





## ORIGINAL ARTICLE

# Usefulness of $^{18}\text{F}$ -FDG PET-CT for the management of invasive fungal infections: A retrospective cohort from a tertiary university hospital

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## Abstract

**Background:**  $^{18}\text{F}$ -FDG PET-CT is a potentially useful technique to help manage invasive fungal infection (IFI), but information on this topic is scarce.

**Objectives:** To describe our experience using  $^{18}\text{F}$ -FDG PET-CT for IFI management.

**Patients/Methods:** Retrospective cohort of IFI episodes in a university hospital from 2018 to 2023 with a  $^{18}\text{F}$ -FDG PET-CT performed during the episode. We analysed its impact on IFI management compared to conventional imaging.

**Results:** Thirty-five patients diagnosed with 36 episodes of IFI (52.8% moulds, 44.4% yeasts and 2.8% *Pneumocystis*) underwent 55  $^{18}\text{F}$ -FDG PET-CT. 74.3% were immunocompromised, including 45.7% solid organ transplant recipients. Indications for  $^{18}\text{F}$ -FDG PET-CT were diagnostic (10.9%), staging (47.3%) and follow-up (41.8%). Altogether  $^{18}\text{F}$ -FDG PET-CT added value to IFI management in 50.9% episodes. In 26 patients who had both staging  $^{18}\text{F}$ -FDG PET-CT and conventional imaging, sites of IFI dissemination were detected in 53.8% and 19.2%, respectively. Staging  $^{18}\text{F}$ -FDG PET-CT unveiled occult sites in 34.6%, uncovering unknown dissemination in 19.2%. In the evaluation of endocarditis in patients with fungemia, it contributed in at least 38.5%.

Follow-up  $^{18}\text{F}$ -FDG PET-CTs had an added value in 47.8% episodes. They were allowed to de-escalate antifungal therapy in 26.1%. There were discordant findings between  $^{18}\text{F}$ -FDG PET-CT and CT follow-up in 40% cases.

**Conclusions:** Overall,  $^{18}\text{F}$ -FDG PET-CT added value to IFI management in more than 50% of the episodes. It increased the diagnosis of occult sites, unveiled disseminated disease missed out by conventional imaging, and contributed to diagnose or rule out

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endocarditis in fungemia. Follow-up  $^{18}\text{F}$ -FDG PET-CT helped adjust the treatment duration and deserves further study.

**KEYWORDS**

$^{18}\text{F}$ -FDG PET-CT, fungal infections, invasive, radiology

## 1 | INTRODUCTION

Fungi are ubiquitous organisms that colonise soil and water and belong to usual human microbiota. They reach human body when we inhale conidia or there is a disruption in the integrity of the mucosal barrier. Often, it is difficult to distinguish infection from colonisation. In most cases, human immunity is able to defend us from their invasion, but in immunocompromised hosts, these become a severe problem, causing disseminated infections and death.

Opportunistic invasive fungal infections (IFIs) affect a great variety of organs and systems. *Candida* spp. are the most common agents of fungemia, but they often also involve other organs such as liver, spleen, heart, skin, or bone. *Aspergillus* spp. produces mainly pulmonary disease; nevertheless, in some cases, the infection disseminates to other distant organs.<sup>1</sup> The heterogeneity of infection sites and clinical manifestations make IFI difficult to evaluate. Biopsy, when it is feasible, is considered the diagnostic gold standard. The European Organisation for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) classification provides a framework to classify the diagnosis according to the certainty.<sup>2</sup> In clinical practice, to diagnose an IFI, we need to consider the patient's susceptibility, microbiological tests, and imaging procedures.

Standard imaging techniques have limitations evaluating the activity of the lesions or the simultaneous involvement of multiple sites, especially in cases lacking a specific source. Disseminated infection can be silent in immunocompromised patients and cause uncontrolled disease or a future relapse. Locating all involved sites may help determine the optimal treatment (antifungal treatment, surgery procedures...) and its length. IFI treatment requires the use of systemic antifungal drugs targeting the isolated pathogen. In some cases, a long-term treatment is needed to avoid future relapse, but evidence about how to monitor the response or when to stop antifungal treatment is scarce.

Fluorine-18 fluorodeoxyglucose positron emission tomography integrated with computed tomography ( $^{18}\text{F}$ -FDG PET-CT) is a hybrid imaging technique that allows one to obtain functional information and correlate it with anatomical images. It is well known that inflammation requires energy obtained by an increase in tissue glycolysis, and therefore, immune cells show higher uptake of glucose and of its analogue  $^{18}\text{F}$ -FDG (the most common PET tracer).<sup>1</sup> Compared to other anatomy-based procedures such as computed tomography (CT) and magnetic resonance imaging (MRI),  $^{18}\text{F}$ -FDG PET-CT

provides metabolic information and is able to quantify it, allowing for future comparison.<sup>2</sup>

This technique is widely used in the evaluation, diagnosis, staging and response assessment of different oncologic diseases, inflammatory diseases, and infectious diseases (such as infectious endocarditis). Similarly, recent data suggest  $^{18}\text{F}$ -FDG PET-CT could be useful to establish IFI diagnosis in cases of fever of unknown origin or to identify silent infection sites and to monitor treatment response and modulate its duration.<sup>3,4</sup>

In this study, we aim to describe our centre's experience using  $^{18}\text{F}$ -FDG PET-CT in the clinical management of IFIs.

## 2 | PATIENTS AND METHODS

### 2.1 | Design, study period and subjects

Our institution is a 613-bed tertiary-care teaching hospital in Madrid, Spain, with solid organ transplantation (kidney, liver, heart and lung) and stem cell transplantation programmes and surgical departments such as heart surgery. This single-centre retrospective cohort study included adult patients admitted to Hospital Puerta de Hierro-Majadahonda between 1st January 2018 and 1st January 2023 diagnosed with IFI and having undergone at least one  $^{18}\text{F}$ -FDG PET-CT as part of the management of the IFI.

### 2.2 | Data collection

Epidemiological, clinical (including type of immunocompromise, localised, or disseminated disease, type of pathogen), laboratory, and imaging data were extracted from electronic medical records (SELENE System, Cerner Iberia, S.L.U., Madrid, Spain) using a standardised data collection form.  $^{18}\text{F}$ -FDG PET-CT indication and impact of the results on IFI management were specifically addressed. All data were included by a primary reviewer and, subsequently, checked by two senior physicians.

### 2.3 | $^{18}\text{F}$ -FDG PET-CT technique

All  $^{18}\text{F}$ -FDG PET-CT was performed according to EANM (European Association of Nuclear Medicine) guidelines in hybrid PET/CT chamber systems.<sup>5</sup> The CT component was non-contrast enhanced. All patients complied with a previous fasting period of at least 6 h (12–18 h

in cases of suspected endocarditis; in this case, a dietary modification protocol was also applied). Ideally, they should maintain blood glucose levels lower than 180mg/dL. If insulin were administered, the injection of  $^{18}\text{F}$ -FDG would be spaced at least 4 h apart. For infectious and inflammatory diseases, the same acquisition, reconstruction, and post-processing described in the procedures of the EANM for tumours were used.<sup>5,6</sup> Full-body  $^{18}\text{F}$ -FDG PET-CT, from cranial vertex to the feet in supine position, was acquired approximately 50–60 min after intravenous of  $370 \pm 30 \text{ MBq}$  depending on patient's weight. When infective endocarditis was a possibility, the study was completed with dedicated cardiac  $^{18}\text{F}$ -FDG PET-CT acquisition.

The  $^{18}\text{F}$ -FDG PET-CT was analysed for increased uptake of  $^{18}\text{F}$ -FDG outside the areas of physiological incorporation. A qualitative analysis was carried out, considering the uptake pattern (focal, linear, diffuse) and the distribution of the radiotracer in the pathological area or lesion (homogeneous or heterogeneous), and semiquantitative considering the intensity of the uptake. The images were interpreted as normal, equivocal or with pathological uptake according to both the standard uptake values (SUV) and a qualitative visual score. SUV is a computer-generated measurement obtained from the VOI (volume of interest) manually selected by the reader (nuclear medicine physician). The SUV is a mathematically derived ratio of tissue radioactivity concentration at a point in time in the VOI (X) and the injected dose of radioactivity per kilogram of the patient's body weight ( $\text{SUV} = X / [\text{injection dose (MBq)} / \text{patient's weight (kg)}]$ ). The visual score was as follows: 0: no pathological uptake; 1: uptake similar to the vascular pool in the mediastinum; 2: uptake higher than the vascular pool but lower than the liver pool; 3: uptake similar or slightly higher than the liver; 4: uptake clearly higher than the hepatic. Where 0 and 1 would be negative and 2, 3 and 4 positive (always assessing location and alternative causes that explain the uptake).

## 2.4 | Other imaging techniques

Diagnostic workup for fungal infection was done at the discretion of treating physicians. In general, in our institution,  $^{18}\text{F}$ -FDG PET-CT is performed in patients with bloodstream infection with suspicion of endocarditis when the alternative imaging techniques are not conclusive, according to a diagnostic algorithm.<sup>7</sup> For every case, the results of conventional imaging techniques performed during the episode were compared with  $^{18}\text{F}$ -FDG PET-CT results, according to the reports by Radiology specialists (or Cardiologists, when applicable). This included X-ray, CT, MRI, and, in the case of fungemia, echocardiography. Median time from other selected imaging techniques to or from PET-CT was 8.5 days.

## 2.5 | Definitions

IFI was considered **proven, probable or possible** according to the revised EORTC/MSG classification.<sup>8</sup>

According to  **$^{18}\text{F}$ -FDG PET-CT indication**, three different categories were established: diagnostic, staging and follow-up. It was considered a **diagnostic** tool when it was performed as part of fever of unknown origin (FUO) management protocol or when other image techniques failed to categorise already-known lesions. We considered "**staging**"  $^{18}\text{F}$ -FDG PET-CT, along the same lines as what we do when we stage cancer, those performed to evaluate extension in patients already diagnosed with IFI (to distinguish between localised or disseminated infection). **Follow-up**  $^{18}\text{F}$ -FDG PET-CT was done during the course of the disease after the primary event, and they intended to assess the response to therapy.

We considered  $^{18}\text{F}$ -FDG PET-CT had an "**added value**" when lesions were detected outside the region assessed by other imaging tests, identified clinically hidden lesions or previously unknown dissemination, reclassified a radiological finding not initially suspicious of IFI, or lead to the performance of a one diagnostic test.<sup>3,4</sup> Additionally, when the information provided by the  $^{18}\text{F}$ -FDG PET-CT allowed clinical decisions regarding antifungal treatment duration or changes in the selected drug in order to improve penetration into involved areas or need for combined treatment or surgical treatment for source control, it was considered it had an added value as well.

## 2.6 | Data analysis

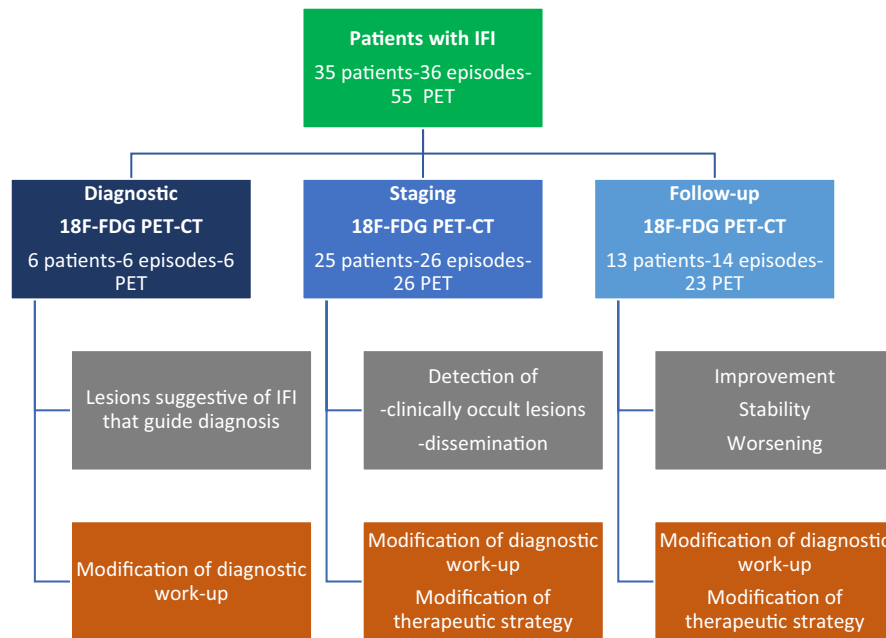
Quantitative variables are expressed as means and standard deviations (SD) and/or medians and interquartile ranges, and qualitative variables are expressed as frequencies and percentages.

## 3 | RESULTS

From January 2018 to January 2023, 35 patients diagnosed with 36 episodes of proven/probable/possible IFI according to the EORTC/MSG criteria, underwent 55  $^{18}\text{F}$ -FDG PET-CT studies (Figure 1).

### 3.1 | Characteristics of patients with IFI who underwent $^{18}\text{F}$ -FDG PET-CT

Table 1 shows the characteristics of the study population. Twenty-six patients (74.3%) were considered immunocompromised due to their underlying disease. There were 16 (45.7%) solid organ transplant recipients and 3 (8.6%) stem cell transplant recipients. Only three (8.6%) IFI cases occurred in patients with no previous medical history. All of them had severe SARS-COV2 pneumonia and had received immunosuppressors to treat it. Another patient with COVID-associated pulmonary aspergillosis was also a kidney transplant recipient.



**FIGURE 1** Patient population and study design.

	Yeasts	Moulds	Pneumocystis	Total
Number of patients	15(42.9%)	19 (54.3%)	1 (2.8%)	35
Sex				
Male	13 (86.7%)	12 (63.2%)	0 (0%)	25 (71.4%)
Female	2 (13.3%)	7 (36.8%)	1 (100%)	10 (28.6%)
Age (years) (mean; median))	63.73; 65	61.05; 59	56; 56	62.06;62
Underlying disease				
Haematological	0 (0%)	6 (31.6%)	0 (0%)	6 (17.1%)
Oncological	2 (13.3%)	2 (10.5%)		4 (11.4%)
Renal	1 (6.7%)	3 (15.8%)	1 (100%)	5 (14.3%)
Pulmonary	0 (0%)	5 (26.3%)	0 (0%)	5 (14.3%)
Liver disease	3 (20%)	1 (5.3%)	0 (0%)	4 (11.4%)
Neurological	2 (13.3%)	0 (0%)	0 (0%)	2 (5.7%)
Heart disease	3 (20%)	1 (5.3%)	0 (0%)	4 (11.4%)
Postsurgical	2 (13.3%)	0 (0%)	0 (0%)	2 (5.7%)
No underlying disease	2 (13.3%)	1 (5.3%)	0 (0%)	3 (8.6%)
Immunocompromise	7 (46.7%)	18 (94.7%)	1 (100%)	26 (74.3%)
Neutropenia (<500 neutrophils/microliter)	0 (0%)	4 (21.1%)	0 (0%)	4 (11.4%)
SARS-COV2	2 (13.3%)	2 (10.5%)	0 (0%)	4 (11.4%)
Stem cell transplantation	0 (0%)	3 (15.8%)	0 (0%)	3 (8.6%)
Solid organ transplantation	5 (33.3%)	10 (52.6%)	1 (100%)	16 (45.7%)
Kidney	0 (0%)	4 (21.1%)	1 (100%)	5 (14.3%)
Lung	0 (0%)	4 (21.1%)	0 (0%)	4 (11.4%)
Heart	2 (13.3%)	1 (5.3%)	0 (0%)	3 (8.6%)
Liver	3 (20%)	1 (5.3%)	0 (0%)	4 (11.4%)

**TABLE 1** Characteristics of 35 patients with IFI.

The most common underlying diseases in patients with yeast infections were liver (20%), and heart (20%) diseases. On the other hand, the most common underlying diseases in patients with mould infection were haematological (31.6%), pulmonary (26.3%) or renal (15.8%).

### 3.2 | Characteristics of IFI

The majority were caused by moulds (52.8%), 14 of them due to *Aspergillus* spp. Among the 16 cases caused by yeasts (44.5%), 12 were invasive candidiasis. One patient suffered two different episodes of fungemia due to different *Candida* species (first, *Candida albicans* and then *Candida parapsilosis*). Only one case of *Pneumocystis jirovecii* was included. Figure 2 shows the aetiology of IFIs.

The lung was the most commonly involved organ (47.2%), and skin and soft tissues followed (13.9%). Among those with mould infections, 3 patients (15.8%) did not present lung involvement initially but presented muscle, biliary or sinonasal involvement instead; and 7 (36.8%) had both lung plus another organ involvement. Eventually, 15 (41.7%) IFIs were considered disseminated infections. Among episodes of fungemia, 8 (57.1%) were disseminated, whereas 6 (42.9%) were isolated fungemia (Table 2).

Twelve-week survival was 85.7%. Median antifungal therapy duration was 95.5 days (Interquartile range (IQR) 34–187 days) (112 days (IQR 40–200 days) when excluding those who died under antifungals).

### 3.3 | Characteristics of $^{18}\text{F}$ -FDG PET-CT

Classification of  $^{18}\text{F}$ -FDG PET-CT according to indication was as follows: diagnostic (10.9%), staging (47.3%) and follow-up (41.8%). (Table 3).

Twenty-six patients (74.3%) had a single  $^{18}\text{F}$ -FDG PET-CT study in the assessment of IFI, whereas 9 patients (25.7%) had more than one  $^{18}\text{F}$ -FDG PET-CT studies to monitor the treatment response. As aforementioned, one patient had two different episodes of candidemia and consequently had more than one  $^{18}\text{F}$ -FDG PET-CT in both episodes; all of them have been included.

Altogether  $^{18}\text{F}$ -FDG PET-CT added value to IFI management in 28 (50.9%) cases. Table 4 (see supplementary data) shows the type of added value according to PET-CT indication and type of fungus. Of 30 patients who had both  $^{18}\text{F}$ -FDG PET-CT and CT, IFI dissemination was detected in 13 (43.3%) and 6 (20%), respectively.

### 3.4 | Diagnostic $^{18}\text{F}$ -FDG PET-CT

We recorded six  $^{18}\text{F}$ -FDG PET-CT (10.91%) performed with diagnostic purposes (half of them to study FUO; the remaining, to evaluate atypical lesions). In cases of study of fever without previous suspicion of IFI,  $^{18}\text{F}$ -FDG PET-CT helped to diagnose 3 IFI cases. One had a *Pneumocystis jirovecii* pneumonia; another had a nasosinusal IFI subsequently identified as fusariosis and the last one had invasive aspergillosis.  $^{18}\text{F}$ -FDG PET-CT also helped to assess the activity of atypical or dubious lesions in two cases of aspergillosis and in one patient who was known to be colonised by *Scedosporium apiospermum*, suggesting infection (pneumonia) and directing the tests that confirmed the diagnosis.

All patients who underwent diagnostic  $^{18}\text{F}$ -FDG PET-CTs had their antifungal therapy initiated or escalated in view of their results.

### 3.5 | Staging $^{18}\text{F}$ -FDG PET-CT

Twenty-six  $^{18}\text{F}$ -FDG PET-CTs (47.3%) were carried out for staging an already-diagnosed IFI. Median time from diagnosis to staging

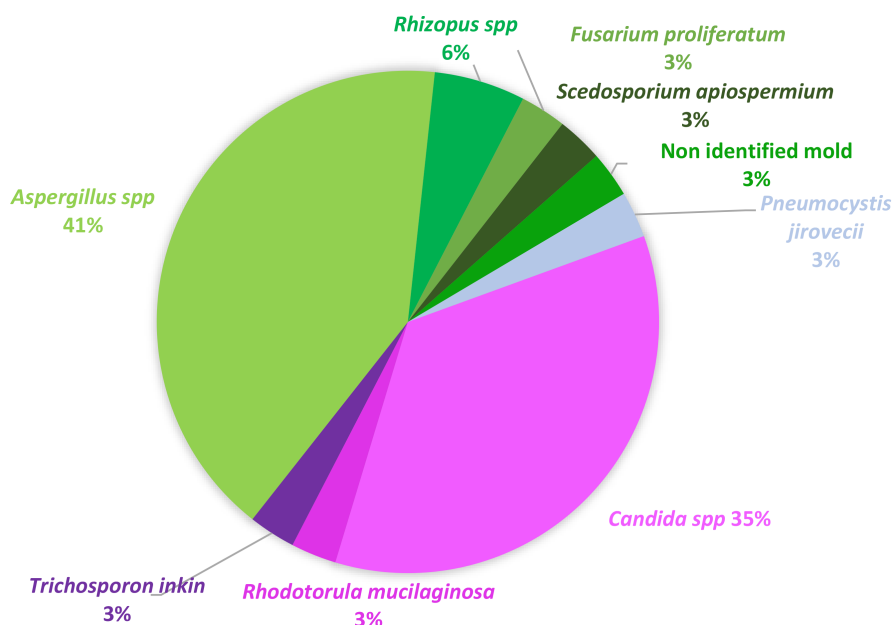


FIGURE 2 Aetiology of 36 IFI episodes.

TABLE 2 Characteristics of 36 IFI episodes.

IFI category	Yeasts	Moulds	Pneumocystis	TOTAL
	16 (44.5%)	19 (52.8%)	1 (2.8%)	36
Possible	0 (0%)	5 (26.3%)	0 (0%)	5 (13.9%)
Probable	0 (0%)	7 (36.8%)	1 (100%)	8 (22.2%)
Proven	16 (100%)	7 (36.8%)	0 (0%)	23 (63.9%)
Localised disease	2 (12.5%)	12 (66.2%)	1 (100%)	15 (41.7 %)
Disseminated disease	8 (0.00%)	7 (36.8%)	0 (0%)	15 (41.7%)
Only fungemia without secondary lesions	6 (7.5%)	0 (0%)	0 (0%)	6(16.7%)
Organs involved				
Lung/pleura	8 (50%)	16 (84.2%)	1 (100%)	17 (47.2%)
Skin/soft tissue	2 (12.5%)	3 (15.8%)	0 (0%)	5 (13.9%)
Heart	2 (12.5%)	0 (0%)	0 (0%)	2 (5.6%)
Endovascular	2 (12.5%)	1 (5.3%)	0 (0%)	3 (8.3%)
Liver	4 (25%)	1 (5.3%)	0 (0%)	5 (13.9%)
Biliary-pancreatic	2 (12.5%)	0 (0%)	0 (0%)	2 (5.6%)
Intestinal	0 (0%)	1 (5.3%)	0 (0%)	1 (2.8%)
Sinuses	0 (0%)	1 (5.3%)	0 (0%)	1 (2.8%)
Eye	0 (0%)	2 (10.5%)	0 (0%)	2 (5.6%)
Urinary-prostate	1 (6.3%)	1 (5.3%)	0 (0%)	2 (5.6%)
CNS	0 (0%)	1 (5.3%)	0 (0%)	1 (2.8%)
Antifungal therapy duration (median)	95.5 d	112 d	21 d	95.5 d

18F-FDG PET-CT	Yeasts	Moulds	Pneumocystis	Total
Total	20 (36.4%)	34 (61.8%)	1 (1.8%)	55
Diagnostic	0 (0%)	5 (5.88%)	1 (100%)	6 (10.9%)
Staging	13 (65%)	13 (50%)	0 (0%)	26 (47.3%)
Follow-up	7 (35%)	16 (44.1%)	0 (0%)	23 (41.8%)

TABLE 3 Indications of 55 18F-FDG PET-CT.

<sup>18</sup>F-FDG PET-CT was 16.5 days (IQR 8.5–30 days). They revealed involvement in 9 previously clinically occult locations (34.6%), and dissemination in 5 (19.2%) and triggered additional diagnostic procedures in 10 (38.5%). Furthermore, the use of staging <sup>18</sup>F-FDG PET-CT in the assessment of IFIs lead to antifungal treatment changes in 3 cases (3/26), escalating therapy in 2 cases and de-escalating in 1 case (11.5%). Globally, it was considered to provide an added value in 10 (38.5%) cases.

Of 26 patients who had both <sup>18</sup>F-FDG PET-CT and conventional imaging (in four cases of fungemia, the only conventional imaging was echocardiography), sites of IFI dissemination were detected in 14 (53.8%) and 5 (19.2%), respectively. However, in 3 of the cases initially classified as disseminated based on <sup>18</sup>F-FDG PET-CT, IFI at the site of dissemination was not confirmed, but neither was an alternative diagnosis, so it was not possible to totally exclude IFI. Nevertheless, those were considered possible false positives and finally classified as localised disease.

Thirteen of them (50%) were done to assess yeast infections, mainly to rule out endocarditis. Table 5 shows the characteristics

of these patients and the results obtained with echocardiogram and <sup>18</sup>F-FDG PET-CT. <sup>18</sup>F-FDG PET-CT unveiled two cases of endocarditis even when previous echocardiography had been negative (one due to *Candida albicans* and one due to *Rhodotorula mucilaginosa*); and ruled out endocarditis in one patient with fungemia and suspicious but not definite heart valve lesions observed by echocardiogram.

Besides the usefulness to confirm or exclude endocarditis in patients with fungemia, <sup>18</sup>F-FDG PET-CT also helped to locate unknown sites of infection in another three fungemia episodes (one due to *Thichosporon inkin*, another due to *C. parapsilosis* and the last due to *C. glabrata*) and disclosed non-cardiac lesions on top of valvular findings in one of the cases of endocarditis. The case caused by *C. parapsilosis* presented a peritube fluid collection impossible to characterise in echocardiography; in <sup>18</sup>F-FDG PET-CT, this finding was described as inflammatory and probably postsurgical event (not infectious) in line with a prior study that showed that non-infected ascending aortic grafts may show increased <sup>18</sup>F-fluorodeoxyglucose activity that could persist beyond the first year because the aortic graft did not show a specific uptake pattern<sup>9</sup>; however, as it identified

TABLE 4 Characteristics of imaging in 28 episodes with added value of 18F-FDG PET-CT according to indication and type of fungus.

PET-CT Indication	Episode number	PET-CT number	Type of fungus	Reference traditional imaging	PET-CT vs. Traditional imaging			Induces new diagnostic tests
					Occult lesions	Dissemination	Antifungal therapy	
Diagnostic	1	1	Mould	CT thorax	Yes	No	Escalated	Yes
	1	1	Mould	CT thorax	Yes	No	Escalated	Yes
	1	1	Mould	CT thorax and sinuses	Yes	No	Escalated	Yes
	1	1	Mould	CT thorax	Yes	No	Escalated	Yes
	1	1	Mould	CT thorax	Yes	Yes	Escalated	Yes
	1	1	Pneumocystis	CT thorax	Yes	No	Escalated	Yes
	1	1	Yeast	TTE, CT abdomen	Rules out suspected endocarditis		De-escalated	No
Staging	1	1	Yeast	ETE, aortic CT	Yes	Yes	Escalated	Yes
	1	1	Yeast	TEE	Yes	Yes	Escalated	Yes
	1	1	Yeast	TEE	Yes	No	Not changed	Yes
	1	1	Yeast	TTE, TAC TAP	Yes	Yes	Not changed	No
	1	1	Mould	CHEST RX and LLL MRI	Yes	Yes	Not changed	Yes
	1	1	Mould	CT thorax and CNS	Yes	Already disseminated	Not changed	Yes
	1	1	Mould	CT thorax	Yes	No <sup>a</sup>	Not changed	Yes
	1	1	Mould	CT thorax	Yes	No <sup>a</sup>	Not changed	Yes
	1	1	Mould	CT thorax, RNM URL	Yes	No <sup>a</sup>	Not changed	Yes
	1	1	Mould	CT thorax and CNS	No	No	surgery	Yes
	1	1	Yeast	TTE, CT thorax	Improvement		De-escalated (suspenden)	No
	2	4	Yeast	Prior PET-CTs	Improvement		De-escalated (suspenden)	No
	1	1	Yeast	CT thorax-abdomen CT CNS, lumbar spine MRI, TTE	Yes	Yes	Not changed	Yes
	1	1	Yeast	CT thorax-abdomen	Improvement		Not changed	No
Follow-up	1	2	Mould	CT thorax-abdomen	Improvement		De-escalated (suspenden)	No
	1	3	Mould	CHEST RX, CT abdomen-pelvis	Improvement		De-escalated (suspenden)	No
	1	4	Mould	Prior PET-CTs	Improvement		De-escalated (suspenden)	No
	1	2	Mould	CT thorax and sinuses	Yes	Yes	Escalated	Yes
	1	2	Mould	Prior PET-CTs	Yes <sup>a</sup>	Already disseminated	Not changed	Yes
	1	2	Mould	Ecography	Yes	Already disseminated	Escalated + Surgery	Yes
	1	3	Mould	Ecography	Yes	Already disseminated	Escalated	Yes
	1	1	Yeast	TTE, CT thorax	Improvement		De-escalated (suspenden)	No
	2	4	Yeast	Prior PET-CTs	Improvement		De-escalated (suspenden)	No
	1	1	Yeast	CT thorax-abdomen CT CNS, lumbar spine MRI, TTE	Yes	Yes	Not changed	Yes

<sup>a</sup>Dissemination was not confirmed: biopsy did not confirm IFI, nor confirm an alternative diagnosis.



TABLE 5 Evaluation of endocarditis and additional added value of <sup>18</sup>F-FDG PET-CT in 13 patients with fungemia.<sup>a</sup>

Patient sex	Yeast causing fungemia	Cardiac valves	Type of echocardiogram	Echocardiogram result	[ <sup>18</sup> F] FDG PET/CT result	EndocarditisValue	Additional lesions
Male	<i>C. albicans</i>	Native	Transthoracic	No signs of infective endocarditis	No signs of infective endocarditis	Rule out	No
Male	<i>C. albicans</i>	Native	Transthoracic	<b>Possible aortic valve endocarditis</b>	No signs of infective endocarditis	Rule out	No
Male	<i>C. albicans</i>	Native	Transesophageal	No signs of infective endocarditis	Infective endocarditis	Diagnosis	IE + lung + gallbladder + retroperitoneal + shoulder
Male	<i>C. glabrata</i>	Native	Transesophageal	No signs of infective endocarditis	No signs of infective endocarditis	Rule out	No
Female	<i>C. glabrata</i>	Native	Transthoracic	No signs of infective endocarditis	No signs of infective endocarditis	Rule out	Uptake by vascular prosthesis + liver + lung new lesions
Male	<i>C. glabrata</i>	Native	Transthoracic	No signs of infective endocarditis	No signs of infective endocarditis	Rule out	No
Female	<i>C. glabrata</i>	Native	Transesophageal	No signs of infective endocarditis	No signs of infective endocarditis	Rule out	No
Male	<i>C. parapsilosis</i>	Native	Transthoracic	No signs of infective endocarditis	No signs of infective endocarditis	Rule out	No
Male	<i>C. parapsilosis</i>	Prosthetic mechanic (aortic tube)	Transesophageal	<b>Fluid collection (abscess vs. hematoma)</b>	No signs of infective endocarditis	<b>Rule out</b>	+muscle abscesses + liver
Male	<i>C. parapsilosis</i>	Native	Transesophageal	No signs of infective endocarditis	No signs of infective endocarditis	Rule out	No
Male	<i>C. parapsilosis</i>	Native	Transthoracic	No signs of infective endocarditis	No signs of infective endocarditis	Rule out	No
Male	<i>R. mucilaginosa</i>	Native (ICD-CRT)	Transesophageal	No signs of infective endocarditis	Infective endocarditis	<b>Diagnosis</b>	IE involving ICD wires
Male	<i>T. inkin</i>	Native	Transthoracic	No signs of infective endocarditis	No signs of infective endocarditis	Rule out	+persistent spondylodiscitis + lung lesions

<sup>a</sup>One patient with fungemia was not included in this table because he did not have a concurrent echocardiogram, as he only had a follow-up PET-CT.



previously unknown muscle and hepatic abscesses,  $^{18}\text{F}$ -FDG PET-CT was considered to have an added value and the case was eventually managed as prosthetic endocarditis.

In summary, it allowed to increase the number of known infection sites in 38.5% (5/13) fungemia episodes, in addition to contributing to ruling out endocarditis in the remaining ones.

Thirteen of the staging  $^{18}\text{F}$ -FDG PET-CT studies (50%) were performed in patients with IFIs caused by moulds. It revealed clinically occult lesions in 5 cases and guided additional diagnostic tests in 6 cases. There were 3 IFI initially considered localised that eventually were categorised as disseminated based on after  $^{18}\text{F}$ -FDG PET-CT results (2 previously unknown cases of muscular involvement, and 1 silent naso-sinusal lesion due to *Aspergillus* spp). In the other 3 cases, as aforementioned, it was not possible to confirm nor exclude the fungal aetiology of the occult lesions (a bone lesion, a nasosinusal involvement and a muscular uptake).

### 3.6 | Follow-up $^{18}\text{F}$ -FDG PET-CT

Twenty-three follow-up  $^{18}\text{F}$ -FDG PET-CT (41.8%) studies were registered in 14 IFI episodes. In 4 of them (17.4%), even if there was not a baseline PET-CT at diagnosis, follow-up PET-CTs were performed to evaluate treatment response. Two were disseminated infections by *Thichosporon inkin* in heart transplantation recipients in whom follow-up  $^{18}\text{F}$ -FDG PET-CT was allowed to end fungal treatment. The remaining two confirmed cure in a case of possible pulmonary aspergillosis and a case of disseminated candidiasis.

Table 6 (see supplementary data) shows the number and timing of the follow-up  $^{18}\text{F}$ -FDG PET-CTs. Median time from IFI diagnosis to first follow-up  $^{18}\text{F}$ -FDG PET-CT was 109 days (IQR 75.8–134.5 days). In one case, follow-up  $^{18}\text{F}$ -FDG PET-CT was performed only 25 days after the diagnosis; the patient suffered a *Fusarium proliferatum* infection and was presenting a poor clinical evolution; the follow-up  $^{18}\text{F}$ -FDG PET-CT showed disseminated infection with naso-sinusal and pulmonary involvement, and antifungal therapy was escalated. Time between the subsequent follow-up  $^{18}\text{F}$ -FDG PET-CTs was very variable. It depended on the patient's clinical course and clinicians' discretion. Globally, median time between subsequent follow-up  $^{18}\text{F}$ -FDG PET-CTs was 81 days (IQR 61–112 days).

Overall, follow-up  $^{18}\text{F}$ -FDG PET-CTs were considered to have an added value in 11 episodes (47.8%). Six follow-up  $^{18}\text{F}$ -FDG PET-CT studies (26.1%) showed improvements of previously reported lesions, whereas five (21.7%) showed worsening. Based on these results, follow-up  $^{18}\text{F}$ -FDG PET-CT allowed to de-escalate in 1 case or discontinue antifungal therapy in 5 episodes as lesions disappeared or improved; guided additional tests in five as new or worsening lesions needed to be evaluated; and escalate antifungal therapy (including surgery in one case) in 3 episodes where  $^{18}\text{F}$ -FDG PET-CT results were interpreted as treatment failure. In one of the cases, additional tests did not allow to confirm or rule out IFI in one of the disseminated lesions but did not provide an alternative diagnosis either.

In some cases, worsening was difficult to evaluate. Interestingly, one of the patients, who was a kidney transplant recipient, showed an increased glucose uptake in  $^{18}\text{F}$ -FDG PET-CT images and an increase in serum inflammation markers in the setting of immunosuppression tapering without clinical deterioration. Several possible causes for the worsening  $^{18}\text{F}$ -FDG PET-CT images were considered including the current IFI (invasive aspergillosis caused by *A. fumigatus*), a new concurrent infection or an immune reconstitution inflammatory syndrome (secondary to immunosuppression withdrawal). New tissue samples were obtained (subcutaneous abscess) to confirm the poor evolution of the fungal infection.

In five patients who had both  $^{18}\text{F}$ -FDG PET-CT and CT follow-up imaging, there were discordant findings between the two in 2 cases (40%), who presented lesions in CT that were considered scarring with no activity when compared to  $^{18}\text{F}$ -FDG PET-CT.

Of note, pathological uptake of fungal lesions persisted for a long period, even in those who eventually had a good evolution and antifungal therapy was withdrawn (median time to de-escalation or discontinuation 173 days (IQR 86–412 days)). Several cases of fungemia had septic methastases, including some who presented persistence of uptake in follow-up and needed a prolonged antifungal therapy. Four solid organ recipients with more than one  $^{18}\text{F}$ -FDG PET-CT included in this study, with a median follow-up of 140.5 days (IQR 87.349.3 days), still had a pathological uptake in their last  $^{18}\text{F}$ -FDG PET-CT and continued receiving antifungal therapy.

### 3.7 | Characteristics of fungal lesions in $^{18}\text{F}$ -FDG PET-CT

The FDG avidity of lesions based on SUVmax is summarised, by pathogen, in Table 7.

Median SUVmax was similar in mould IFI and yeast IFI; however, median SUVmax in aspergillosis was considerably higher as compared to mucormycoses. Initial  $^{18}\text{F}$ -FDG PET-CT median SUVmax values were above 2.5 in 90.3% of the cases, versus only in 73.9% of follow-up  $^{18}\text{F}$ -FDG PET-CT. Globally, SUVmax values were lower in follow-up  $^{18}\text{F}$ -FDG PET-CT as compared to diagnostic or staging  $^{18}\text{F}$ -FDG PET-CT, except for one case with a poor evolution.

## 4 | DISCUSSION

Our study results support that  $^{18}\text{F}$ -FDG PET-CT has an added value compared to conventional imaging in the evaluation of IFI from diagnosis to staging and assessment of response to therapy, guiding diagnostic tests and treatment modifications.

Only a small number of studies have evaluated  $^{18}\text{F}$ -FDG PET-CT with a focus in fungi. The present study has the advantage of including not only haematology patients but other populations susceptible to IFI that are increasingly common. Nowadays, neutropenic onco-haematological diseases are not anymore the most prevalent underlying disease in patients with IFI<sup>28</sup>. In contrast with prior studies,

TABLE 6 Characteristics of follow-up  $^{18}\text{F}$ -FDG PET-CT of 14 episodes of IFI.

Sex	Fungus species	PET-CT (total)	Follow-up PET (total)	Time from diagnosis to FIRST follow-up PET-CT (days)	Time from diagnosis to SECOND follow-up PET-CT (days)	Time from diagnosis to THIRD follow-up PET-CT (days)	Time from diagnosis to FOURTH follow-up PET-CT (days)
Female	<i>A. fumigatiformis</i>	3	2	127	161		
Female	<i>A. fumigatus</i>	3	2	77	138		
Male	<i>A. fumigatus</i>	5	4	82	293	342	412
Male	<i>A. fumigatus</i>	2	1	120			
Male	<i>A. lentulus</i>	4	3	75	164	245	
Female	<i>A. versicolor</i>	2	1	102			
Male	<i>A. niger</i>	1	1	51			
Male <sup>a</sup>	<i>C. albicans</i>	2	1	116			
Male <sup>a</sup>	<i>C. parapsilosis</i>	4	3	157	355	545	
Male	<i>C. parapsilosis</i>	1	1	116			
Male	<i>Fusarium proliferatum</i>	2	1	24			
Male	<i>Scedosporium apiospermum</i>	2	1	76			
Male	<i>T. inkin</i>	1	1	177			
Male	<i>T. inkin</i>	1	1	239			
MEDIAN				109	164	342	412

<sup>a</sup>Same patient, different IFI episodes.

**TABLE 7** Median SUV max of  $^{18}\text{F}$ -FDG PET-CT lesions according to type of fungus and PET-CT indication.

Fungus	SUV max (median)	SUV max (median)	% SUV above 2.5
Diagnostic/staging PET-CT (31)	5.5 (IQR 4.1–8.0)	5.6	90.32
YEASTS (13)	5.6 (IQR 4.1–6.6)	5.6	92.31
<i>Candida</i> spp (11)	5.3 (IQR 3.6–6.7)	5.3	90.91
<i>Trichosporon inkin</i> (1)	6.3	6.3	100
<i>Rhodotorula mucilaginosa</i> (1)	5.6	5.6	100
MOULDS (18)	5.7 (IQR 4.0–9.3)	5.7	88.89
<i>Aspergillus</i> spp (13)	7.9 (IQR 4.9–11.2)	7.9	92.3
<i>Rhizopus arrhizus</i> (2)	2.45	2.45	50
<i>Scedosporium apiospermium</i> (1)	6.2	6.2	100
<i>Fusarium proliferatum</i> (1)	4.3	4.3	100
Non specified (1)	4.7	4.7	100
<i>Pneumocystis jirovecii</i> (1)	5.9	5.9	100
Follow-up PET-CT (23)	4.9 (IQR 2.5–6.5)	4.9	73.91
YEASTS (7)	5.6 (IQR 2.5–5.9)	5.6	71.43
<i>Candida</i> spp (5)	5.6 (IQR 2.8–6.2)	5.6	80
<i>Trichosporon inkin</i> (2)	2.8	2.8	50
MOULDS (16)	4.55 (IQR 2.1–9.0)	4.55	75
<i>Aspergillus</i> spp (14)	4 (IQR 1.8–7.5)	4	71.42
<i>Scedosporium apiospermium</i> (1)	5.4	5.4	100
<i>Fusarium proliferatum</i> (1)	10.3	10.3	100

only 17.1% of our patients were haematological, including 11.4% that were neutropenic. However, more than 74% were immunocompromised. Interestingly, the highest proportion of patients were solid organ transplant recipients. Eleven percent of the patients had suffered a recent episode of COVID that predisposed them to IFI<sup>29</sup>. Therefore, we consider that our data are generalizable to the wider population currently at risk for IFI.

Several prior studies have shown the usefulness of  $^{18}\text{F}$ -FDG PET-CT in the study of FUO and also specifically in febrile neutropenia,<sup>10,11</sup> where it can help adjust empirical antimicrobial therapy. Only a small proportion of these patients were eventually diagnosed with IFI, and negative PET-CT results allowed them to discontinue empirical antifungals. On the other hand, the usefulness of  $^{18}\text{F}$ -FDG PET-CT for the early diagnosis of invasive mould disease in high-risk patients has already been highlighted,<sup>12</sup> in particular in non-neutropenic patients, whose diagnosis might be especially difficult due to a lower fungal burden and amount of necrosis. In the present study, three such cases of unsuspected IFI were elicited thanks to the use of  $^{18}\text{F}$ -FDG PET-CT. Of interest, these IFI were clinically silent and involved extrapulmonary sites in one case. One of the cases was a *Pneumocystis* pneumonia (PJP) that presented as FUO.  $^{18}\text{F}$ -FDG PET-CT has already been reported to detect infiltrates caused by PJP earlier than the standard chest radiograph.<sup>13</sup>

In addition, in our study,  $^{18}\text{F}$ -FDG PET-CT helped diagnose IFI in cases with lesions considered atypical when evaluated by other means, and to confirm invasive infection as opposed to simple

colonisation by showing activity in those lesions that guided the final diagnostic tests. In this sense, our data support the work by Kim JY et al.,<sup>14</sup> who compared patients with invasive and non-invasive aspergillosis and found that  $^{18}\text{F}$ -FDG PET-CT could help assess the invasiveness of pulmonary lesions in pulmonary aspergillosis based on the predominant pattern (hypermetabolic nodule versus isometabolic halo) and the median SUVpeak.

The concept of “staging” IFI, along the same line as we do with tumours, is beginning to take root.<sup>15</sup> IFI presentation can be very heterogeneous, and multiple organ involvement is not uncommon. Depending on the host immune response, its dissemination can remain clinically silent.<sup>12</sup> Notwithstanding, detecting these occult lesions is important to completely eradicate the IFI. It may bring to light the need for an antifungal with a good penetration in a particular site, the intensification of antifungal therapy (for instance, in cases of endocarditis) or the use other procedures for source control such as surgical debridement in cases refractory to antifungal therapy.  $^{18}\text{F}$ -FDG PET-CT has been shown to be able to detect occult IFI sites, and in addition, as a whole-body imaging procedure, it has the advantage of enabling the detection of IFI involvement at different sites of the body in a single imaging session.

Several studies have evaluated  $^{18}\text{F}$ -FDG PET-CT in invasive candidiasis, finding that  $^{18}\text{F}$ -FDG PET-CT is more sensitive than CT or ultrasound for detection of dissemination of *Candida*, particularly of hepatosplenic involvement,<sup>13,16,17</sup> but few have investigated its role in fungal endocarditis. In the case of fungemia, staging should include the evaluation for endocarditis. The usefulness of  $^{18}\text{F}$ -FDG PET-CT for

the diagnosis of infectious endocarditis has been recognised in the guidelines,<sup>18</sup> especially in prosthetic endocarditis (IB). Current guidelines recommend its use in symptomatic patients to detect peripheral lesions (IB) and to consider it even in asymptomatic patients (IIbB). Series published so far include only a small number of fungal endocarditis.<sup>19</sup> In a cohort of *Candida* endocarditis where <sup>18</sup>F-FDG PET-CT was available in 7 cases (including 2 native valve endocarditis), the authors report a sensitivity of 57.1% for <sup>18</sup>F-FDG PET-CT compared to trans-oesophageal echocardiography; however, in that series, the necessary suppression of myocardial uptake was not routinely performed.<sup>20</sup> The authors underline that the strength of <sup>18</sup>F-FDG PET-CT in patients with *Candida* endocarditis might be in diagnosing other foci or septic emboli, or to confirm endocarditis in uncertain cases. In their series evaluating different types of IFI, Leroy-Freschini et al.<sup>16</sup> found a limited impact of <sup>18</sup>F-FDG PET-CT in patients with fungemia and normal conventional imaging investigations, but patients with *Candida* endocarditis were not included. On the contrary, in the present series, where <sup>18</sup>F-FDG PET-CT was compared to echocardiography (100%) and CT (69.2%) in 92.9% of episodes of fungemia, it showed an added value at least in 6/13 (46.2%) of them, not only to confirm or rule out endocarditis but to detect other sites of fungal involvement. It is relevant to underline the value of a negative <sup>18</sup>F-FDG PET-CT in this setting due to its high negative predictive value for IFI that allows early discontinuation of antifungals,<sup>13</sup> although in native valve endocarditis, it is considered that the diagnosis of endocarditis cannot be excluded in the absence of abnormal <sup>18</sup>F-FDG uptake.<sup>18</sup> Similar to Sharma et al.,<sup>21</sup> who found <sup>18</sup>F-FDG PET-CT is particularly useful in cases where other tests were equivocal or with diagnosis of "possible endocarditis", in our series, <sup>18</sup>F-FDG PET-CT was especially helpful in cases with dubious or negative echocardiography.

Regarding mould infections, other authors have identified that <sup>18</sup>F-FDG PET-CT detected lesions even when CT scans were normal<sup>16</sup> or outside the regions imaged by the anatomy-based studies in almost 50% of the studies.<sup>3</sup> In our series, the most common extrapulmonary abnormalities detected solely on staging <sup>18</sup>F-FDG PET-CT of mould infection were soft tissue (muscle) and sinonasal involvement. These findings conditioned therapeutic approach. Moreover, two of those cases were not previously known to have disseminated disease. Thanks to <sup>18</sup>F-FDG PET-CT, an adequate therapy and follow-up could be established, making sure that all IFI involvement was addressed and solved. Interestingly, in a case of aspergillosis that presented with initial muscle involvement, silent pulmonary lesions were detected thanks to <sup>18</sup>F-FDG PET-CT. Overall, <sup>18</sup>F-FDG PET-CT disclosed disseminated IFI in more than one-third of the cases. The management of disseminated fungal disease is challenging,<sup>22</sup> and it is important not to miss out on occult lesions in order to adapt therapy and follow-up in consequence.

<sup>18</sup>F-FDG PET-CT detected occult lesions in 3 additional cases that could not be confirmed as IFI involvement. Even considering that no other aetiology of these lesions was found, we decided to classify them as <sup>18</sup>F-FDG PET-CT false positives. In the evaluation of pathological glucose uptake, it is necessary to consider a differential diagnosis, especially in Oncology patients. At the beginning of

the use of <sup>18</sup>F-FDG PET-CT, a SUVmax threshold of 2.5 was used to differentiate malignancy from benign lesions; however, the present study, among others,<sup>4</sup> highlights that IFI lesions frequently present a SUVmax of  $\geq 2.5$  (Table 7). Tissue diagnosis should be pursued in doubtful cases.

Not all fungal species display such high SUVmax. In our series, Mucorales had substantially lower SUV max, but there were too few cases to draw a firm conclusion. Further studies should evaluate if different fungal species characteristically associate different FDG-uptake patterns in <sup>18</sup>F-FDG PET-CT.

The optimal antifungal duration is a controversial issue, especially in mould infection in immunocompromised hosts<sup>15</sup> and in fungal endocarditis. Recommendations on antifungal treatment length remain unclear,<sup>23</sup> and antifungal duration is highly variable.<sup>24</sup> The assessment of the response to antifungal therapy is based on clinical signs, fungal biomarkers and imaging.<sup>25</sup> But anatomic changes may persist even when IFIs are controlled or cured. Recent studies suggest metabolic changes in follow-up <sup>18</sup>F-FDG PET-CT, which often precede anatomic changes, may be useful to monitor the response to antifungal therapy, particularly when the patient has clinically responded, has had adequate duration of therapy, and CT shows persistent lesions.<sup>4</sup> This might be especially helpful in patients who continue to be immunocompromised, such as solid organ transplant recipients, or who need to resume chemotherapy or undergo a stem cell transplant after a recent IFI. In addition, the whole-body imaging provided by <sup>18</sup>F-FDG PET-CT allows to assess overall response.<sup>17</sup>

Unfortunately, and similar to other series,<sup>17</sup> in the present series, in many cases there was not a concurrent CT available to compare with follow-up <sup>18</sup>F-FDG PET-CT. Still, <sup>18</sup>F-FDG PET-CT was useful to make decisions regarding therapy. It has been emphasised that negative <sup>18</sup>F-FDG PET-CT results can help stopping antifungal therapy.<sup>4,16</sup> Importantly, in our series, it allowed us to de-escalate or discontinue antifungals in several cases but also suggested inadequate outcome in others, in some of them before it was clinically obvious.

In our study, in contrast with other that included mainly Haematology patients,<sup>4</sup> we found a prolonged glucose uptake in some patients with continued immunosuppression (mainly solid organ transplant recipients), but also in fungal endocarditis. We cannot exclude, as a retrospective study, that follow-up <sup>18</sup>F-FDG PET-CT was performed more often in patients with worse evolution. In some cases, this was an indication of non-resolution. In other cases, it may reflect that the natural history of the IFI is different depending on the patient's immunity. We believe that in the context of continuing immunosuppression, <sup>18</sup>F-FDG PET-CT can be particularly helpful. When it comes to the duration of antifungal therapy, it is not possible to generalise, and it is of paramount importance to rely on functional tests to confirm resolution of the infection.

Other authors have suggested a persistent <sup>18</sup>F-FDG PET-CT activity related to inflammation that surrounds non-viable fungal elements, as in chronic disseminated candidiasis.<sup>16,17,26</sup> As follow-up <sup>18</sup>F-FDG PET-CTs were not performed systematically at specific time points during the course of the IFI, it is difficult to assess the meaning of persistent uptake. In fact, the natural history of IFI from

an  $^{18}\text{F}$ -FDG PET-CT perspective is unknown, and obviously will depend on the interplay between fungus and host immunity. In one of our cases, deterioration in the setting of immunosuppression withdrawal made necessary to perform invasive sampling to distinguish between IFI and systemic inflammatory response syndrome.

The present study has several limitations. It is a single-centre study, and results might not be generalizable to other hospitals with different characteristics. Two cases of possible IFI were included; we considered that in this setting, the use of  $^{18}\text{F}$ -FDG PET-CT could add to the certainty of the diagnosis or to ruling it out. Due to its retrospective nature, we cannot exclude selection bias, leading to the inclusion of patients who underwent  $^{18}\text{F}$ -FDG PET-CT because of the negativity of the usual imaging tests. In some cases, the PET-CT indication was not to study IFI but oncology. In addition, time from IFI diagnosis to  $^{18}\text{F}$ -FDG PET-CT was not standardised, and they were performed at very different time intervals. Only one-fourth of the episodes had follow-up  $^{18}\text{F}$ -FDG PET-CTs.

When evaluating the imaging in retrospective it is complicated to take into consideration factors such as the presence of coinfection or systemic inflammatory syndrome. The contribution of the  $^{18}\text{F}$ -FDG PET-CT to the decision making is difficult to assess in this scenario, as decisions are based on clinical and microbiological parameters and not only in  $^{18}\text{F}$ -FDG PET-CT results.

Including  $^{18}\text{F}$ -FDG PET-CT in IFI management seems to be useful; nevertheless, many unresolved questions remain. First, the natural history of the  $^{18}\text{F}$ -FDG PET-CT imaging of IFI is unknown, and the optimal timing to perform  $^{18}\text{F}$ -FDG PET-CT studies after the beginning of medical treatment remains undetermined. The uptake threshold to safely discontinue antifungal therapy needs to be defined, as glucose uptake by IFI lesions can be prolonged even in cases with a fair clinical evolution. The differential diagnosis between underlying oncologic disease, immune reconstitution inflammatory syndrome, or concurrent bacterial or viral infections has to be perfected. Differences in  $^{18}\text{F}$ -FDG PET-CT imaging in different kinds of host and suffering IFI caused by different pathogens need to be studied.

Prospective, controlled studies are much needed to clarify these issues. At least two prospective studies are ongoing. A comparative French study in haematology patients with invasive aspergillosis intends to determine whether systematic 6-week  $^{18}\text{F}$ -FDG PET-CT identifies resolution of aspergillosis earlier than CT (OPTIFIL study, <https://ichgcp.net/es/clinical-trials-registry/NCT02955966>). In Spain, our group is leading a multicentre comparative study of systematic  $^{18}\text{F}$ -FDG PET-CT for the management of IFIs versus conventional imaging (PETIFI PROJECT,<sup>27</sup> Clinical [trials.gov](https://clinicaltrials.gov) identifier NCT05688592). Hopefully, these works will shed light over the remaining uncertainties.

## AUTHOR CONTRIBUTIONS

**Isabel Gutiérrez Martín:** Conceptualization; investigation; writing – original draft; methodology; writing – review and editing; formal analysis; data curation; supervision; resources. **S. García-Prieto:** Data curation. **K. Velásquez:** Methodology; data curation. **E.V. Gutiérrez-Abreu:** Data curation; writing – review and editing. **Itziar Diego-Yagüe:**

Data curation. **Jorge Calderon Parra:** Data curation; writing – review and editing. **Andrea Gutiérrez-Villanueva:** Data curation; supervision; writing – review and editing. **Antonio Ramos-Martínez:** Writing – review and editing; data curation. **Elena Muñoz Rubio:** Data curation; writing – review and editing. **Alejandro Callejas Díaz:** Writing – review and editing; data curation. **Sara De la Fuente Moral:** Writing – review and editing; data curation. **Alberto Díaz de Santiago:** Writing – review and editing; data curation. **Isabel Sánchez-Romero:** Writing – review and editing; data curation. **Rodríguez Alfonso B.:** Investigation; conceptualization; formal analysis; supervision; writing – review and editing. **Ana Fernández-Cruz:** Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; formal analysis; project administration; data curation; supervision; resources.

## ACKNOWLEDGMENTS

The authors wish to acknowledge the Internal Medicine Department, the Nuclear Medicine Department and the Infectious Diseases Unit.

## FUNDING INFORMATION

This research received no external funding. Andrea Gutiérrez Villanueva is contracted by the Fundación para la Investigación Biomédica del Hospital Universitario Puerta de Hierro-Majadahonda and the Fondo de Investigación Sanitaria (FIS) CM22/00248.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

After publication, the data will be made available to others upon reasonable requests to the corresponding author. A proposal with a detailed description of study objectives and statistical analysis plan will be needed for evaluation of the reasonability of requests. It might also be required during the process of evaluation. Deidentified participant data will be provided after approval from the principal researchers of Hospital Universitario Puerta de Hierro (Majadahonda).

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**How to cite this article:** Gutiérrez-Martín I, García-Prieto S, Velásquez K, et al. Usefulness of <sup>18</sup>F-FDG PET-CT for the management of invasive fungal infections: A retrospective cohort from a tertiary university hospital. *Mycoses*. 2024;67:e13701. doi:[10.1111/myc.13701](https://doi.org/10.1111/myc.13701)