18F-FDG-PET/CT optimizes treatment in *Staphylococcus aureus* bacteremia and is associated with reduced mortality

Marvin A.H. Berrevoets[1*], Ilse J.E. Kouijzer[1*], Erik H.J.G. Aarntzen[2], Marcel J.R. Janssen[2], Lioe-Fee De Geus-Oei[3,4],

Heiman F.L. Wertheim[5], Bart-Jan Kullberg[1], Jaap Ten Oever[1], Wim J.G. Oyen[2,6], Chantal P. Bleeker-Rovers[1]

[1]Department of Internal Medicine and Radboud Center for Infectious Diseases, Radboud university medical center, Nijmegen, the Netherlands

[2]Department of Radiology and Nuclear Medicine, Radboud university medical center, Nijmegen, the Netherlands

[3]Department of Radiology and Nuclear Medicine, Leiden university medical center, Leiden, the Netherlands

[4]MIRA Institute for Biomedical Technology and Technical Medicine, Biomedical Photonic Imaging Group, University of Twente, the Netherlands

[5]Department of Medical Microbiology and Radboud Center for Infectious Diseases, Radboud university medical center, Nijmegen, the Netherlands

[6]Institute of Cancer Research and Royal Marsden NHS Foundation Trust, London, UK

* Both authors contributed equally to this article

Corresponding author:

Marvin A.H. Berrevoets (resident Internal Medicine and Infectious Diseases)

Department of Internal Medicine and Infectious Diseases

P.O. box 9101, 6500 HB, Nijmegen, the Netherlands

E-mail: Marvin.Berrevoets@radboudumc.nl

Word count: 4952 words

Short running title: FDG-PET/CT in *S. aureus* bacteremia

ABSTRACT

Metastatic infection is an important complication of *Staphylococcus aureus* bacteremia (SAB). Early diagnosis of metastatic infection is crucial, as specific treatment is required. However, metastatic infection can be asymptomatic and difficult to detect. In this study, we investigated the role of ^{18}F-FDG-PET/CT in patients with SAB for detection of metastatic infection and its consequences for treatment and outcome.

Methods

All patients with SAB at Radboud university medical center were included between January 2013 and April 2016. Clinical data and results of ^{18}F-FDG-PET/CT and other imaging techniques, including echocardiography, were collected. Primary outcomes were newly diagnosed metastatic infection by ^{18}F-FDG-PET/CT, subsequent treatment modifications, and outcome.

Results

A total of 184 patients were included and ^{18}F-FDG-PET/CT was performed in 105 patients of whom 99 had a high-risk bacteremia. ^{18}F-FDG-PET/CT detected metastatic infectious foci in 73.7% of these high-risk patients. In 71.2% of patients with metastatic infection, no signs and symptoms suggesting metastatic complications were present before ^{18}F-FDG-PET/CT was performed. ^{18}F-FDG-PET/CT led to a total of 104 treatment modifications in 74 patients. Three-month mortality was higher in high-risk bacteremia patients without ^{18}F-FDG-PET/CT performed compared to those in whom ^{18}F-FDG-PET/CT was performed (32.7% versus 12.4%, p=0.003). In multivariate analysis, ^{18}F-FDG-PET/CT was the only factor independently associated with reduced mortality (p=0.005; OR, 0.204; 95% CI, 0.066-0.624). A higher co-morbidity score was independently associated with increased mortality (p=0.003; OR, 1.254; 95% CI, 1.078-1.457).

Conclusion

^{18}F-FDG-PET/CT is a valuable technique for early detection of metastatic infectious foci, often leading to treatment modification. Performing ^{18}F-FDG-PET/CT is associated with significantly reduced three-month mortality.

Keywords: ^{18}F-FDG-PET/CT, *Staphylococcus aureus*, metastatic infection

INTRODUCTION

SAB is a severe infection known for its high morbidity and is associated with a 30-day overall mortality of 20% (*1*). An important complication of SAB is metastatic infection, with a reported incidence between 16 and 68% (*2-7*). Known risk factors for development of metastatic infection in SAB patients are community acquisition of the bacteremia, signs of infection present for more than 48 hours before initiation of appropriate antibiotic treatment, fever more than 72 hours after initiation of appropriate antibiotic treatment, and positive blood cultures more than 48 hours after initiation of appropriate antibiotic treatment (*3*). Early detection of metastatic infection is crucial, as morbidity and mortality are higher in the presence of these foci, probably due to incomplete eradication during treatment (*8*). However, metastatic infectious foci are often asymptomatic. In up to one-third of patients with Gram-positive bacteremia and metastatic foci, localizing signs and symptoms are absent (*8*).

During the past years, ^{18}F-fluorodeoxyglucose positron emission tomography combined with computed tomography (^{18}F-FDG-PET/CT) has been extensively used in diagnosing infectious diseases. Previous studies on the value of ^{18}F-FDG-PET/CT in metastatic infection have demonstrated that ^{18}F-FDG-PET/CT detects infectious foci in patients with bacteremia or infective endocarditis and leads to a decrease in relapse and mortality rate (*9,10*). Furthermore, ^{18}F-FDG-PET/CT has shown to be cost-effective in patients with Gram-positive bacteremia (*11*). The previous studies, however, did not report on how ^{18}F-FDG-PET/CT optimizes treatment in SAB, while the positive effect on outcome is undoubtedly caused by treatment modification. Therefore, the aim of this study was to investigate the diagnostic value of ^{18}F-FDG-PET/CT for newly diagnosed metastatic infection, subsequent treatment modifications, and outcome in patients with SAB, with a focus on patients with high-risk bacteremia.

MATERIALS AND METHODS

Study design and patients

This retrospective cohort study was performed at Radboud university medical center, Nijmegen, the Netherlands. All consecutive adult SAB cases between January 2013 and April 2016 were included. SAB was defined as one or more blood cultures positive for *S. aureus*. SAB cases were designated hospital-acquired if patients had been admitted for at least 48 hours before the first positive blood culture, or as community acquired in all other cases. Exclusion criteria were pregnancy, and death within 48 hours after the first positive blood culture with *S. aureus*. According to the Dutch law, this study was exempt from approval by an ethics committee, because of the retrospective character of this study and the anonymous processing of data. The regional institutional review board approved this retrospective study and the requirement to obtain informed consent was waived.

Data collection

We reviewed the medical records of all patients and collected data on patient demographic characteristics, estimated prognosis of preexisting underlying disease and comorbidity according to the Charlson comorbidity score (*12*), onset of bacteremia, presence of intravascular catheters or foreign body material, resistance of *S. aureus* to methicillin, foci of infection, and clinical parameters at SAB onset, diagnostic investigations, antimicrobial therapy, and outcomes. The data were retrieved electronically from clinical charts and reports of diagnostic studies (including laboratory, microbiological and imaging data).

Diagnostic work-up

According to definitions established previously (*3,8*), cases were designated high-risk SAB if one of the following criteria for increased risk of metastatic infection were met: community acquisition of the bacteremia, signs of infection for more than 48 hours before initiating of appropriate antibiotic treatment, fever more than 72 hours after initiating of appropriate antibiotic treatment, positive blood cultures more than 48 hours after initiating of appropriate antibiotic treatment, or already confirmed metastatic foci at the moment of presentation. For all patients with high-risk SAB, echocardiography and ^{18}F-FDG-PET/CT were

4

recommended.

An integrated PET/CT scanner (Biograph 40 mCT; Siemens Healthcare) was used. Before ^{18}F-FDG injection, patients fasted and any glucose or insulin-containing infusions were discontinued for at least six hours. In 66.7% of patients, a low carbohydrate fat-allowed diet was performed 24 hours before ^{18}F-FDG-PET/CT. Blood glucose samples were taken from all patients prior to ^{18}F-FDG administration. At the time of ^{18}F-FDG injection, glucose was below 12 mmol/l in all patients, including diabetic patients. One hour after intravenous injection of an average dosage of 3.3 MBq x body weight (kg)/min/bed position ^{18}F-FDG (Mallinckrodt Pharmaceuticals, Petten, The Netherlands or IBA Molecular, Amsterdam, The Netherlands), a whole body low-dose CT was acquired for anatomic correlation and attenuation correction of the PET data. Emission images of the same area were acquired. ^{18}F-FDG-PET/CT scans were considered abnormal if focal accumulation of ^{18}F-FDG was detected. Normal test results were considered true-negative when no complicating infectious foci were diagnosed within two weeks after ^{18}F-FDG-PET/CT was performed. Normal test results were considered false-negative when a localized infectious focus was diagnosed but not reported on ^{18}F-FDG-PET/CT. Abnormal test results not related to metastatic infection that were caused by a confirmed alternative diagnosis (i.e. cancer) were categorized as non-infectious relevant.

In all patients with SAB, the local antimicrobial stewardship program recommends bedside consultation by an infectious disease specialist (ID specialist), as well as echocardiography. Transthoracic echocardiography (TTE) was used as a first-line screening technique, except for those patients with prosthetic valves, in whom transesophageal echocardiography (TEE) was the first-line technique. TEE was recommended in all patients in whom TTE was negative for endocarditis, especially when imaging was hampered by technical or anatomical problems. Endocarditis was defined according to the modified Duke criteria (*13*).

Patients were treated according to the national guideline for SAB which is concordant with the IDSA guideline (*14*). However, for patients with risk factors for metastatic foci but without evidence of endocarditis after echocardiography and without signs of metastatic infection on ^{18}F-FDG-PET/CT, the institutional guideline recommends antimicrobial therapy for two weeks. These patients were considered as having uncomplicated bacteremia instead of complicated bacteremia.

Diagnosis and patient follow-up

Patient outcome and recurrent infection were assessed by reviewing patients' medical records . Patient follow-up after end of antimicrobial therapy was at least three months in order to capture SAB relapse, mortality, and cause of death. Patients were considered to be cured if no symptoms or signs of infection were present three months after the discontinuation of antibiotic treatment. Relapse of SAB was defined as a second episode of SAB within three months after end of treatment.

^{18}F-FDG-PET/CT and treatment modifications

The impact of ^{18}F-FDG-PET/CT on treatment was determined by the investigators for all cases in a two step approach. First, treatment duration was determined based on all clinical information available before ^{18}F-FDG-PET/CT was performed. Second, the results of the ^{18}F-FDG-PET/CT were provided, and the modifications of therapy based on these results were noted. During a weekly multidisciplinary meeting, all results of ^{18}F-FDG-PET/CT scans performed in patients with SAB were discussed with a panel of ID specialist and nuclear medicine physicians and treatment modifications based on these results were also noted in the patient's chart.

The impact of ^{18}F-FDG-PET/CT on treatment was classified as follows: 1) extension of antibiotic treatment including 1a) prolonged intravenous antibiotic therapy, e.g. instead of oral antibiotic therapy, 1b) addition of a second antimicrobial drug, e.g. rifampin in patients with foreign body material infection, or 1c) extension of total treatment duration, e.g. in case of joint or vascular prosthesis infection, 2) surgical or radiological intervention, e.g. abscess drainage, removal of foreign body material, and 3) shortening of treatment duration. If the results of the ^{18}F-FDG-PET/CT did not result in any intervention, this was also reported. To prevent interpretation bias, two independent physician observers (MAHB and IJEK) reviewed hospitalization records and determined treatment modification before and after ^{18}F-FDG-PET/CT results. If there was no consensus, a third independent infectious disease specialist (CPBR) with broad experience in SAB and ^{18}F-FDG-PET/CT made the final judgment. In patients with high-risk SAB, a comparison was made between patients who underwent ^{18}F-FDG-PET/CT and patients who did not.

Statistical analysis

SPSS (version 22.0; SPSS, Inc.) was used for analyzing data. Descriptive statistics for continuous variables were represented as median +/- standard deviation. Unpaired student's *t* tests were used to compare continuous variables. Categorical variables were compared by use of the chi-square test or Fisher's exact test when the chi-square test was not appropriate. Differences were considered to be statistically significant at a two-sided *p*-value of <0.05. To determine independent predictors of three-month mortality in the high-risk bacteremia group, we performed a multivariate analysis, including prognostic factors associated with a *p*-value <0.20 in univariate analysis. To limit the amount of variables in the model, the Charlson comorbidity score was used as a composite variable for age and co morbidity. As a composite variable for risk-factors for metastatic infection, a risk score previously described by Fowler et al *(3)* was used; community-acquisition, persistent fever >72 hours, and skin findings suggesting the presence of metastatic infection were separately scored as 1 point, and positive follow-up blood culture results were scored as 2 points.

RESULTS

During the study period, 195 events of SAB were identified. A total of 11 patients (5.6%) were excluded: 6 patients died within 48 hours, and 5 patients were lost to follow-up. A total of 184 patients were included in the final analysis. Of these, 148 (80.0%) had ≥1 risk factor for metastatic infection, and were classified as high-risk SAB. ^{18}F-FDG-PET/CT was performed in 99 of 148 (66.9%) high-risk SAB cases. In addition, ^{18}F-FDG-PET/CT was performed in 6 of 36 (16.7%) patients without risk factors for metastatic infection.

Definite endocarditis according to the modified Duke criteria was diagnosed in 16 patients (8.7%). Forty-six patients (25.0%) were admitted to the ICU within 24 hours before and one week after SAB onset. Of 184 *S. aureus* strains isolated, only 5 (2.7%) were methicillin-resistant. Central venous catheter infection was considered responsible for 35 episodes (19.0%) of SAB. Baseline characteristics of all patients with and without ^{18}F-FDG-PET/CT are shown in Table 1.

Detection of metastatic infection by ^{18}F-FDG-PET/CT

^{18}F-FDG-PET/CT was performed in 105 of 184 study patients at a median of 8.0 days (mean 8.7 days) after the first blood culture became positive. In 5 of 6 patients without risk factors for metastatic infection in whom ^{18}F-FDG-PET/CT was performed, no metastatic infection was found on ^{18}F-FDG-PET/CT. In one patient with a history of portal vein thrombosis, without risk factors for metastatic infection and removal of a central venous catheter one day after positive blood cultures, an ^{18}F-FDG-PET/CT was performed and detected septic thrombophlebitis. This patient received intravenous antibiotic treatment for 6 weeks. ^{18}F-FDG-PET/CT detected metastatic infectious foci in 73 of 99 patients with high-risk bacteremia (73.7%). In 52 out of these 73 patients (71.2%) eventually diagnosed with metastatic infection, no signs and symptoms suggesting metastatic complications were present before ^{18}F-FDG-PET/CT was performed. Metastatic infection was most often diagnosed in the lungs, skin and soft tissue, and as osteoarticular foci (Table 2). Of all 73 patients with metastatic infection, 47 patients (64.4%) were diagnosed with metastatic foci in more than one organ system. Eighteen patients had increased ^{18}F-FDG uptake in a cardiac valve suspected for endocarditis, of whom 5 had a definite endocarditis according to the modified Duke criteria, 10 had a possible endocarditis, and in 3 patients the diagnosis of endocarditis was rejected.

Patient outcome

The relapse rate three months after treatment discontinuation was 2.2% (4/184). Overall three-month mortality was 18.5% (34/184). In the univariate analysis, age (59 versus 69 years, p <0.05), intensive care admission (22.0% versus 38.2%, p <0.05), Charlson comorbidity score (4.3 versus 6.5, p <0.05), and no ^{18}F-FDG-PET/CT performed (38.0% versus 64.7%, p=0.005) were significantly different between survivors and non-survivors.

Patients with risk factors for metastatic infection

The group with a risk factor for metastatic infection who did not undergo ^{18}F-FDG-PET/CT (Risk+/PET-) was compared with the group of patients with a risk factor for metastatic infection and a ^{18}F-FDG-PET/CT performed (Risk+/PET+) (Table 3). In patients with risk factors for metastatic infection in whom an ^{18}F-FDG-PET/CT was performed, three-month mortality was significantly lower compared to the 'Risk+/PET-' group (12.1% versus 32.7%, p=0.003). Multivariate analysis of risk factors for three-month

8

mortality in the high-risk group is shown in Table 4. ^{18}F-FDG-PET/CT was the only factor that was significantly associated with reduced mortality (p=0.005; OR, 0.204; 95% confidence interval (CI), 0.066-0.624). A higher co-morbidity score was significantly associated with increased mortality (p=0.003; OR, 1.254; 95% CI, 1.078-1.457).

Treatment modifications in high-risk patients

In the 99 patients with high-risk SAB who underwent ^{18}F-FDG-PET/CT, 104 treatment modifications were made in 74 patients (74.7%) after the results of ^{18}F-FDG-PET/CT became available (Table 5). In 22 patients (22.2%), more than one treatment modification was made. In 25 patients (25.3%), treatment duration was shortened because no metastatic infection was detected. In 15 patients (15.2%), intravenous antibiotic therapy was prolonged based on the ^{18}F-FDG-PET/CT results, in 10 patients (10.1%) a second antimicrobial drug was prescribed, and in 35 patients (35.4%), the total treatment duration was extended. In most cases, treatment was extended because of bone or joint involvement (22.2%), vascular prosthesis infection (19.4%), or other endovascular infection (17%). Percutaneous or surgical drainage was performed in 19 patients (19.2%) based on the outcome of ^{18}F-FDG-PET/CT (Fig. 1 and Fig. 2). No treatment modification was made in 25 patients (25.3%) (Table 5).

Of all patients with a planned treatment duration of 6 weeks or more before ^{18}F-FDG-PET/CT was performed, one or more treatment modifications were performed in 23 out of 46 patients (50.0%) based on ^{18}F-FDG-PET/CT results (Fig. 3), compared to 51 out of 53 (96.2%) in the group with a planned treatment duration of less than 6 weeks.

The following relevant diseases not related to SAB were diagnosed in 7 patients (7.1%): pulmonary carcinoma, mediastinal carcinoid tumour, recurrent adenocarcinoma of the rectum, recurrent vaginal carcinoma, benign thyroid adenoma, inflammatory bowel disease, and esophageal candidiasis. Irrelevant findings were found in 8 patients: in these patients two colonoscopies, three esophago-gastro-duodenoscopies, three ultrasounds, and one CT-scan were performed without a clear diagnosis.

DISCUSSION

In this study, we investigated the value of ^{18}F-FDG-PET/CT in patients with SAB for detecting metastatic infection and its role in treatment modification in these patients. In a previous prospective study on 115 patients with high-risk Gram-positive bacteremia (*9*), the addition of ^{18}F-FDG-PET/CT to standard care led to significantly more patients who were diagnosed with metastatic infection compared to a matched historical control group of 230 patients in whom no ^{18}F-FDG-PET/CT was performed (67.8% versus 35.7% in the control group). Furthermore, six-month mortality rate decreased from 32.2% to 19.1% when ^{18}F-FDG-PET/CT was performed. An explanation for the slightly higher detection level in our study (73.7%) could be the fact that metastatic infection is more often seen in SAB than in other types of Gram-positive bacteremia. Another study on the value of ^{18}F-FDG-PET/CT for the diagnosis of metastatic infection in 47 patients with infectious endocarditis found that ^{18}F-FDG-PET/CT was associated with a twofold reduction in the number of relapses and ^{18}F-FDG-PET/CT enabled significantly more infectious complications to be diagnosed (57.4% versus 18% in matched controls) (*10*). Orvin et al. (*15*) prospectively studied the value of ^{18}F-FDG-PET/CT in 40 consecutive patients with definite endocarditis according to the Duke criteria. ^{18}F-FDG-PET/CT demonstrated extracardiac complications in 17 patients (42.5%), and these findings led to a change of treatment in 14 patients (35%) while these patients already had an indication for prolonged antibiotic treatment because of endocarditis. This is comparable to our results, as treatment was still adapted in 50% of patients with an indication for prolonged treatment before ^{18}F-FDG-PET/CT was performed.

In the present study, the early detection of metastatic infectious foci facilitated the adaptation of treatment in patients at high risk of relapse. The three-month relapse rate was only 2.2%, which is low compared to the rates reported in the literature for complicated SAB (2.1-23%) (*16*). An important finding of the present study is that patients with risk factors for metastatic infection who did not undergo ^{18}F-FDG-PET/CT had a significantly higher mortality rate compared to those who underwent ^{18}F-FDG-PET/CT (32.7% versus 12.1%, *p*=0.003), even though the average number of risk factors for metastatic infection in the latter group was higher. This emphasizes the importance of the risk assessment for metastatic infection, and suggests that physicians should not refrain from ordering ^{18}F-FDG-PET/CT with high-risk SAB based on personal judgment. Early death may be hypothesized to be a confounding factor, as those patients were

10

unable to undergo ^{18}F-FDG-PET/CT. However, in a sensitivity analysis excluding patients who died within seven days after admission, the results regarding three-month mortality were similar. Another potential confounder could be the difference in ID specialist consultation, because ID consults have been associated with reduced mortality in patients with SAB (*5,17-21*). However, multivariate logistic regression analysis did not show this to be an independent predictor of survival, probably due to the high frequency of ID consultation in both groups in the present study. In our study, ^{18}F-FDG-PET/CT detected endocarditis in 18 patients and was the first imaging technique detecting endocarditis in 11 patients. In contrary, 8 patients were diagnosed with a definite endocarditis according to the modified Duke criteria but had a negative ^{18}F-FDG-PET/CT. Whether ^{18}F-FDG-PET/CT could be used for diagnosing native valve endocarditis needs further investigation, as small studies performed on this subject show limited evidence (*22*).

Our study has several limitations. First, this is a single-center study that was not prospectively conducted. In 26.6% of patients, ^{18}F-FDG-PET/CT was indicated but not performed. The reasons for non-adherence to the local guidelines are not known, and this could potentially have led to selection bias. Second, although we used a two-reviewer adjudication process to determine treatment modification, it is possible that misclassification occurred. To reduce bias, the two reviewers were blinded from each other and disagreements were resolved by a third experienced reviewer.

CONCLUSION

In conclusion, performance of ^{18}F-FDG-PET/CT is significantly associated with reduced mortality in patients with high-risk SAB, and leads to the detection of metastatic infectious foci in 73.7% of patients, resulting in, important treatment modifications. ^{18}F-FDG-PET/CT should be recommended as standard imaging technique for all patients with ≥1 risk factor for metastatic infection in SAB guidelines.

FINANCIAL DISCLOSURE

None.

REFERENCES

1.   van Hal SJ, Jensen SO, Vaska VL, Espedido BA, Paterson DL, Gosbell IB. Predictors of mortality in Staphylococcus aureus Bacteremia. *Clin Microbiol Rev*. 2012;25:362-386.

2.   Jensen AG, Wachmann CH, Espersen F, Scheibel J, Skinhoj P, Frimodt-Moller N. Treatment and outcome of Staphylococcus aureus bacteremia: a prospective study of 278 cases. *Arch Intern Med*. 2002;162:25-32.

3.   Fowler VG Jr., Olsen MK, Corey GR, et al. Clinical identifiers of complicated Staphylococcus aureus bacteremia. *Arch Intern Med.* 2003;163:2066-2072.

4.   Fowler VG Jr., Sanders LL, Sexton DJ, et al. Outcome of Staphylococcus aureus bacteremia according to compliance with recommendations of infectious diseases specialists: experience with 244 patients. *Clin Infect Dis*. 1998;27:478-486.

5.   Jenkins TC, Price CS, Sabel AL, Mehler PS, Burman WJ. Impact of routine infectious diseases service consultation on the evaluation, management, and outcomes of Staphylococcus aureus bacteremia. *Clin Infect Dis*. 2008;46:1000-1008.

6.   Lautenschlager S, Herzog C, Zimmerli W. Course and outcome of bacteremia due to Staphylococcus aureus: evaluation of different clinical case definitions. *Clin Infect Dis*. 1993;16:567-573.

7.   Rieg S, Peyerl-Hoffmann G, de With K, et al. Mortality of S. aureus bacteremia and infectious diseases specialist consultation--a study of 521 patients in Germany. *J Infect*. 2009;59:232-239.

8.   Cuijpers ML, Vos FJ, Bleeker-Rovers CP, et al. Complicating infectious foci in patients with Staphylococcus aureus or Streptococcus species bacteraemia. *Eur J Clin Microbiol Infect Dis*. 2007;26:105-113.

9.   Vos FJ, Bleeker-Rovers CP, Sturm PD, et al. 18F-FDG PET/CT for detection of metastatic infection in gram-positive bacteremia. *J Nucl Med*. 2010;51:1234-1240.

10.   Kestler M, Munoz P, Rodriguez-Creixems M, et al. Role of (18)F-FDG PET in patients with Infectious Endocarditis. *J Nucl Med*. 2014;55:1093-1098.

11.   Vos FJ, Bleeker-Rovers CP, Kullberg BJ, Adang EM, Oyen WJ. Cost-effectiveness of routine (18)F-FDG PET/CT in high-risk patients with gram-positive bacteremia. *J Nucl Med*. 2011;52:1673-1678.

12.   Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *J Clin Epidemiol*. 2004;57:1288-1294.

13.   Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30:633-638.

14.   Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. *Clin Infect Dis*. 2011;52:e18-55.

15.   Orvin K, Goldberg E, Bernstine H, et al. The role of FDG-PET/CT imaging in early detection of extra-cardiac complications of infective endocarditis. *Clin Microbiol Infect*. 2015;21:69-76.

16.   Thwaites GE, Edgeworth JD, Gkrania-Klotsas E, et al. Clinical management of Staphylococcus aureus bacteraemia. *Lancet Infect Dis.* 2011;11:208-222.

17.   Choi SH, Cho SY, Park JH, Chung JW. Impact of infectious-disease specialist consultations on outcomes of Staphylococcus aureus bacteremia in a hospital with a low volume of patients with S. aureus bacteremia. *J Infect.* 2011;62:181-185.

18.   Forsblom E, Ruotsalainen E, Ollgren J, Jarvinen A. Telephone consultation cannot replace bedside infectious disease consultation in the management of Staphylococcus aureus Bacteremia. *Clin Infect Dis*. 2013;56:527-535.

19.   Fries BL, Licitra C, Crespo A, et al. Infectious diseases consultation and the management of Staphylococcus aureus bacteremia. *Clin Infect Dis*. 2014;58:598-599.

20.   Honda H, Krauss MJ, Jones JC, Olsen MA, Warren DK. The value of infectious diseases consultation in Staphylococcus aureus bacteremia. *Am J Med.* 2010;123:631-637.

21.   Lahey T, Shah R, Gittzus J, Schwartzman J, Kirkland K. Infectious diseases consultation lowers mortality from Staphylococcus aureus bacteremia. *Medicine (Baltimore).* 2009;88:263-267.

22.   Gomes A, Glaudemans AWJM, Touw DJ, Van Melle JP, Willems TP, Maass AH, et al. Diagnostic value of imaging in infective endocarditis: a systematic literature review and a proposal of an updated diagnostic work-up. *Lancet Infect Dis.* 2017;17:e1-e14.
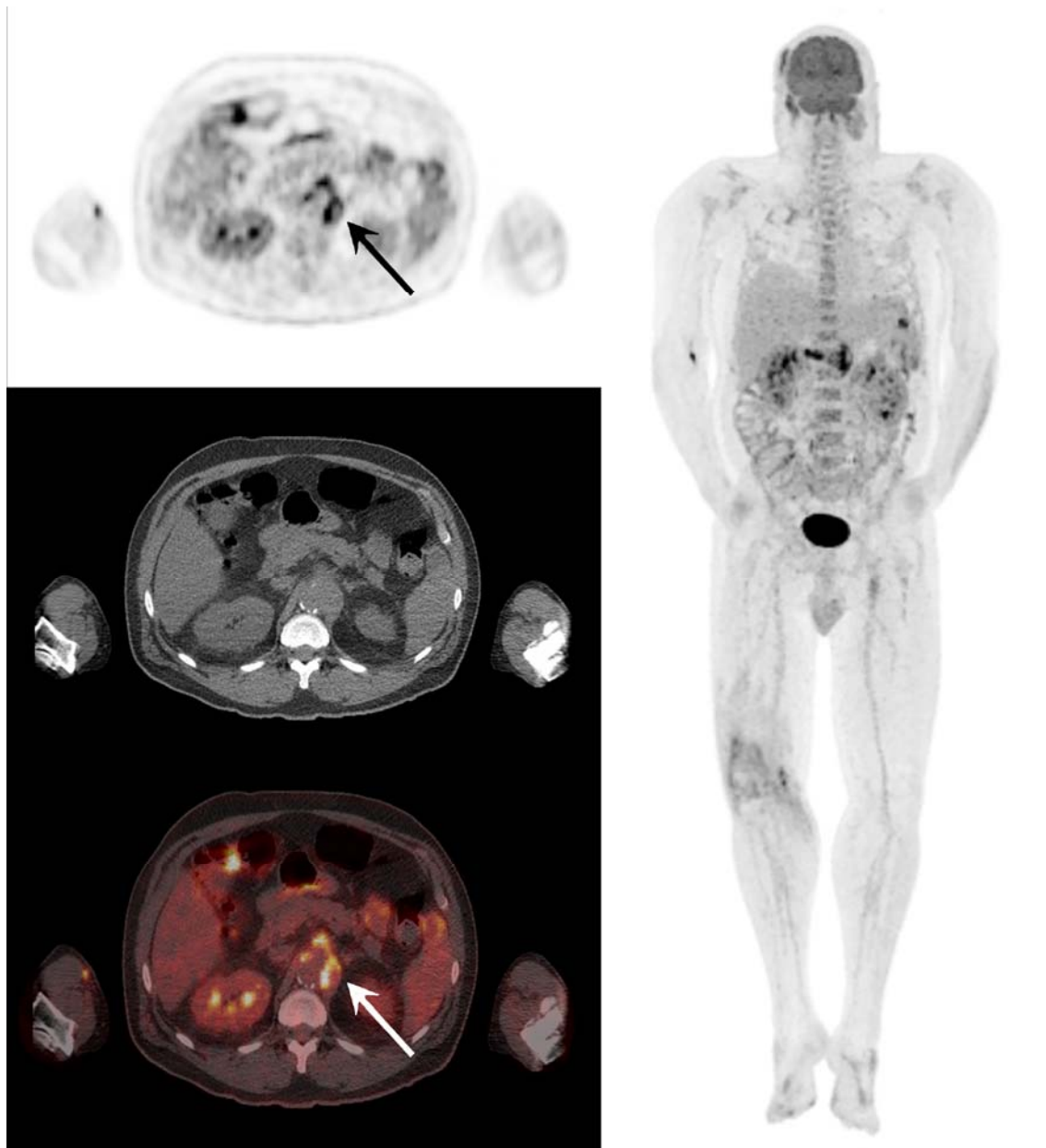
FIGURE LEGENDS

FIGURE 1. Transversal ^{18}F-FDG-PET/CT images at the level of the celiac trunk (left) and maximum intensity projection (MIP) image (right) of a 60-year-old man who was admitted because of a septic arthritis of his right knee. Blood cultures grew methicillin-susceptible *Staphylococcus aureus*. A transesophageal echocardiography was negative for endocarditis. Besides an arthritis of his right knee ^{18}F-FDG-PET/CT also showed a mycotic aneurysm of the celiac trunk (arrows) and multiple small abscesses in liver and spleen. This patient underwent a surgical repair of the celiac trunk and was successfully treated with flucloxacillin intravenously for six weeks after surgery.
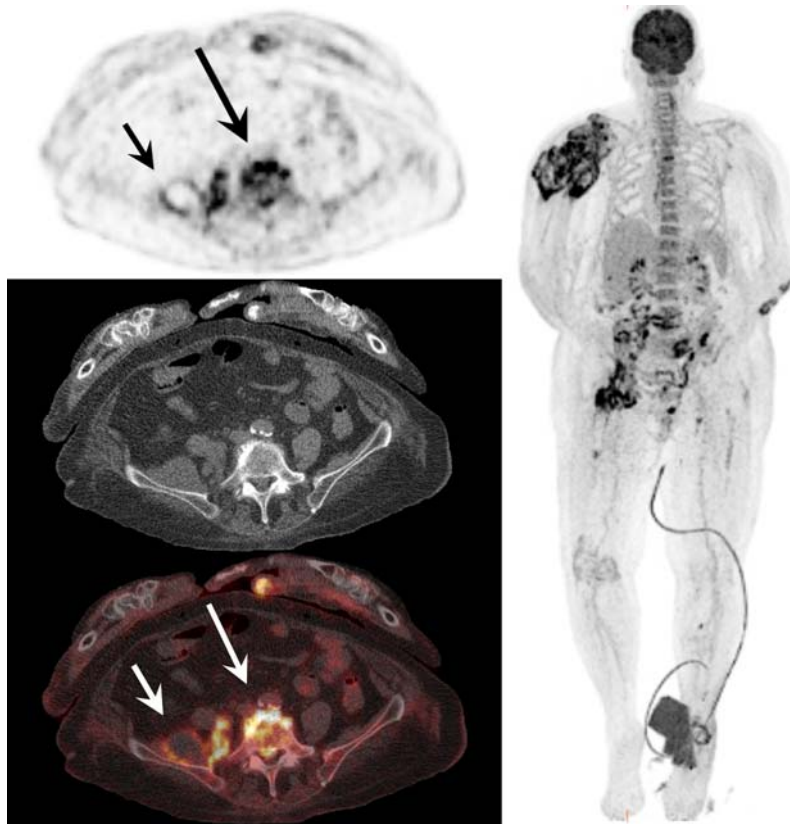
FIGURE 2. ^{18}F-FDG-PET/CT images of a 84-year-old woman with a right-sided closed humerus fracture after a fall. Two weeks later she developed arthritis of her left metacarpophalangeal joints and blood cultures were positive for methicillin-susceptible *Staphylococcus aureus.* Transesophageal echocardiography was negative for endocarditis. Besides arthritis of her left metacarpophalangeal joints ^{18}F-FDG-PET/CT also showed metastatic infection in her right hip prosthesis, left ankle, right humerus with surrounding abscesses, and lumbar spine (L4-L5) with a right psoas abscess. This patient underwent CT-guided drainage of the psoas abscess and was treated with cephazolin, because of allergy to flucloxacillin.
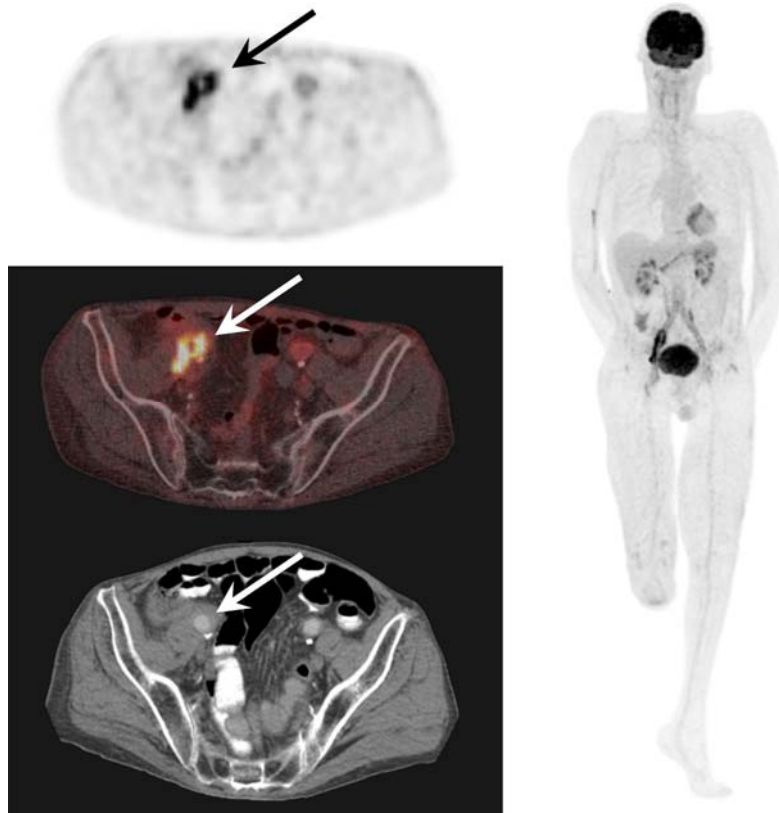
FIGURE 3. ^{18}F-FDG-PET/CT images in combination with contrast-enhanced CT images (lower-left panel) of a 75-year-old man with a medical history of COPD, a right femoropopliteal bypass and aortobifemoral bypass who was admitted because of fever. Blood cultures were positive for methicillin-susceptible *Staphylococcus aureus.* Transesophageal echocardiography was negative for endocarditis. ^{18}F-FDG-PET/CT showed an infected right iliac vascular prosthesis. This patient was treated with antibiotic therapy for 5 months and because of extensive infection he finally underwent vascular surgery.

TABLES

TABLE 1. Baseline characteristic of all 184 patients with SAB

	Number of patients (%)
Total	184
Male	113 (61.4)
Mean age (range)	61.1 (18-80)
Risk factors	
- Community acquisition	120 (65.2)
- Treatment delay >48h	45 (28.1) *
- Persistent fever	54 (30.7) †
- Persistent positive blood cultures	39 (21.2)
Rifampin treatment	48 (26.1)
ID specialist bedside consultation	140 (76.1)
Additional risk factors	
- Charlson comorbidity score	4.7
- Diabetes mellitus	42 (22.8)
- Metastatic malignancy	16 (8.7)
- Immunocompromised	61 (33.2)
- Joint prosthesis	26 (14.1)
- Heart valve prosthesis	23 (12.5)
- Vascular prosthesis	20 (10.9)
- Pacemaker/ICD	18 (9.8)
- Intravascular catheter	35 (19.0)
- Total parenteral nutrition	19 (10.3)
TTE	104 (56.5)
TEE	64 (34.8)
TTE/TEE	123 (66.8)

ID: Infectious Disease; ICD: Implantable Cardioverter Defibrillator; TTE: transthoracic echocardiography; TEE:

transesophageal echocardiography; * No data available in 24 patients; † No data available in 8 patients

TABLE 2. Localization of metastatic foci and number of foci first detected by ^{18}F-FDG-PET/CT in 99 high-risk SAB patients

Metastatic foci identified	Total	First detected by ^{18}F-FDG PET/CT (%)
Vertebral osteomyelitis/spondylodiscitis	14	8 (57.1)
Arthritis or joint prosthesis	19	7 (36.8)
Non vertebral osteomyelitis	10	4 (40.0)
Skin and soft tissue	31	20 (64.5)
Psoas abscess	7	3 (42.9)
Lung	31	17 (54.8)
Spleen	5	5 (100.0)
Liver/gallbladder	3	2 (66.7)
Kidney	1	1 (100.0)
Endocarditis	18	11(61.1)
Endovascular infection (excluding endocarditis)	20	15 (75.0)
Pericarditis or mediastinitis	4	3 (75.0)
Total	**164**	**97 (59.1)**

TABLE 3. Characteristics of patients with ≥1 risk factor for metastatic infection in whom ^{18}F-FDG-PET/CT was performed (PET+) or not (PET-)

	PET- n = 49 (%)	PET+ n = 99 (%)	*p*-value
Male	32 (65.3)	60 (60.6)	0.579
Mean age (SD)	60.33 (14.2)	60.61 (16.3)	0.714
Risk factors			
Treatment delay >48 hours*	9 (22.0)	36 (43.4)	0.020
Fever >72 hours after treatment initiation†	13 (27.7)	43 (45.3)	0.043
Persistent positive blood cultures >48 hours after treatment initiation‡	7 (15.6)	32 (32.7)	0.033
Community acquired bacteremia	31 (63.3)	88 (88.9)	<0.001
Foreign body material present	15 (30.6)	46 (46.5)	0.065
Infectious disease specialist consultation	30 (61.2)	89 (89.9)	<0.001
Echocardiograpy§	20 (40.8)	90 (90.9)	<0.001
Charlson comorbidity score (SD)	5.12 (3.4)	4.43 (2.9)	0.314
Intensive care admission	14 (28.6)	26 (26.3)	0.766
Three-month outcome			
Death	16 (32.7)	12 (12.1)	0.003
Recurrent infection	0	3 (3.0)	0.560

Percentage for each variable is indicated in brackets, unless otherwise specified

* No data available in 16 patients

† No data available in 7 patients

‡ No follow-up blood cultures performed in 5 patients

§ Either transthoracic echocardiography or transesophageal echocardiography

TABLE 4. Univariate and multivariate analysis of risk factors for three-month mortality in patients with ≥1 risk factor for metastatic infection (n=148)

	Alive at 3 months follow-up (n=120)	Death at 3 months follow-up (n=28)	Univariate analysis *p*-value	Multivariate analysis *p*-value	OR (95% CI) in multivariate analysis
Male	67 (60.8)	19 (67.9)	0.490		
Echocardiography performed	91 (75.8)	19 (67.9)	0.384		
Composite risk score* (SD)	1.65 (1.14)	1.93 (1.09)	0.067	0.052	1.537 (0.997-2.371)
Charlson comorbidity score (SD)	4.24 (2.90)	6.46 (3.49)	0.002	0.003	1.254 (1.078-1.457)
^{18}F-FDG-PET/CT performed	87 (72.5)	12 (42.9)	0.003	0.005	0.204 (0.066-0.624)
ID specialist consultation	99 (82.5)	20 (71.4)	0.184	0.786	0.851 (0.266-2.721)
ICU admission	29 (24.2)	11 (39.3)	0.105	0.125	2.147 (0.809-5.698)

Percentage for each variable is indicated in brackets, unless otherwise specified

ICU: Intensive Care Unit

ID: infectious disease

* Composite risk score: community-acquisition, persistent fever >72 hours, and skin findings suggesting the presence of metastatic infection were separately scored as 1 point, and positive follow-up blood culture results were scored as 2 points *(3).*

TABLE 5. Treatment modifications in 99 patients with high-risk SAB based on ^{18}F-FDG-PET/CT results

Treatment modification	n (%)
1) Extension of treatment	
a) Prolonged intravenous antibiotic therapy	15 (15.2)
b) Addition of a second antimicrobial drug	10 (10.1)
c) Extension of treatment duration	35 (35.3)
2) Surgical or radiological intervention	19 (19.2)
3) Shortening of treatment duration	25 (25.3)
No treatment modification	25 (25.3)

The Journal of NUCLEAR MEDICINE

18F-FDG-PET/CT optimizes treatment in Staphylococcus aureus bacteremia and is associated with reduced mortality

Marvin A.H. Berrevoets, Ilse J.E. Kouijzer, Erik H.J.G. Aarntzen, Marcel J.R. Janssen, Lioe-Fee De Geus-Oei, Heiman F.L. Wertheim, Bart-Jan Kullberg, Jaap Ten Oever, Wim J. G. Oyen and Chantal P. Bleeker-Rovers

This article and updated information are available at:
http://jnm.snmjournals.org/content/early/2017/03/22/jnumed.117.191981

Information about reproducing figures, tables, or other portions of this article can be found online at:
http://jnm.snmjournals.org/site/misc/permission.xhtml

Information about subscriptions to JNM can be found at:
http://jnm.snmjournals.org/site/subscriptions/online.xhtml

JNM ahead of print articles have been peer reviewed and accepted for publication in *JNM*. They have not been copyedited, nor have they appeared in a print or online issue of the journal. Once the accepted manuscripts appear in the *JNM* ahead of print area, they will be prepared for print and online publication, which includes copyediting, typesetting, proofreading, and author review. This process may lead to differences between the accepted version of the manuscript and the final, published version.

SNMMI | SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING