ELSEVIER

Seminars in
NUCLEAR
MEDICINE

Practice of ^{18}F-FDG-PET/CT in ICU Patients: A Systematic Review

Bram van Leer, MD,[*,†] Nick D. van Rijsewijk, MD,[*] Maarten W.N. Nijsten, MD, PhD,[†] Riemer H.J.A. Slart, MD, PhD,[*,‡] Janesh Pillay, MD, PhD,[†,§] and Andor W.J.M. Glaudemans, MD, PhD[*]

^{18}F-FDG-PET/CT imaging has become a key tool to evaluate infectious and inflammatory diseases. However, application of ^{18}F-FDG-PET/CT in patients in the intensive care unit (ICU) is limited, which is remarkable since the development of critical illness is closely linked to infection and inflammation. This limited use is caused by perceived complexity and risk of planning and executing ^{18}F-FDG-PET/CT in such patients. The aim of this systematic review was to investigate the feasibility of ^{18}F-FDG-PET/CT in ICU patients with special emphasis on patient preparation, transport logistics and safety. Therefore, a systematic search was performed in PubMed, Embase, and Web of Science using the search terms: intensive care, critically ill, positron emission tomography and ^{18}F-FDG or derivates. A total of 1183 articles were found of which 10 were included. Three studies evaluated the pathophysiology of acute respiratory distress syndrome, acute lung injury and acute chest syndrome. Three other studies applied ^{18}F-FDG-PET/CT to increase understanding of pathophysiology after traumatic brain injury. The remaining four studies evaluated infection of unknown origin. These four studies showed a sensitivity and specificity between 85%-100% and 57%-88%, respectively. A remarkable low adverse event rate of 2% was found during the entire ^{18}F-FDG-PET/CT procedure, including desaturation and hypotension. In all studies, a team consisting of an intensive care physician and nurse was present during transport to ensure continuation of necessary critical care. Full monitoring during transport was used in patients requiring mechanical ventilation or vasopressor support. None of the studies used specific patient preparation for ICU patients. However, one article described specific recommendations in their discussion. In conclusion, ^{18}F-FDG-PET/CT has been shown to be feasible and safe in ICU patients, even when ventilated or requiring vasopressors. Specific recommendations regarding patient preparation, logistics and scanning are needed. Including ^{18}F-FDG-PET/CT in routine workup of infection of unknown origin in ICU patients showed potential to identify source of infection and might improve outcome.

*Medical Imaging Center, Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

†Department of Critical Care, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

‡Biomedical Photonic Imaging Group, Faculty of Science and Technology, University of Twente, Enschede, The Netherlands.

§Groningen Research Institute for Asthma and COPD (GRIAC), University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

Address reprint requests to: B. van Leer, MD, Medical Imaging Center, Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, PO box: 30001, Hanzeplein 1, 9700 RB, EB45, Groningen, The Netherlands. E-mail: b.van.leer@umcg.nl

Introduction

The use of ^{18}F-FDG-PET/CT in the management of infectious and inflammatory diseases has steadily increased in patient care.[1] This noninvasive imaging technique is an effective diagnostic tool to investigate fever and inflammation of unknown origin,[2] bacteremia,[3] fungal infection,[4] bone infections,[5] vascular graft infection,[6] prosthetic joint infections,[7] endocarditis,[8] and infected renal or liver cysts.[9]

Infection and inflammation are important drivers of organ failure and critical illness. Major syndromes encountered in the Intensive Care Unit (ICU) are sepsis, defined as dysregulated

https://doi.org/10.1053/j.semnuclmed.2023.05.003

response to infection, and acute respiratory distress syndrome (ARDS), which necessitates the administration of high levels of oxygen to maintain arterial oxygen pressure due to bilateral lung opacities, often induced by pulmonary infections or systemic inflammation.[10-14] These syndromes may comprise more than 30% of all ICU admissions, and are associated with a mortality of more than 30%.[10-12]

In addition, ICU patients are at elevated risk of developing secondary nosocomial infections, such as bacteremia, surgical site infections, and ventilator associated pneumonia, which contribute to increased or prolonged organ failure and mortality.[15-18]

Thus, as both primary and secondary acquired infection and inflammation play a major role in ICU patients, timely and accurate localization of infectious and inflammatory foci facilitates early therapy and control of infectious source. In acute cases delay of appropriate therapy may result in an hourly increase of risk of death, regardless of the causative pathogen and source of infection.[19-22]

^{18}F-FDG-PET/CT has the potential to considerably improve the detection of infectious and inflammatory foci in ICU patients. However, to date, application of ^{18}F-FDG-PET/CT in these patients is uncommon.[23] The limited use of ^{18}F-FDG-PET/CT in the ICU may be related to the perceived complexity of planning, preparing, and transporting ill patients who receive circulatory and ventilatory support.[23] Nonetheless, transport to CT-scan facilities is regularly carried out if benefits are perceived to outweigh the risks.[24,25] It could be argued that despite differences in patient preparation, transport to a ^{18}F-FDG-PET/CT suite may not be fundamentally more challenging than transport to a CT suite.[26]

However, the preparation of ICU patients to obtain high-quality imaging may be a more significant challenge, as organ failure, such as kidney and liver failure, will alter tracer pharmacokinetics and dynamics.[27-30] In addition, recently performed surgical interventions, and the extensive use of antibiotics or insulin for glucose control may interfere with ^{18}F-FDG uptake.[31-33]

The aim of this review is to evaluate the ^{18}F-FDG-PET/CT procedure in ICU patients, with emphasis on safety, preparation and transportation logistics. In addition, our objective is to produce a comprehensive overview of ICU tailored implementations of ^{18}F-FDG-PET/CT and determine the potential indications for ^{18}F-FDG-PET/CT in the ICU patients.

Methods

A systematic search was conducted in PubMed, Web of Science, and Embase databases on January 6th 2023. The search terms included Mesh and Emtree terms for intensive care, critically ill, Positron Emission Tomography and ^{18}F-FDG or derivates (Supplementary Fig. 1). Languages were restricted to English and Dutch. Studies mentioning the investigation of ^{18}F-FDG-PET/CT or PET only in ICU patients in title and abstract were included. Exclusion criteria were: case series with less than four patients, studies with a main population <18 years (>50%) and if full-text was not available to the authors. Furthermore, study populations with subacute neurological diagnoses were excluded after 10 days of ICU stay, as their main reason for ICU stay is impaired neurology and in this stage of their ICU stay they do not share the characteristics of organ failure with other ICU patients. Articles lacking a clear and reproducible description of patient preparation and transport logistics for ^{18}F-FDG-PET/CT were also excluded from the analysis. Review articles were included for full-text analysis to ensure that new described patient preparation and transport logistics were not overlooked, but only original articles were included in the subsequent analysis. Two physician researchers (B.L. and N.R.) screened the titles and abstracts, and assessed the full-text articles. Any disagreements were resolved through discussion, and a third person (A.G.) was involved if necessary for the final decision. Complementary, selected full-text articles were screened for references to identify missing articles.

From the selected articles we extracted the first author, study type, study year, country of origin, study population, type of used control group, number of study subjects, mean age, sex-type distribution, main research topic, primary outcome, sensitivity, specificity and helpfulness. Helpfulness was defined as the percentage of nuclear imaging investigations contributing to the clinical diagnosis or aiding in decision making.[2] Furthermore, we examined the patient and transport preparation described in the articles, either using the procedure described in the method or the advisory described in the discussion section. This preparation and scan acquisition was categorized into different categories: prehydration, preparation diet, sedation, kidney replacement therapy, kidney function, glucose regulation, glucose at time of scan, acidotic state, hemodynamics, steroids, PET-camera system, admitted dose, injection scan time interval, scan coverage, usage of EARL reconstruction, type of quantification, advisory on transport procedure and personnel radiation safety.

Results

After excluding duplicates, a total of 1185 articles were found. After excluding articles based on title and abstract, a total of 53 articles remained and were included for full-text evaluation. Exclusions after full-text evaluation were mainly review papers. Cross-referencing resulted in 3 additional articles, which were subjected to the same selection procedure. Of those, only Bellani et al.[34] was included. The reviews did not provide new evidence or insights from our perspective. Finally, 10 original articles were included (Figure 1).

All included studies used a hybrid PET/CT system. Four studies used dynamic PET scanning in addition to the regular static scan.[34-37] The maximum standardized uptake value (SUV_{max}) combined with visual assessment was used by De Prost et al. and Akbik et al.[38,39] Other studies used visual assessment only, with Kluge et al. and Pijl et al. using a multidisciplinary team for final conclusion and image quality, respectively.[40-43]

A total of six prospective and four retrospective studies with in total 183 included patients were investigated.

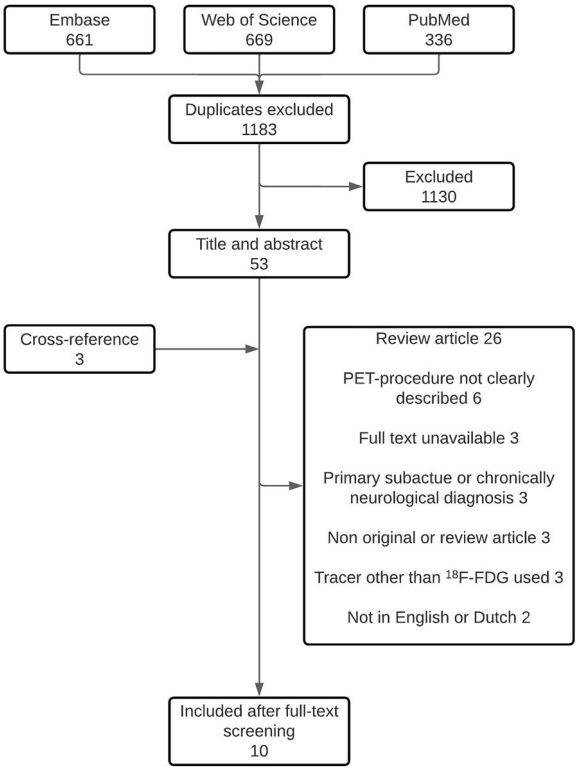

Figure 1 PRISMA flow diagram of systematic review search.

However, the studies of Belanni et al. partly overlapped by using same patients.[34,35] An overview of the characteristics of the included studies is shown in Table 1.

Pathophysiology of Lung Injury

The pathophysiology of lung injury was studied in three studies. In their first study, Belanni et al.[34] showed that ^{18}F-FDG uptake was diffuse throughout the entire lung in varying densities of patients with acute lung injury or ARDS. Strikingly, in this study, ^{18}F-FDG uptake was observed in apparently healthy lung regions on CT, although uptake varied widely between patients. In their second study, Bellani et al.[35] assessed the same study population to gain insight in the impact of gas volume changes on the lungs. This was done in order to elucidate the pathophysiological mechanism behind ventilator induced lung injury (VILI). ^{18}F-FDG uptake was used as a marker for neutrophil activity. Lung inflammation was found to be associated with plateau pressure and inspiratory volume, corrected for end-expiratory lung volume, in normally aerated and whole lung. However, Bellani et al. stated that there was no increase in metabolic ^{18}F-FDG activity in areas of cyclic recruitment-decruitment (ie, opening and collapsing of the alveoli during the respiratory cycle), which is believed to be one of the mechanisms

Table 1 ^{18}F-FDG-PET/CT Study Characteristics

Author	Country	Study Design	Research Topic	Study Population (N)	Mean Age	Male %
Bellani et al.[34]	Italy	Prospective	Inflammatory metabolic activity in the lungs	ALI and ARDS patients (10), Controls: spontaneously breathing (4), mechanically ventilated neurologic disorder patients (2)	66	80
Bellani et al.[35]	Italy	Prospective	Ventilator induced lung injury	ALI and ARDS patients (13)	63	85
De Prost et al.[38]	France	Prospective	Neutrophilic infiltration during acute chest syndrome	Intensive and intermediate care with acute chest syndrome, non-MV (17). Controls: Sickle cell disease without acute chest syndrome (7)	28	58
Akbik et al.[39]	United States of America	Retrospective	Ictal origin, primary or secondary	ICU patients with seizure or interictal continuum (6)	66	83
Vespa et al.[36]	United States of America	Prospective	Glucose regulation in TBI	Acute traumatic brain injury (13)	43	77
Hermanides et al.[37]	United Kingdom	Prospective	Glucose delivery following TBI	TBI patients requiring sedation and ventilation (26) Control: Healthy volunteers (47)	40	85
Kluge et al.[40]	Germany	Retrospective	Septic shock of unknown origin	ICU patients with severe sepsis or septic shock (18)	56	78
Mandry et al.[41]	French	Prospective	Severe sepsis with no definite diagnosis	Sepsis or septic shock of unknown origin (17)	55	59
Pijl et al.[42]	The Netherlands	Retrospective	Bloodstream infections of (secondary) unknown origin	Intensive care patients with bloodstream infection (30)	56	57
Simons et al.[43]	The Netherlands	Retrospective	(Suspicion of) infection of unknown origin	ICU patients with suspected infection (33)	58	73

ALI, acute lung injury; ACS, acute chest syndrome; ARDS, acute respiratory distress syndrome; MV, mechanical ventilation; TBI, traumatic brain injury.

Table 2 Diagnostic performance of ^{18}F-FDG-PET/CT in Infection of Unknown Origin

Author	Disease Type	N	Sensitivity	Specificity	Helpfulness
Kluge et al.[40]	Septic shock of unknown origin	18	100%	57%	61%
Mandry et al.[41]	Severe sepsis or septic shock of unknown origin	17	85%	50%	71%
Pijl et al.[42]	Bloodstream infections of unknown origin	30	91%	88%	37%
Simons et al.[43]	Infection of unknown origin	33	100%	79%	91%

behind VILI. ^{18}F-FDG-PET/CT was also used in the study of de Prost et al.[38] as a marker of neutrophil infiltration in sickle cell patients with acute chest syndrome. They observed a significantly higher ^{18}F-FDG uptake in patients with acute chest syndrome than in sickle cell patients without acute chest syndrome, with an increase in denser lung areas. Interestingly, this study showed that patients with higher ^{18}F-FDG uptake had a longer ICU-stay.

Pathophysiology of Acute Neurological Diseases

Akbik et al.[39] evaluated whether ^{18}F-FDG PET/CT could differentiate between ictal and non-ictal components in six patients with seizures or interictal continuum. They performed ^{18}F-FDG PET/CT scans before and during burst suppression. When ^{18}F-FDG uptake foci were absent during burst suppression, the authors concluded that this was primary ictal pathology, which was confirmed by clinical follow-up. Persistent ^{18}F-FDG uptake during burst suppression was linked to non-ictal pathologies in two patients, as this was confirmed by obduction in one patient and improvement under immunotherapy in the other patient. Both Vespa et al. and Hermanides et al. investigated the glucose delivery to the brain during traumatic brain injury.[36,37] Hermanides et al. showed that brain glucose delivery was dependent on plasma glucose levels and cerebral blood flow, but that a higher metabolic rate was associated with reduced blood flow and oxygen metabolism. Vespa et al. showed that tight glycemic control resulted in a higher metabolic rate in the brain.

Infection of Unknown Origin

In contrast to the studies aimed at pathophysiology, four studies addressed the role of ^{18}F-FDG-PET/CT in the diagnosis of infections of unknown origin.[40–43] These studies clearly demonstrate the clinical potential of ^{18}F-FDG-PET/CT. They all showed a remarkably high sensitivity of 85% to 100% (weighted mean 94.6%) for identifying a focus. ^{18}F-FDG-PET/CT was found to be helpful between 37% and 91% (65.5% weighted mean) (Table 2). Helpfulness was defined differently across studies. Kluge et al.[40] defined helpfulness for all true positive scans, which meant that ^{18}F-FDG-PET/CT results had to be confirmed by additional investigations. In the studies by Mandry et al. and Pijl et al. ^{18}F-FDG-PET/CT results that were followed by therapy modifications were considered helpful.[41,42] In the study by Simons et al.[43] all true positives and true negative findings were considered helpful.

Patient Preparation

All studies included ^{18}F-FDG-PET/CT patient preparation in their methods (Table 3). However, only Pijl et al.[42] provided recommendations on the preparation of ICU patients in their discussion. All studies used a fasting method as a dietary preparation between 4 and 8 hours prior to ^{18}F-FDG administration. Bellani et al.[34] used a standard time of 6 AM to start fasting in their study. Overnight fasting was used by Mandry et al.[41] A low-carbohydrate diet for 24 hours was recommended by Pijl et al.[42] in addition to the 6 hour fasting period in the case of suspected cardiogenic focus. Glucose administration during fasting was withheld in all but one of the reporting studies. As Vespa et al.[36] randomized their patients between high and low glucose therapy, they regulated the blood glucose levels with insulin and glucose infusion.

When reported, blood glucose levels were below the threshold of 11 mmol/L (200 mg/dL) in all studies.[34-37,43] Most studies also mentioned stopping insulin infusion.[34,35,38,42,43] Pijl et al.[42] advised to withdraw insulin administration for a period of time equivalent to the pharmaceutical dynamic duration of insulin.

Only three studies reported on kidney function which mainly means the investigators excluded patients with an insufficient kidney function.[34,38,42] Pijl et al. stated that insufficient kidney function can result in a reduced image quality due to the increased background activity. More studies reported on patient hydration, although this was mostly due to disease-related treatment protocols.[34-38] Only Pijl et al. advised an ^{18}F-FDG-PET/CT related prehydration of 1L of nonglucose containing fluids 2 hours prior to the scan.

In the studies that report the use of sedation, most used a combination of sedation and neuromuscular blockade.[34-39]

None of the studies reported the use of steroids. Acid-base status played a role in exclusion in one study and it was reported by De Prost et al.[36,38] Hermanides et al. used hyperventilation to strive for normal arterial pH as part of their treatment protocol.[37]

Transport Procedure

Described transport procedures did not differ materially between studies (Table 4). A team consisting of an ICU physician and nurse was available during transport and stay in the nuclear medicine facilities.[34,35,38,40,41] Continuous monitoring of hemodynamics and respiratory status was described, including electrocardiographs, invasive arterial blood pressure, peripheral saturation and expired CO_2 during mechanically ventilation. Vespa et al. excluded

Table 3 Patient Preparation for ^{18}F-FDG-PET/CT Procedure

Author	Prehydration	Diet	Glucose Regulation	Sedation	Kidney Function
Bellani et al.[34]	Fluid therapy was maintained constant	Fasting starting at 6 AM to ensure fasting period of 6 - 8 h	Insulin and glucose infusion stopped 6 to 8 h. Glucose between 80 and 140 mg/dL	Sedation levels were maintained constant	Urinary output of <0.5 mL*kg-1*hr-1 were excluded
Bellani et al.[35]	Fluid therapy was maintained constant	Fasting 6 to 8 h	Insulin and glucose infusion stopped 6 to 8 h. Glucose between 80 and 140 mg/dL	Sedated and paralyzed	NR
De Prost et al.[38]	Protocol ACS: 30 ml*kg^{-1}/day limited to 2 L/day	Fasting 6 h	Glucose or insulin-containing infusions discontinued for 6 hours.	Morphine analgesia	Exclusion of creatinine clearance <30 mL/min
Akbik et al.[39]	NR	Fasting 4 h	NR	Midazolam, propofol and/or pentobarbital for treatment. One patient was sedated for PET procedure.	NR
Vespa et al.[36]	Hypertonic saline for intracranial pressure control	NR	Target: 4.4-6.1 mmol/L or 6.7-8.3 mmol/L. Insulin was used for glucose control. Glucose was used for glucose increase.	Midazolam 2-4 mg/h Vecuronium 0.1 mg/kg	NR
Hermanides et al.[37]	Osmotic therapy	NR	NR	Propofol and fentanyl Neuromuscular blockade	NR
Kluge et al.[40]	NR	Fasting 4 h	Glucose infusion stopped during fasting. Blood glucose levels were checked every hour before FDG application. PET/CT was canceled in case of >200 mg/dL	NR	NR
Mandry et al.[41]	NR	Overnight fasting	Overnight withdrawn of solutions containing glucose. Glucose had to be <160 mg/dL	NR	NR
Pijl et al.[42]	1L of water 2h before ^{18}F-FDG-PET/CT	Fasting 4-6 h Low-carbohydrate diet for 24h + 6h fasting when cardiogenic focus	Rapid, short and intermediate or long acting insulin should not be used resp 4h, 6h and on the day. Glucose infusion should be stopped during diet	Patients should avoid exercise and not subjected to cold 1h before	Renal insufficiency may result in reduced clearance of FDG resulting in high background activity and lower PET images quality
Simons et al.[43]	NR	Fasting 6 hours	Glucose or insulin-containing infusions discontinued for 6 h.	NR	NR

NR, not reported.

hemodynamically unstable patients and de Prost et al. did not include mechanically ventilated patients.[36,38] Five studies mentioned adverse events.[35,40–43] The study by Mandry et al. reported one episode of desaturation and one episode with a decreased blood pressure. Both responded rapidly to therapy. Other studies reported no adverse events, resulting in an overall adverse event rate of only 2% in a total of 111 patients. None of the studies reported on staff radiation safety. Pijl et al. suggested that the tracer could be administered on the ICU, limiting the time duration that the patient is not in the ICU and therefore potential associated risks.

Discussion

The field of molecular imaging of infectious and inflammatory diseases is rapidly evolving. Apparently in the ICU,

Table 4 Transport Procedure

Author	Accompanying Staff	Hemodynamics	Respiratory
Bellani et al.[34]	Physician and nurse uninvolved in the study procedure	Monitoring: Invasive arterial blood pressure, ECG	MV using ICU ventilator. Monitoring: SaO_2 and expired O_2
Bellani et al.[35]	Physician and nurse uninvolved in the study procedure	Continues monitoring	MV by a high-performance mechanical ventilator
De Prost et al.[38]	Attending physician	Cardio monitoring	Pursuing oxygen delivery (non-MV) Respiratory monitoring
Akbik et al.[39]	NR	NR	NR
Vespa et al.[36]	NR	Hemodynamic instability was excluded	NR
Hermanides et al.[37]	NR	NR	NR
Kluge et al.[40]	Qualified ICU physician and a registered nurse	Fully monitoring	Fully monitoring
Mandry et al.[41]	ICU team, involving at least one senior physician and one nurse	Continues monitoring. When needed vasopressor. ECG, blood pressure	MV, continues monitoring. SaO_2
Pijl et al.[42]	NR	NR	NR
Simons et al.[43]	NR	NR	NR

ECG, electrocardiogram; MV, mechanical ventilation; NR, not reported; SaO_2, peripheral oxygen saturation.

physicians have been reluctant to use ^{18}F-FDG-PET/CT, although evidence to support this reluctance is lacking. Despite their small number, the studies reviewed seem to agree that ^{18}F-FDG-PET/CT can be performed safely in this patient group, even when patients are mechanically ventilated or require vasopressors. Standard patient preparations and transport procedures were applied in the reviewed studies, but the reporting was scarce.

Arguably, the prime indication to perform ^{18}F-FDG-PET/CT in ICU patients is infection of unknown origin. Yet, in all studies ^{18}F-FDG-PET/CT was performed as a late-stage diagnostic procedure, that is, ^{18}F-FDG-PET/CT was only performed when other modalities failed. Despite this, the performance of ^{18}F-FDG-PET/CT was good with a pooled sensitivity of 94.6% and specificity of 72.7% in 98 patients. The high sensitivity is consistent with findings in non-ICU

Table 5 Reported Recommendations for ^{18}F-FDG-PET/CT Scans in ICU Patients

	Advice
Dietary	Fasting for 6 h prior to administration of ^{18}F-FDG. 24 h of high protein, high fat, low carbohydrate, followed by 6 h of fasting, should be considered for a cardiogenic focus.
Glucose regulation	Continuous insulin administration is allowed. Avoid insulin boluses. Treat hypoglycemia ($\leq$3.5 mmol/L). Consider discontinuation of metformin to reduce ^{18}F-FDG bowel uptake.
Prehydration	Sensible approach to pre-hydration, as it may result in fluid overload.
Sedation	Agitation of patients should be treated to reduce excessive muscle activity up to 24 hours prior to ^{18}F-FDG-PET/CT. At time of tracer administration, muscle use should be limited if possible.
Tracer administration	Tracer administration within the ICU unit to shorten time away from the ICU.
Transport procedure	Standard procedures of in-house transportation can be followed. Transportation should be performed by qualified ICU staff (nurse and physician) to ensure continuation of care. Respiratory and hemodynamic remote monitoring should be available during PET/CT procedure. IV lines and wiring should be checked for sufficient length before tracer injection. Empty catheter-system before transport.
LAFOV scanner	When available, long axial field of view scanner should be used to reduce procedure time, limit bed movement and improve image quality.
Staff safety	The '"As low as reasonably achievable" (ALARA) principle is applicable at any time of the procedure. Keep distance to the patients by employing remote monitoring and reduce bedside time to the bare minimum trough adequate preparation. Reduce contact with urine and blood. Ensure ICU staff training (eg, abbreviated applied course in radiation safety).

patients. Recently, a large review by van Rijsewijk et al.,[2] including over 5000 patients, found a sensitivity of almost 85% with an helpfulness of 61%. The helpfulness of ^{18}F-FDG-PET/CT in ICU patients ranged between 37% and 91% (weighted mean of 65.5% in 98 patients), the large range may be related to differences in definition. Importantly, helpfulness is not restricted to positive scans in ICU patients. A negative scan is also relevant as it might lead to modification of a therapy component (eg, steroid therapy). Given this good sensitivity and helpfulness application of ^{18}F-FDG-PET/CT in ICU patients with an unknown source of infection deserves wider consideration.

Although ^{18}F-FDG-PET/CT is rarely used in ICU patients, the results indicate that this technique is feasible and can be safely performed in this patient group. Adverse events were only reported for 2% of the procedures and were restricted to desaturation and hypotension during transport. Compared to CT, this is remarkably low. Aliaga et al.[24] reported an overall adverse event rate in CT scanning of 22.3% in a large prospective study. This is comparable to the reported adverse event rate of 26.2% during in-house transportation of ICU patients reported by Murata et al.[24] in their meta-analysis. Looking at major adverse events alone, a rate of 8% was reported for CT-only transports and 1.5% for all types of transport, whereas no major adverse events were reported in the studies in our review.[24,25] A factor contributing to this low adverse event rate, may be that most ^{18}F-FDG-PET/CT scans were performed after 48 hours of admission.[24] Furthermore, the iodinated contrast agents used during the acquisition of CT-scans can cause allergic reactions, which is not the case when using ^{18}F-FDG in combination with low-dose attenuation correction CT.[44] Another advantage of ^{18}F-FDG is that it does not have nephrotoxic effects, for which CT contrast agents are known. For example, Aliaga et al.[24] reported that 13% of the cases developed kidney injury after the use of a contrast agent.

Well prepared transport can help to further reduce an already low risk. A team with an intensive care physician and nurse was used in all studies to ensure continuation of critical care. Full monitoring during transport, including invasive blood pressure measurements, electrocardiography and peripheral saturation was used for patients requiring mechanical ventilation or vasopressors (Table 5). This is consistent with accepted standards for the in house transport of ICU patients.[45,46] However, none of the published articles mentioned a standard operating procedure. The Dutch Association of Nuclear Medicine (NVNG) has published a protocol for performing ^{18}F-FDG-PET/CT in ICU patients. In this protocol, it is advised to administer the tracer at the ICU (Table 5).[26,42] It also advises sufficient length of intravenous lines and emptying of the urinary collection system or bladder before transport. Another problem may occur when patients are agitated, as in delirium. Heavy physical activity should be restricted for up to 24 hours prior to the ^{18}F-FDG-PET/CT scan (Table 5).[47] Sedation may therefore be helpful, although this may affect the brain uptake and alter the results.[26]

However, a good preparation is not only logistics. Proper patient preparation is essential when performing an ^{18}F-FDG-PET/CT scan. This can be a problem in ICU patients as they are more likely to have compromised organ functions such as kidney and liver failure,[27-29] and they are more likely to have acidosis or hyperglycemia that requires insulin administration.[48] As with any other patient undergoing an ^{18}F-FDG-PET/CT scan, ideally patients should be switched to a more ketogenic metabolism to reduce both glucose and insulin levels, thereby limiting competition between glucose and ^{18}F-FDG and improving ^{18}F-FDG biodistribution. Although several guidelines recommend at least 4 hours of fasting, 6 hours is the most common practice.[49] Another option is to use a high protein, high fat, low-carbohydrate diet for 12 to 24 hours, which achieves a similar result.[26,42] The advantage of the latter is that this also reduces ^{18}F-FDG uptake in the heart, making it suitable for imaging endocarditis on prosthetic valves (Table 5). Although it may be difficult to motivate awake patients for a high-protein, high fat, low-carbohydrate diet, this is not an issue in ICU patients, since these patients are typically fed with an enteral tube so, therefore dietary changes are easy to apply.

Glucose and insulin infusion should be stopped in patients considering the desired effect, as most studies did. However, this can be difficult since ICU patients are then prone to develop marked hyperglycemia.[48,50,51] If not managed correctly, this may result in increased morbidity. But also hypoglycemia can occur more frequently, which can be life-threatening if not treated properly. In their study, Vespa et al.[36] used glucose (dextrose) and insulin to regulate blood glucose and were still able to measure relevant differences. This suggests that a more liberal policy might be possible. This is already supported by the statement of the EANM that higher glucose levels are acceptable in infection and inflammation imaging compared to tumor imaging.[52] Furthermore, continuous insulin infusion is common practice in the ICU which may less affect image quality than insulin boluses.[50,53] Metformin should also be discontinued since this leads to increased bowel accumulation of ^{18}F-FDG (Table 5).[42]

Acute kidney injury is a common complication in ICU patients.[54] Although data are limited, reduced kidney function appears to have a negative impact on image quality by limiting the urinary excretion of ^{18}F-FDG, resulting in higher tissue background uptake.[27,28,30] To our knowledge, no solution has been found. Pre-hydration is advised to ensure a sufficient ^{18}F-FDG excretion.[42,47,49] However, fluid intake is closely managed in the ICU, as either too little or too much fluid administration may lead to increased morbidity.[55] With this in mind, excess fluid administration should be avoided (Table 5).

Another important consideration is the radiation safety of ICU staff. None of the included studies reported on this issue. To our knowledge, few studies have been published evaluating the effective dose to ICU staff while performing ^{18}F-FDG-PET in ICU settings. The study of Studenski evaluated radiation safety in the use of a mobile bedside PET/SPECT system, and discovered that for a single weekly acquisition, a reduction in administered activity with ^{18}F was needed to about 220 MBq to follow regulations for nonexposed employees.[56] Also, the basic principles for reducing

exposure to radiation always apply: reducing the exposure time, increasing the distance, and increasing dedicated shielding. A study by Leide et al.[57] provided an excellent overview of the radiation exposure of hospital staff emitted after ^{18}F-FDG administration and demonstrated that the exposed dose rate clearly decreases with increased distance, in line with the inverse-square law. Applied to ICU staff these basic principles imply that monitoring of the patient is preferably done remotely, for example using remote monitoring systems and cameras and keep bedside time to the bare minimum, as the longer the exposure time and/or proximity to the patients, the more they are exposed to radiation. Another important aspect to keep in mind is that urine and blood products are contaminated with radioactivity after ^{18}F-FDG injection, so staff should take particular care to handle these with extra caution to avoid contamination of the surroundings and/or themselves. Therefore, to reduce the risk, a short applied course for ICU staff is recommended (Table 5).

Although the above suggests that PET/CT can already be an important diagnostic tool in ICU patients, current and future innovations are expected to increase the use of PET/CT as a diagnostic tool in these patients. One of the major limitations of conventional PET/CT scanners is acquisition time (up to more than 20 minutes). However, the recent introduction of long axial field-of-view PET/CT scanners makes it possible to scan patients much faster (3 minutes or less).[58] A big advantage of these long axial field-of-view PET/CT scanners is that patients can be scanned in one non-moving bed position, which makes it more practical to scan ICU patients who may have many lines and tubes (Table 5). This innovation may lower the initial threshold due to a longer acquisition time and bring the overall logistical procedure on par with performing a CT, which is a significant improvement. Two examples of ^{18}F-FDG-PET/CT scans using a LAFOV scanner (106 cm) within 3 minutes (one bed position) in ICU patients are given in Figure 2 and 3. Another important innovation is the development of more specific PET tracers, such as radiolabeled antibiotics and antimicrobial peptides, to distinguish infection from inflammation. To date, only a few have made the translation to clinical studies. For example, radiolabeled ubiquicidin (^{68}Ga-NOTA-UBI) has been tested in humans for imaging bacterial infections and appears to have the potential in targeting bacterial infections.[59-61] Other investigated targets for bacterial infection imaging with PET are radiolabeled antibodies, sugars and sugar alcohols (eg, mannitol and sorbitol) which cannot be efficiently metabolized by the human body.[62] However, all mentioned tracers did not make the translation to clinical practice yet. The radiolabeled Fibroblast Activated Protein Inhibitor ^{68}Ga-FAPI is a recently introduced tracer that has made this translation to the clinic.[63,64] This tracer enables non-invasive imaging of tissue remodeling and may provide insight into persistent organ failure and ICU acquired weakness.[65-70]

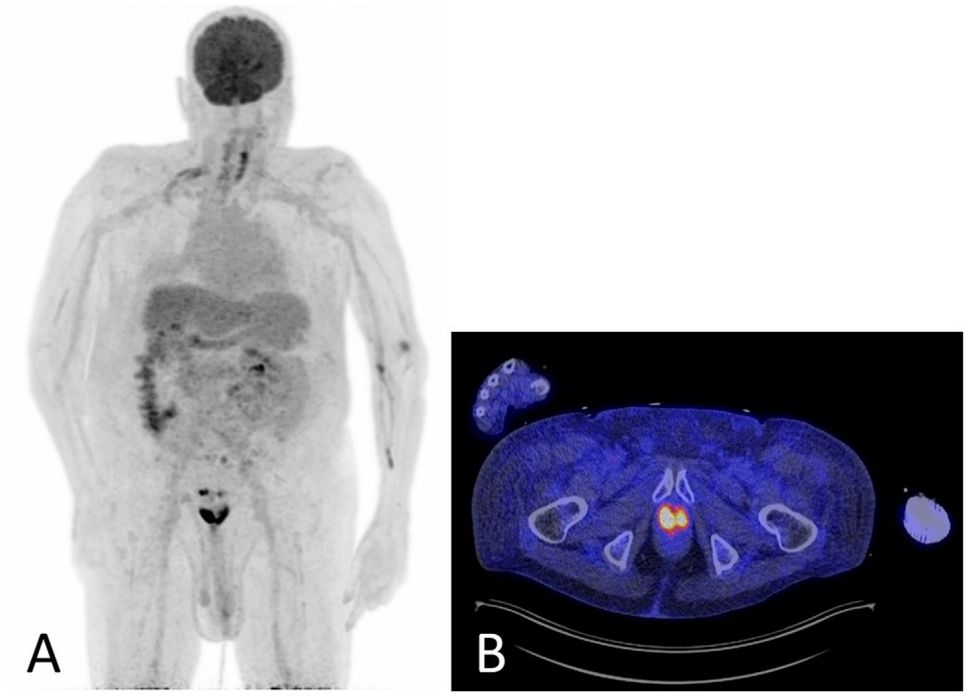

Figure 2 A nonsedated 65-year-old ICU patient presented with septic shock containing Staphylococcus aureus and Klebsiella pneumoniae of unknown origin. The maximum intensity projection of the ^{18}F-FDG-PET/CT scan (A) shows less brain activity than usual, probably caused by the followed ketogenic diet, and more activity in secondary respiratory muscles. There is slightly elevated liver uptake and renal clearance is less, both due to organ failure. Most pronounced is the ^{18}F-FDG uptake in the prostate, which is suggestive for prostatitis (B). No other infectious foci could be found. Biograph Vision Quadra (Siemens Healthineers, Erlangen, Germany), axial field-of-view 106 cm, scan-time of 3 minutes in one bed position.

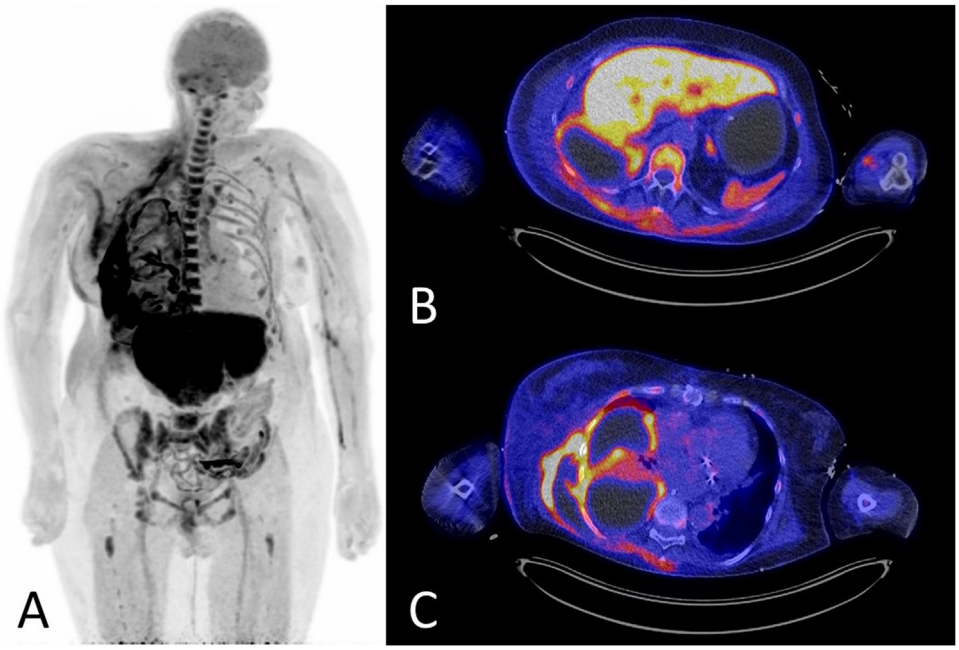

Figure 3 A sedated and intubated 75-year-old patient suffering from sepsis of unknown origin was referred for ^{18}F-FDG-PET/CT. The maximum intensity projection visualizes a severe and extensive infection and inflammation (A). Remarkable is the high ^{18}F-FDG uptake in the liver, which might have been caused by acute liver failure (B). Most important for the clinical presentation is the extensive fluid collections in the right hemithorax, extending to the thoracic wall with intense ^{18}F-FDG uptake on the edges and at the level of interlobular septa (C). There is also induration in the surrounding soft tissues. These findings are most consistent with extensive thoracic empyema. Biograph Vision Quadra (Siemens Healthineers, Erlangen, Germany), axial field-of-view 106 cm, scan-time of 3 minutes in one bed position.

Conclusion

^{18}F-FDG-PET/CT has been shown to be feasible and safe, even in ventilated and unstable patients. However, to date, the use of ^{18}F-FDG-PET/CT in ICU patients is uncommon and there is only scant specific procedural information. Infection or inflammation of unknown origin is a typical ICU specific indication for ^{18}F-FDG-PET/CT, that could become part of routine imaging. The use of ^{18}F-FDG-PET/CT in ICU patients is associated with new challenges, and therefore specific recommendations on patient preparation, logistics and scanning are needed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

JP is supported by a research grant from the Netherlands Organization for Health Research and Development, the Netherlands (ZonMw Clinical Fellowship grant 09032212110044).

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.semnuclmed.2023.05.003.

References

1. Glaudemans AWJM, Gheysens O: Expert opinions in nuclear medicine: Finding the "holy grail" in infection imaging. Front Med 10:320, 2023
2. van Rijsewijk ND, IJpma FFA, Wouthuyzen-Bakker M, et al: Molecular imaging of fever of unknown origin: An update. Semin Nucl Med 53:4-17, 2023
3. Pijl JP, Glaudemans AWJM, Slart RHJA, et al: FDG-PET/CT for detecting an infection focus in patients with bloodstream infection: Factors affecting diagnostic yield. Clin Nucl Med 44:99-106, 2019
4. Ankrah AO, Lawal IO, Dierckx RAJO, et al: Imaging of invasive fungal infections- The role of PET/CT. Semin Nucl Med 53:57-69, 2023
5. Glaudemans AWJM, Jutte PC, Cataldo MA, et al: Consensus document for the diagnosis of peripheral bone infection in adults: A joint paper by the EANM, EBJIS, and ESR (with ESCMID endorsement). Eur J Nucl Med Mol Imaging 46:957-970, 2019
6. Lauri C, Signore A, Glaudemans AWJM, et al: Evidence-based guideline of the European Association of Nuclear Medicine (EANM) on imaging infection in vascular grafts. Eur J Nucl Med Mol Imaging 49:3430-3451, 2022
7. Signore A, Sconfienza LM, Borens O, et al: Consensus document for the diagnosis of prosthetic joint infections: A joint paper by the EANM, EBJIS, and ESR (with ESCMID endorsement). Eur J Nucl Med Mol Imaging 46:971-988, 2019
8. Habib G, Lancellotti P, Antunes MJ, et al: 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC).

Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 36:3075-3123, 2015
9. Neuville MF, Lovinfosse P, Jadoul A, et al: The use of a visual 4-point scoring scale improves the yield of 18F-FDG PET-CT imaging in the diagnosis of renal and hepatic cyst infection in patients with autosomal dominant polycystic kidney disease. Eur J Nucl Med Mol Imaging 48:254-259, 2021
10. Sakr Y, Jaschinski U, Wittebole X, et al: Sepsis in intensive care unit patients: Worldwide data from the intensive care over Nations Audit. Open Forum Infect Dis 5, 2018
11. Hendrickson KW, Peltan ID, Brown SM: The epidemiology of acute respiratory distress syndrome before and after coronavirus disease 2019. Crit Care Clin 37:703, 2021
12. Bellani G, Laffey JG, Pham T, et al: Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 315:788-800, 2016
13. Singer M, Deutschman CS, Seymour C, et al: The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 315:801-810, 2016
14. Ranieri VM, Rubenfeld GD, Thompson BT, et al: Acute respiratory distress syndrome: The Berlin definition. JAMA 307:2526-2533, 2012
15. Tabah A, Koulenti D, Laupland K, et al: Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: The EUROBACT International Cohort Study. Intensive Care Med 38:1930-1945, 2012
16. Blot S, Ruppé E, Harbarth S, et al: Healthcare-associated infections in adult intensive care unit patients: Changes in epidemiology, diagnosis, prevention and contributions of new technologies. Intensive Crit Care Nurs 70:103227, 2022
17. Prowle JR, Echeverri JE, Ligabo EV, et al: Acquired bloodstream infection in the intensive care unit: Incidence and attributable mortality. Crit Care 15:1-11, 2011
18. Talmor M, Hydo L, Barie PS: Relationship of systemic inflammatory response syndrome to organ dysfunction, length of stay, and mortality in critical surgical illness: Effect of intensive care unit resuscitation. Arch Surg 134:81-87, 1999
19. Kumar A, Roberts D, Wood KE, et al: Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 34:1589-1596, 2006
20. Bassetti M, Righi E, Ansaldi F, et al: A multicenter multinational study of abdominal candidiasis: epidemiology, outcomes and predictors of mortality. Intensive Care Med 41:1601-1610, 2015
21. Kollef M, Micek S, Hampton N, et al: Septic shock attributed to candida infection: Importance of empiric therapy and source control. Clin Infect Dis 54:1739-1746, 2012
22. Kollef MH, Shorr AF, Bassetti M, et al: Timing of antibiotic therapy in the ICU. Crit Care 25:1-10, 2021
23. van Hulst A, van Rijk M, Bavelaar-Croon C, et al: The value of F-18-fluorodeoxyglucose positron emission tomography (FDG-PET/CT) in the intensive care unit: A review. Neth J Crit Care 27:108-114, 2019
24. Aliaga M, Forel JM, De Bourmont S, et al: Diagnostic yield and safety of CT scans in ICU. Intensive Care Med 41:436-443, 2015
25. Murata M, Nakagawa N, Kawasaki T, et al: Adverse events during intrahospital transport of critically ill patients: A systematic review and meta-analysis. Am J Emerg Med 52:13-19, 2022
26. Braat A, Huijbregts J. *Procedure Guidelines Nuclear Medicin - Part 1 - 1.9 Specific Preparations for [18]F-FDG-PET/CT in Critically Ill Patients on Intensive Care Units*. (Esser J, van den Heuvel J, van Dalen J, eds.). HGP Vullers; 2016. www.guidelinesnuclearmedicine.com. Accessed July 14, 2022
27. Toriihara A, Kitazume Y, Nishida H, Kubota K, Nakadate M, Tateishi U: Comparison of FDG-PET/CT images between chronic renal failure patients on hemodialysis and controls. Am J Nucl Med Mol Imaging 5:204, 2015. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4396005/. Accessed April 17, 2023. PMCID: PMC4396005
28. Minamimoto R, Takahashi N, Inoue T: FDG-PET of patients with suspected renal failure: standardized uptake values in normal tissues. Ann Nucl Med 21:217-222, 2007
29. Verloh N, Einspieler I, Utpatel K, et al: In vivo confirmation of altered hepatic glucose metabolism in patients with liver fibrosis/cirrhosis by 18F-FDG PET/CT. EJNMMI Res 8:1-9, 2018
30. van Praagh GD, Nienhuis PH, de Jong DM, et al: Toward reliable uptake metrics in large vessel vasculitis studies. Diagnostics (Basel, Switzerland) 11, 2021
31. Scholtens AM, Van Aarnhem EEHL, Budde RP: Effect of antibiotics on FDG-PET/CT imaging of prosthetic heart valve endocarditis. Eur Hear J - Cardiovasc Imaging 16, 2015. 1223-1223
32. Finfer S, Chittock DR, Yu-Shuo Su S, et al: Intensive versus conventional glucose control in critically Ill patients. N Engl J Med 360:1283-1297, 2009
33. Jamar F, Buscombe J, Chiti A, et al. EANM/SNMMI guideline for 18 F-FDG use in Inflammation and Infection. *J Nucl Med*. 54. doi:10.2967/jnumed.112.112524
34. Bellani G, Messa C, Guerra L, et al: Lungs of patients with acute respiratory distress syndrome show diffuse inflammation in normally aerated regions: A [18F]-fluoro-2-deoxy-D-glucose PET/CT study. Crit Care Med 37:2216-2222, 2009
35. Bellani G, Guerra L, Musch G, et al: Lung regional metabolic activity and gas volume changes induced by tidal ventilation in patients with acute lung injury. Am J Respir Crit Care Med 183:1193-1199, 2011
36. Vespa P, McArthur DL, Stein N, et al: Tight glycemic control increases metabolic distress in traumatic brain injury: A randomized controlled within-subjects trial. Crit Care Med 40:1923-1929, 2012
37. Hermanides J, Hong YT, Trivedi M, et al: Metabolic derangements are associated with impaired glucose delivery following traumatic brain injury. Brain 144:3492-3504, 2021
38. De Prost N, Sasanelli M, Deux JF, et al: Positron emission tomography with 18F-Fluorodeoxyglucose in patients with sickle cell acute chest syndrome. Medicine (Baltimore) 94:e821, 2015
39. Akbik F, Robertson M, Das AS, Singhal T, Lee JW, Vaitkevicius H: The PET sandwich: Using Serial FDG-PET Scans with interval burst suppression to assess ictal components of disease. Neurocrit Care 33:657-669, 2020
40. Kluge S, Braune S, Nierhaus A, et al: Diagnostic value of positron emission tomography combined with computed tomography for evaluating patients with septic shock of unknown origin. J Crit Care 27:316.e1-316.e7, 2012
41. Mandry D, Tatopoulos A, Chevalier-Mathias E, et al: ^{18}F-fluorodeoxyglucose positron emission tomography combined with whole-body computed tomographic angiography in critically ill patients with suspected severe sepsis with no definite diagnosis. Eur J Nucl Med Mol Imaging 41:1924-1930, 2014
42. Pijl JP, Londema M, Kwee TC, et al: FDG-PET/CT in intensive care patients with bloodstream infection. Crit Care 25, 2021
43. Simons KS, Pickkers P, Bleeker-Rovers CP, et al: F-18-fluorodeoxyglucose positron emission tomography combined with CT in critically ill patients with suspected infection. Intensive Care Med 36:504-511, 2010
44. Namasivayam S, Kalra MK, Torres WE, et al: Adverse reactions to intravenous iodinated contrast media: A primer for radiologists. Emerg Radiol 12:210-215, 2006
45. Wallace PGM, Ridley SA: ABC of intensive care: Transport of critically ill patients. BMJ Br Med J 319:368, 1999
46. Warren J, Fromm RE, Orr RA, Rotello LC, Mathilda Horst H: Guidelines for the inter- and intrahospital transport of critically ill patients. Crit Care Med 32:256-262, 2004
47. Boellaard R, Delgado-Bolton R, Oyen WJG, et al: FDG PET/CT: EANM procedure guidelines for tumour imaging: Version 2.0. Eur J Nucl Med Mol Imaging 42:328-354, 2015
48. Simon Finfer, Dean R Chittock, Yu-Shuo Su Steve, et al: Intensive versus conventional glucose control in critically ill patients. N Engl J Med 360:1283-1297, 2009.
49. Surasi DS, Bhambhvani P, Baldwin JA, Almodovar SE, O'Malley JP: 18F-FDG PET and PET/CT patient preparation: A review of the literature. J Nucl Med Technol 42:5-13, 2014
50. Van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in critically ill patients. N Engl J Med 345:1359-1367, 2001

51. Inzucchi SE: Management of hyperglycemia in the hospital setting. N Engl J Med 355:1903-1911, 2006
52. Jamar F, Buscombe J, Chiti A, et al: EANM/SNMMI guideline for 18F-FDG use in inflammation and infection. J Nucl Med 54:647-658, 2013
53. Vogelzang M, Zijlstra F, Nijsten MWN: Design and implementation of GRIP: A computerized glucose control system at a surgical intensive care unit. BMC Med Inform Decis Mak 5:1-10, 2005
54. Case J, Khan S, Khalid R, et al: Epidemiology of acute kidney injury in the intensive care unit. Crit Care Res Pract 2013, 2013
55. Claure-Del Granado R, Mehta RL: Fluid overload in the ICU: Evaluation and management. BMC Nephrol 17:1-9, 2016
56. Studenski MT: Effective dose to patients and staff when using a mobile PET/SPECT system. J Appl Clin Med Phys 14:215, 2013
57. Leide-Svegborn S: Radiation exposure of patients and personnel from a PET/CT procedure with 18F-FDG. Radiat Prot Dosimetry 139:208-213, 2010
58. Slart RHJA, Tsoumpas C, Glaudemans AWJM, et al: Long axial field of view PET scanners: A road map to implementation and new possibilities. Eur J Nucl Med Mol Imaging 48:4236-4245, 2021
59. Bhatt J, Mukherjee A, Shinto A, et al: Gallium-68 labeled Ubiquicidin derived octapeptide as a potential infection imaging agent. Nucl Med Biol 62-63:47-53, 2018
60. Bhusari P, Bhatt J, Sood A, et al: Evaluating the potential of kit-based 68Ga-ubiquicidin formulation in diagnosis of infection: A pilot study68Ga. Nucl Med Commun 40:228-234, 2019
61. Ebenhan T, Sathekge MM, Lengana T, et al: 68Ga-NOTA-Functionalized Ubiquicidin: Cytotoxicity, biodistribution, radiation dosimetry, and first-in-human PET/CT imaging of infections. J Nucl Med 59:334-339, 2018
62. Dadachova E, Rangel DEN: Highlights of the latest developments in radiopharmaceuticals for infection imaging and future perspectives. Front Med 9:819702, 2022
63. Acharya PS, Zukas A, Chandan V, et al: Fibroblast activation protein: A serine protease expressed at the remodeling interface in idiopathic pulmonary fibrosis. Hum Pathol 37:352-360, 2006
64. Hicks RJ, Roselt PJ, Kallur KG, et al: FAPI PET/CT: Will it end the hegemony of 18F-FDG in oncology? J Nucl Med 62:296-302, 2021
65. Meduri GU, Tolley EA, Chinn A, Stentz F, Postlethwaite A: Procollagen types I and III aminoterminal propeptide levels during acute respiratory distress syndrome and in response to methylprednisolone treatment. Am J Respir Crit Care Med 158:1432-1441, 1998
66. Bergmann C, Distler JHW, Treutlein C, et al: 68Ga-FAPI-04 PET-CT for molecular assessment of fibroblast activation and risk evaluation in systemic sclerosis-associated interstitial lung disease: A single-centre, pilot study. Lancet Rheumatol 3:e185-e194, 2021
67. Röhrich M, Leitz D, Glatting FM, et al: Fibroblast activation protein-specific PET/CT imaging in fibrotic interstitial lung diseases and lung cancer: A Translational Exploratory Study. J Nucl Med Off Publ Soc Nucl Med 63:127-133, 2022
68. Yang P, Fang Q, Fu Z, et al. Comprehensive analysis of Fibroblast Activation Protein (FAP) expression in interstitial lung diseases (ILDs). 2022;2022:10. doi:10.1164/RCCM.202110-2414OC
69. Conen P, Pennetta F, Dendl K, et al: [68 Ga]Ga-FAPI uptake correlates with the state of chronic kidney disease. Eur J Nucl Med Mol Imaging 49:3365-3372, 2022
70. Zhou Y, Yang X, Liu H, et al: Value of [68Ga]Ga-FAPI-04 imaging in the diagnosis of renal fibrosis. Eur J Nucl Med Mol Imaging 48:3493-3501, 2021