodiscitis, FDG-PET/CT should even precede general investigations such as CT scanning or ultrasonography.
2. **Timing:** The timing depends on the condition of the patient and available resources. CRP values should be at least >5 mg/l.^[31] When a definite diagnosis cannot be made with conventional methods, we believe that FDG-PET/CT should not be postponed.

3. **Preparation:** Blood glucose levels should be <11 mmol/L. Cessation of nutrition, both enteral and parenteral, should preferably commence six hours prior to the FDG injection.^[20] If this is not feasible nutrition should be stopped at least four hours before injection of FDG. A carbohydrate-free diet should be given for 24 hours if there is a possibility of endocarditis. Corticosteroids may suppress FDG uptake in infection, if possible these agents should be discontinued. If infection of the intestines is probable, metformin should be replaced by other glucose-regulating medication.
4. **Scanning:** FDG-PET/CT from head to toe should be performed in all patients to ensure that possible sites of inflammation will not be missed.
5. **Results:** FDG-PET/CT can be both false positive or false negative. If doubt remains regarding the definitive diagnosis, the result should be confirmed with other diagnostic tools.

Disclosures

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Appendix 1: Search strategy

Pubmed		
((((((((((((("intensive care"[Text Word]) OR "intensive care unit"[Text Word]) OR ICU[Text Word]) OR IC[Text Word]) OR "critical care"[Text Word]) OR "critical care unit"[Text Word]) OR CCU[Text Word]) OR "Critical illness"[Text Word]) OR Sepsis[Text Word]) OR Bacteremia*[Text Word]) OR Bacteraemia*[Text Word]) OR "septic shock"[Text Word]) OR "blood poisoning"[Text Word]) OR Septicemia*[Text Word]) OR Septicaemia*[Text Word]) OR Critical Care[MeSH Terms]) OR intensive care units[MeSH Terms]) OR sepsis[MeSH Terms]	AND	((((("Positron emission tomograph"[Text Word]) OR "Positron-emission tomograph"[Text Word]) OR "Positron-emission-tomograph"[Text Word]) OR PET-CT*[Text Word]) OR PET-CT*[Text Word]) OR PET-CT*[Text Word]) OR Positron-Emission Tomography [MeSH]
Embase		
'intensive care':ti,ab,kw OR 'intensive care unit':ti,ab,kw OR icu:ti,ab,kw OR ic:ti,ab,kw OR 'critical care':ti,ab,kw OR 'critical care unit':ti,ab,kw OR 'intensive care'/exp OR sepsis:ti,ab,kw OR bacteremia*:ti,ab,kw OR bacteraemia*:ti,ab,kw OR 'septic shock':ti,ab,kw OR 'blood poisoning':ti,ab,kw OR septicemia*:ti,ab,kw OR septicaemia*:ti,ab,kw OR 'sepsis'/exp	AND	'positron emission tomograph':ti,ab,kw OR 'positron-emission tomograph':ti,ab,kw OR 'positron-emission-tomograph':ti,ab,kw OR 'pet scan':ti,ab,kw OR 'pet-scan':ti,ab,kw OR 'pet-ct':ti,ab,kw OR 'pet-ct*':ti,ab,kw OR 'pet ct*':ti,ab,kw OR 'positron emission tomography'/exp OR 'pet scanner'/exp
Cochrane		
((((((((((((("intensive care") OR "intensive care unit") OR ICU) OR IC) OR "critical care") OR "critical care unit") OR CCU) OR "Critical illness") OR Sepsis) OR Bacteremia*) OR Bacteraemia*) OR "septic shock") OR "blood poisoning") OR Septicemia*) OR Septicaemia*	AND	((((("Positron emission tomograph") OR "Positron-emission tomograph") OR "Positron-emission-tomograph") OR "PET scan") OR PET-scan*) OR PET-CT*) OR PET-CT*) OR PET CT*)