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ORIGINAL ARTICLE

Persistent Candidemia in adults: underlying causes and clinical significance in the antifungal stewardship era

Caroline Agnelli[1,2,3] · Maricela Valerio[1,2] · Emilio Bouza[1,2,4,5] · Antonio Vena[1,2,5] · Jesús Guinea[1,2,4,5] · María del Carmen Martínez-Jiménez[1,2] · Laura Judith Marcos-Zambrano[1,2,5,6] · Pilar Escribano[1,2,5] · Patricia Muñoz[1,2,4,5] · on behalf of the COMIC Study Group (Collaborative Group on Mycosis)

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Abstract

To investigate the causes and the clinical significance of persistent candidemia (PC) in adults diagnosed in a tertiary hospital with an active antifungal stewardship program. Retrospective cohort including all adults with candidemia from 2010 to 2018. PC was defined as any positive follow-up blood culture (BC) obtained ≥ 5 days from the first BCs yielding the same *Candida* species. PC was detected in 35/255 (13.7%) patients. There were no differences regarding antifungal adequacy in PC vs. non-PC (94.3% vs. 82.3%, $p = 0.084$) and primary source control (63.3% vs. 76.4%, $p = 0.172$) at the time of the follow-up BCs. The average time until source control (2 [0–37] vs. 2 days [0–44], $p = 0.311$) or adequate antifungal treatment (2 [0–26] vs. 2 days [− 2–10], $p = 0.748$) was similar. Patients with PC had more non-ocular complications (31.4% vs. 10.5%, $p = 0.002$). No impact on 30-day mortality was observed (31.4% vs. 22.3%, $p = 0.238$). The only independent factor associated with PC was to have a previously undetected site of infection [OR 4.28, 95%CI (1.77–10.34), $p = 0.001$]. Persistent candidemia was not associated with inadequate or delayed therapeutic management, nor higher 30-day mortality rates. Timely screening and control of unexpected infection sources are encouraged to shorten hospitalization and improve patient care.

Keywords Persistent candidemia · Antifungal stewardship · Mortality · Candidemia

Introduction

Persistent candidemia is frequently referred to as a complication of candidemia related to treatment failure and poor prognosis [1–4]. Literature on the topic is scarce and difficult to interpret due to the heterogeneity of definitions proposed for persistence [5]. That probably explains incidence rates going all the way from 8 to 93% of the episodes of candidemia [1–5].

Purportedly underlying factors for persistent candidemia include baseline characteristics of the host, microbiological aspects such as biofilm production, ineffective therapeutic management, and delayed or unaccomplished source control [5, 6].

Although persistent candidemia has been associated with higher mortality rates, much of the available data is either derived from studies not specifically designed to address this issue, or just in neonatal population [2, 3, 5, 6]. Moreover, the clinical significance and impact of persistent candidemia in adults managed in settings with an optimized antifungal stewardship (AFS) program are unknown.

We sought to assess the underlying causes and the clinical significance of persistent candidemia in a large teaching institution with an ongoing AFS program.

✉ Caroline Agnelli
agnelli.carol@gmail.com

1 Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Calle Doctor Esquerdo 46, 28007 Madrid, Spain

2 Gregorio Marañón Sanitary Research Institute, Madrid, Spain

3 Department of Medicine, Division of Infectious Diseases, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil

4 CIBER de Enfermedades Respiratorias (CIBERES CB06/06/0058), Madrid, Spain

5 Department of Medicine, Faculty of Medicine, Universidad Complutense de Madrid, Madrid, Spain

6 Computational Biology Group, Precision Nutrition and Cancer Research Program, IMDEA Food Institute, Madrid, Spain

Methods

Study design, population, and setting

Retrospective study including all adult patients ≥ 18 years of age with one or more positive peripheral blood culture yielding a *Candida* species, who were admitted from May 2010 to February 2018 to a 1550-bed tertiary hospital in Madrid, Spain.

Our multidisciplinary antifungal stewardship program was progressively implemented starting in 2010. Among other measures, a bedside intervention is provided with non-coercive diagnostic and therapeutic advice by an infectious diseases physician using a bundle of care during the episode of candidemia [7]. A detailed description of the program and its impact on healthcare has been reported elsewhere [8, 9].

For this study, a pre-establish protocol was fulfilled for each patient according to laboratory and medical history until hospital discharge or death. Data included demographics, comorbidities, Charlson Comorbidity Index, Department of Admission, and risk factors for candidemia. The clinical presentation was also registered, along with Pitt Scores, primary source of infection, *Candida* species, antifungal treatment, source control, metastatic complications, and outcomes. Information on survival at 30 days from the diagnosis was confirmed through medical records even for patients discharged before this period. No patients had to be excluded due to missing data.

Persistent candidemia was defined as any positive blood culture taken after ≥ 5 days from the first ones, yielding the same species of *Candida* in patients receiving antifungal treatment. All the remaining patients with follow-up blood cultures were referred to as those with "non-persistent" candidemia.

Patients with persistent vs. non persistent candidemia were compared to assess the underlying causes and clinical significance of PC with respect to complications (ocular candidiasis, septic thrombophlebitis, endocarditis, or dissemination to other organs) and 30-day mortality.

Other definitions

The diagnosis of candidemia was set at "day 0", which was the date the first positive blood cultures were drawn. Follow-up blood cultures (BCs) were referred to as those performed at least 24 hours after the first positive set of BCs, any time during the course of the candidemia infection. There was no pre-specified routine for follow-up BCs.

Primary candidemia was defined when there was no apparent focus for the infection and no other origin criteria was met [10]. A central venous catheter (CVC)-related candidemia was defined according to current guidelines [11]. Other origins required a culture from the site of infection source with the same *Candida* species found in peripheral blood cultures [10].

Adequate antifungal therapy was defined according to current guidelines [12]. To have received a treatment containing antibiofilm activity was defined when either liposomal amphotericin B or echinocandins were prescribed for at least three consecutive days.

Source control was individualized, including catheter withdrawal, invasive procedures to resolve urinary tract obstruction, intra-abdominal abscess drainage, among others. Source control was considered "early" when performed within 48 hours from the initial antifungal treatment.

Microbiology and biofilm detection

Candida species were identified by classical phenotypical methods combined with matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS). Antifungal susceptibility testing was performed according to the EUCAST recommendations [13].

Candida isolates were incubated for 24 hours at 35 °C on Sabourad dextrose agar plates before the study of biofilm production according to its metabolic activity using the tetrazolium-salt (XTT) reduction assay, as previously described [14, 15]. Biofilm production was studied only in strains isolated in the first positive blood cultures. Strains with a moderate-high biofilm forming profile were those with an optic density (OD_{490nm}) ≥ 0.097 [14].

Statistical analysis

Data was summarized using descriptive statistics. Categorical variables were reported as counts (%) and compared using either Fisher's exact test or chi-square test, as appropriate. Quantitative variables with a normal distribution were reported as mean ± standard deviation (SD) and compared using the Student's *t* test. Those with a non-normal distribution were described as median and interquartile range (IQR) and compared using the Mann-Whitney *U* test. Statistical significance was set at a two-tailed p value < 0.05. Variables with a $p < 0.1$ in the univariate model were included in the multivariate logistic regression. Analysis was performed using SPSS V24 software package (SPSS Inc., Chicago, IL, USA).

Results

Study population and incidence of persistent candidemia

During the period of study, 322 adults with a first episode of candidemia were diagnosed in our hospital. Overall, 255/322 (79.2%) had at least one set of follow-up blood cultures. The

main single reason for not having follow-up BCs was early death, which occurred in 39/67 cases (58.2%), with a median of time until death of 3 days from the initial blood cultures. The definition of persistent candidemia was fulfilled by 35/255 (13.7%) patients.

Epidemiology

Baseline characteristics of our study population are shown in Table 1. When comparing patients with and without PC, there were no significant differences regarding demographics and comorbidities, although there was a trend towards a higher proportion of solid malignancy patients among those with PC (62.9% vs. 47.7%, $p = 0.095$).

Microbiology and biofilm detection

We did not find any differences between PC and non-PC patients regarding *Candida* species, antifungal resistance, or biofilm production. Although there was a higher percentage of biofilm production among patients with PC, such difference did not reach statistical significance (Table 2).

Clinical manifestation and infection source

The distribution of the primary source of candidemia and patients' clinical manifestations were not significantly different between groups (Table 2). A CVC-related infection was the most frequent source of candidemia in both groups (71.4% vs. 55.0%, $p = 0.097$), and similar rates of Pitt Score values [0 (0–10) vs. 1 (0–9), $p = 0.312$] and septic shock (14.3% vs. 12.7%, $p = 1$) were observed.

Therapeutic management

Infection management is detailed in Table 3. Overall, fluconazole was the most frequent initial antifungal agent, prescribed in 61.2% of cases. Although an echinocandin was the first drug in 33.3%, they were prescribed in up to 49.4% of cases throughout the course of the candidemia episode. When comparing patients with PC vs. non-PC at the moment the follow-up blood cultures were drawn, there were no differences regarding the rates of antifungal adequacy (94.3% vs. 82.3%, $p = 0.084$), and primary source control (63.3% vs. 76.4%, $p = 0.172$). The median of days until initiation of adequate antifungal therapy since diagnosis [2 (− 2–10) vs. 2 (0–26), $p = 0.748$] or until source control since initial antifungal treatment [2 (0–44) vs. 2 (0–37), $p = 0.311$] was similar.

Clinical outcomes

The clinical outcomes and the distribution of complications are shown in Table 3. Although rates of ocular candidiasis were comparable (11.4% vs. 11.8%, $p = 1$), patients with PC had non-ocular sites of infection more often (31.4% vs. 10.5%, $p = 0.002$). Despite requiring a longer hospital length of stay among survivors [41.5 (8–112) vs. 28 days (5–254), $p = 0.021$] and extended duration of antifungal treatment [24 (4–66) vs. 19 (0–63) days, $p = 0.026$], no statistically significant impact on mortality at 30 days (31.4% vs. 22.3%, $p = 0.238$), or after 30 days during hospitalization (42.9% vs. 30.9%, $p = 0.177$) was observed.

Risk factors for persistent candidemia

The only independent factor associated with PC according to the multivariate regression model was to have a previously unsuspected site of infection [OR 4.28; 95%CI (1.77–10.34), $p = 0.001$], as shown in Table 4.

Discussion

We studied the underlying causes and the clinical significance of persistent candidemia in a large series of unselected adult patients. Our findings support that in a setting with a structured antifungal stewardship program, PC was not associated with inadequate or delayed therapeutic management, nor higher 30-day mortality rates. In addition, our definition of PC proved to be clinically useful, indicating the need for prompt complementary screening of unexpected sites of infection that usually require specific management.

Persistent candidemia has been associated with aspects related to the host, including onco-hematological diseases, neutropenia, and other markers of the net state of immunosuppression [5, 6, 16]. Distinct mechanisms of immune dysfunction seem to contribute to a delay in microbiological clearance from blood, hindering infection control [17]. However, even though there was a trend towards a higher proportion of solid malignant tumors among patients with PC (62.9% vs. 47.7%, $p = 0.095$) in our series, we did not find significant demographic nor epidemiologic differences between groups. Recent developments in the management of invasive fungal infections in immunocompromised hosts such as better control of baseline diseases and more invasive diagnostic and therapeutic approaches [18] might have contributed to prevent infection persistence.

Regarding the source of infection, Kang et al. reported the sole presence of a central venous catheter (CVC) during the episode of candidemia as an independent risk factor of PC [6]. According to other authors, such finding could be related not only to a higher systemic fungal burden expected in intravascular sources but also to biofilm formation [5, 19]. Interestingly, the group of non-PC in such study had an intra-abdominal site of infection as the leading source of infection, most likely with a lower circulating fungal burden comparing

Table 1 Baseline characteristics of adult patients with persistent vs. non-persistent candidemia diagnosed in a tertiary hospital from 2010 to 2018

Variables	Total ($n = 255$)	Non-persistent ($n = 220$)	Persistent ($n = 35$)	p value
Demographics				
Age (years), median (IQR)	68 (23–91)	68 (23–90)	71 (39–91)	0.533
Gender (male), *n* (%)	161 (63.1)	139 (63.2)	22 (62.9)	1
Department of admission, *n* (%)				
Medical	84 (32.9)	75 (34.1)	9 (25.7)	0.344
Surgical	83 (32.5)	68 (30.9)	15 (42.9)	0.177
Onco-hematology	30 (11.8)	27 (12.3)	3 (8.6)	0.594
Intensive care units	58 (22.7)	50 (22.7)	8 (22.9)	1
Comorbidities, *n* (%)				
Cardiovascular disease	80 (31.4)	66 (30.0)	14 (40.0)	0.244
Lung disease	53 (20.8)	48 (21.8)	5 (14.3)	0.376
Chronic kidney failure	62 (24.3)	54 (24.5)	8 (22.9)	0.840
Diabetes mellitus	68 (26.7)	62 (28.2)	6 (17.1)	0.218
Neurological disorder	60 (23.5)	52 (23.6)	8 (22.9)	1
Chronic liver disease	30 (11.8)	28 (12.7)	2 (5.7)	0.277
Gastrointestinal disease	93 (36.5)	79 (35.9)	14 (40.0)	0.706
Solid cancer	127 (49.8)	105 (47.7)	22 (62.9)	0.095
Hematological malignancy	11 (4.3)	10 (4.5)	1 (2.9)	0.719
Bone marrow transplant	7 (2.7)	6 (2.7)	1 (2.9)	1
Solid organ transplant	9 (3.5)	9 (4.1)	0	0.370
HIV	6 (2.4)	5 (2.3)	1 (2.9)	1
Charlson Comorbidity Index, median (IQR)	6 (0–14)	6 (0–14)	7 (1–10)	0.771
Risk factors of candidemia, *n* (%)				
Chemotherapy	49 (19.2)	42 (19.1)	7 (20.0)	1
Neutropenia (< 500 cells/μL)	18 (7.1)	14 (6.4)	4 (11.4)	0.285
Surgery	129 (50.6)	108 (49.1)	21 (60.0)	0.276
Abdominal surgery	99 (38.8)	83 (37.7)	16 (45.7)	0.455
Total parenteral nutrition	151 (59.2)	126 (57.3)	25 (71.4)	0.139
Central venous catheter	188 (73.7)	160 (72.7)	28 (80.0)	0.415
Antibiotic use	232 (91)	201 (91.4)	31 (88.6)	0.750
Antifungal use	64 (25.1)	56 (25.5)	8 (22.9)	0.836
Corticosteroids	78 (30.6)	65 (29.5)	13 (37.1)	0.430
Other immunosuppressives	21 (8.2)	19 (8.6)	2 (5.7)	0.748

HIV human immunodeficiency virus

with cases of CVC-related candidemia [19]. Diversely, a CVC was the leading primary source of infection in both PC and non-PC groups in our study (71.4% vs. 55.0%, $p = 0.097$), which might explain why no significant correlation was found. Yet, our patients with PC presented a trend towards less cases of intra-abdominal source (5.7% vs. 18.2%, $p = 0.084$), suggesting that this spectrum of disease may be easier to clear from blood when compared to cases of intravascular origin.

A few authors have proposed a positive correlation between *Candida* biofilm production and persistent candidemia [20, 21]. In parallel, echinocandins have been reported as a better treatment choice in cases of PC because of their fungicide anti-biofilm activity [22]. In our study, although there was a higher percentage of biofilm production in cases of persistent candidemia, its role as an independent risk factor for PC was not confirmed ($p = 0.107$). Importantly, techniques and breakpoints to quantify biofilm production vary widely among studies [23]. Also, such differences could be due to the limited sample size of our series, or even to the similar proportion of treatment with anti-biofilm activity in both groups ($p = 0.472$).

Modifiable underlying causes of persistent candidemia have also been described, including inadequate antifungal prescription and delayed or unaccomplished source control [5, 6, 16, 21, 22]. Our center endorses a multi-faceted AFS program that could potentially reduce the burden of such underlying causes [7–9, 24]. In fact, at the moment the follow-up blood cultures were drawn, we found no differences concerning

Table 2 Clinical and microbiological characteristics of 255 adult patients with persistent vs. non-persistent candidemia diagnosed in a tertiary hospital from 2010 to 2018

Variables	Total ($n = 255$)	Non-persistent ($n = 220$)	Persistent ($n = 35$)	p value
Clinical presentation				
Septic shock, *n* (%)	33 (12.9)	28 (12.7)	5 (14.3)	1
Pitt Score, median (IQR)	0 (0–10)	0 (0–9)	1 (0–10)	0.312
Infection source, *n* (%)				
Primary	30 (11.8)	26 (11.8)	4 (11.4)	1
CVC-related	146 (57.3)	121 (55.0)	25 (71.4)	0.097
Intra-abdominal	42 (16.5)	40 (18.2)	2 (5.7)	0.084
Urinary tract	22 (8.6)	21 (9.5)	1 (2.9)	0.224
Others	15 (5.9)	12 (5.5)	3 (8.6)	0.701
Candida species, *n* (%)				
C. albicans	121 (48)	101 (45.9)	20 (57.1)	0.274
C. parapsilosis	61 (23.9)	53 (24.1)	8 (22.9)	1
C. tropicalis	20 (7.8)	18 (8.2)	2 (5.7)	0.750
C. glabrata	39 (15.3)	35 (15.9)	4 (11.4)	0.619
C. krusei	8 (3.1)	7 (3.2)	1 (2.9)	1
C. guilliermondi	2 (0.8)	2 (0.9)	0	1
Other species	9 (3.5)	8 (3.6)	1 (2.9)	1
> 1 *Candida* species	5 (2)	4 (1.8)	1 (2.9)	1
Biofilm production, *n* (%)				
Moderate–high metabolic activity[a]	158/207 (76.3)	131/177 (74.0)	27/30 (90.0)	0.064

CVC central venous catheter

[a] Moderate–high biofilm producing strains were assessed through metabolic activity and had an optic density (OD490nm) ≥ 0.097

antifungal adequacy (94.3% vs. 82.3%, $p = 0.084$) or control of the presumed source of infection (63.3% vs. 76.4%, $p = 0.172$). Noteworthy, many patients with PC had more time since initial blood cultures were obtained. This allowed for treatment adjustment to definitive microbiological results, justifying the higher percentage of antifungal adequacy.

The impact of early source control on the duration of candidemia is controversial [5, 22, 25, 26]. Nucci et al. evaluated the outcomes of early CVC removal in patients with candidemia and did not observe any impact on time to blood culture sterilization [25], suggesting that other aspects could play a more important role in patients with anti-biofilm antifungals. In our series, source control within 48 h of initial treatment was not significantly more frequent among patients without PC (60.7% vs. 53.8%, $p = 0.525$). As much as there is room for improvement, severely ill patients are often no candidates for prompt catheter withdrawal or other invasive procedures [5, 6]. This could partially clarify why rates of early source control were not higher, along with the fact that our AFS program is based on non-coercive measures. Contrasting with other authors [6], time to primary source control was also not longer for patients with PC ($p = 0.255$), probably due to AFS interventions.

In our experience, the only factor independently associated with persistent candidemia was to have an unsuspected additional site of infection, which included thrombophlebitis, endocarditis, and infection in other organs. Similarly, PC has been previously linked to occult metastatic infections, including deep-tissue abscesses, new endovascular sources, or secondary infection of prosthetic devices [5, 6, 16, 21]. As opposed to ocular candidiasis in patients with non-PC, septic thrombophlebitis was the leading complication for patients with PC. Such condition has been classically related to persistent bloodstream infections, although it is still often underdiagnosed [27]. In this context, advances on imaging such as the whole-body 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) could be a valid tool for challenging cases with occult sites of infection [28, 29].

Our findings suggest that even in cases of optimized therapeutic management, follow-up blood cultures remain useful. Considering that there is no consensus on the best timing for the screening of complications [12, 30, 31], our definition of persistent candidemia may function as a marker of unexpected additional infection sources that require either a longer treatment or a specific management. Thus, given that adequate antifungal treatment and control of the presumed source of infection have been guaranteed, the next step in cases of patients with a positive follow-up blood culture ≥ 5 days from diagnosis should be to search for occult non-ocular complications. Furthermore, in agreement with other authors [6], patients with PC required a longer hospital stay ($p = 0.021$), probably owing to the additional

Table 3 Therapeutic management and clinical outcomes of 255 adults with persistent vs. non-persistent candidemia diagnosed in a center with a non-coercive antifungal stewardship program

Variables	Non-persistent ($n = 220$)	Persistent ($n = 35$)	p value
Antifungal therapy, *n* (%)			
Empirical	33 (15.0)	6 (17.1)	0.800
Adequate empirical	29/33 (87.9)	5/6 (83.3)	1
Echinocandin as initial AF	74 (33.8)	11 (31.4)	0.849
Adequate AF at follow-up BC	181 (82.3)	33 (94.3)	0.084
Adequate targeted AF	219 (99.5)	34 (97.1)	0.256
Anti-biofilm AF	117 (53.2)	21 (60.0)	0.472
Time to adequate AF, median in days (IQR)	2 (− 2–10)	2 (0–26)	0.748
Duration of AF treatment, median in days (IQR)	19 (0–63)	24 (4–66)	0.026
Days of adequate AF at follow-up BC, median (IQR)	3 (− 2–25)	4 (1–16)	0.003
Infection source control, *n* (%)			
Time to source control from initial AF, median in days (IQR)	2 (0–44)	2 (0–37)	0.311
Early source control[a]	99 (60.7)	14 (53.8)	0.525
Source control at follow-up BC	133 (76.4)	19 (63.3)	0.172
Source control during the course of infection in applicable cases	163/174 (93.7)	26/30 (86.7)	0.245
Complementary screening, *n* (%)			
Ophthalmoscopy	185 (84.1)	27 (77.1)	0.332
Echocardiogram	196 (89.1)	32 (91.4)	0.779
Doppler ultrasound of deep vessels	26 (11.8)	12 (34.3)	0.002
Complications, *n* (%)			
Ocular candidiasis	26 (11.8)	4 (11.4)	1
Non-ocular complications	23 (10.5)	11 (31.4)	0.002
Septic thrombophlebitis	13 (5.9)	5 (14.3)	0.082
Endocarditis	4 (1.8)	3 (8.6)	0.056
Other organs	6 (2.7)	3 (8.6)	0.066
Outcomes, *n* (%)			
ICU admission due to candidemia	21 (9.5)	6 (17.1)	0.231
30-day mortality	49 (22.3)	11 (31.4)	0.283
> 30-day mortality[b]	68 (30.9)	15 (42.9)	0.177
Hospital length of stay, median in days (IQR)	28 (5–254)	41.5 (8–112)	0.021

AF antifungal, *BC* blood culture, *ICU* intensive care unit

[a] Source control was defined as "early" when performed within 48 h from the initial antifungal treatment

[b] Death at any time after 30 days during hospitalization

interventions such complications may suppose or to an extended duration of treatment, which was also observed ($p = 0.026$).

Finally, there is controversy regarding the potential impact that persistent candidemia could have on mortality [1, 3, 5, 32–34]. In our study, the higher 30-day mortality rate found among patients with PC was not statistically significant (31.4% vs. 22.3%, $p = 0.283$), consistent with previous reports [6, 32, 35]. Nevertheless, the relatively low number of deaths in our series may have contributed to the lack of statistical significance despite clinical relevance. This may also rely on the adjusted therapeutic management, which is known to impact the prognosis of candidemia [36, 37]. In fact, a previous study from our group measuring the impact of AFS on quality of care outcomes reported a reduction of candidemia-related mortality [7, 8]. Thus, the potential influence of AFS on therapeutic adequacy and consequently on persistent candidemia may have diminished the mortality gap between groups.

Our study is subject to limitations, mainly owing to its single-center, retrospective nature. Follow-up blood cultures until sterile are strongly recommended but not guaranteed in a timeline fashion by our AFS team. Thus, patients identified as with non-PC could have been classified otherwise if daily blood cultures had been performed. Yet, monitoring infection clearance through blood cultures is often neglected in real-life practice, especially if patients respond well to treatment [5, 6, 19]. However, there are no recent large studies with adult

Table 4 Multivariate logistic regression model for independent factors associated with persistent candidemia in 255 adult patients diagnosed from 2010 to 2018

Variables	OR (95%CI)	*p* value
Solid malignancy	2.18 (0.995–4.794)	0.051
CVC-related candidemia	1.90 (0.847–4.269)	0.119
Biofilm production	2.83 (0.798–10.07)	0.107
Unsuspected sites of infection[a]	4.28 (1.774–10.34)	*0.001*

OR odds ratio, *CI* confidence interval, *CVC* central venous catheter

[a] Unsuspected sites of infection were additional candidemia sources not diagnosed or managed previous to follow-up blood cultures in patients with an established initial source of candidemia. These additional sources comprised non-ocular complications, such as thrombophlebitis, endocarditis, and infection in other organs

patients designed to evaluate the clinical significance of persistent candidemia in settings that actively monitor and promote an optimized antifungal management.

In conclusion, persistent candidemia in adults managed in a setting with an active antifungal stewardship program was not associated to inadequate or delayed therapeutic management, nor a higher 30-day mortality rate. The diagnosis of persistent candidemia demands from clinicians to search for unexpected sites of infection in order to promote a faster mycological eradication, reduce the length of hospital stay, and improve patient care.

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Compliance with ethical standards

This study was approved by the institutional ethics committee (Comité Ético de Investigación Clínica del Hospital Gregorio Marañón [CEIC-A1], study code MICRO.HGUGM.2015–071). The need for an informed consent was waived owing to the non-interventional, retrospective design of the study.

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Noyola DE, Fernandez M, Moylett EH, Baker CJ (2001) Ophthalmologic, visceral, and cardiac involvement in neonates with candidemia. Clin Infect Dis 32(7):1018–1023
2. Fraser VJ, Jones M, Dunkel J, Storfer S, Medoff G, Dunagan WC (1992) Candidemia in a tertiary care hospital: epidemiology, risk factors, and predictors of mortality. Clin Infect Dis 15(3):414–421
3. Luzzati R, Amalfitano G, Lazzarini L et al (2000) Nosocomial candidemia in non-neutropenic patients at an Italian tertiary care hospital. Eur J Clin Microbiol Infect Dis 19(8):602–607
4. Zaoutis TE, Greves HM, Lautenbach E, Bilker WB, Coffin SE (2004) Risk factors for disseminated candidiasis in children with candidemia. Pediatr Infect Dis J 23(7):635–641
5. Nucci M (2011) Persistent candidemia: causes and investigations. Curr Fungal Infect Rep 5(1):3–11
6. Kang SJ, Kim SE, Kim UJ et al (2017) Clinical characteristics and risk factors for mortality in adult patients with persistent candidemia. J Infect Elsevier 75(3):246–253
7. Vena A, Munoz P, Corisco R, et al. Efficacy of a "check-list" intervention bundle on the clinical evolution of patients with *Candida* bloodstream infections. 27th ECCMID. 2017. p. 24–25
8. Valerio M, Muñoz P, Rodríguez CG et al (2015) Antifungal stewardship in a tertiary-care institution: a bedside intervention. Clin Microbiol Infect 21(5):492.e1–492.e9
9. Muñoz P, Valerio M, Vena A, Bouza E (2015) Antifungal stewardship in daily practice and health economic implications. Mycoses 58:14–25
10. Vena A, Bouza E, Valerio M et al (2017) Candidemia in non-ICU surgical wards: comparison with medical wards. PLoS One Public Libr Sci 12(10):e0185339
11. Mermel LA, Allon M, Bouza E et al (2009) Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 49(1):1–45
12. Pappas PG, Kauffman CA, Andes DR et al (2016) Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis Oxford Univ Press 62(4):e1–e50
13. Arendrup MC, Cuenca-Estrella M, Lass-Flörl C, Hope W (2012) EUCAST-AFST. EUCAST technical note on the EUCAST definitive document EDef 7.2: method for the determination of broth dilution minimum inhibitory concentrations of antifungal agents for yeasts EDef 7.2 (EUCAST-AFST)*. Clin Microbiol Infect 18(7):E246–E247
14. Marcos-Zambrano LJ, Escribano P, Bouza E, Guinea J (2014) Production of biofilm by *Candida* and non-*Candida* spp. isolates causing fungemia: comparison of biomass production and metabolic activity and development of cut-off points. Int J Med Microbiol 304(8):1192–1198
15. Marcos-Zambrano LJ, Gómez-Perosanz M, Escribano P, Zaragoza O, Bouza E, Guinea J (2016) Biofilm production and antibiofilm activity of echinocandins and liposomal amphotericin B in echinocandin-resistant yeast species. Antimicrob Agents Chemother 60(6):3579–3586
16. Nucci M, Perfect JR (2008) When primary antifungal therapy fails. Clin Infect Dis 46(9):1426–1433

17. Baden LR, Bensinger W, Angarone M et al (2012) Prevention and treatment of cancer-related infections. J Natl Compr Cancer Netw 10(11):1412–1445
18. Ruhnke M, Schwartz S (2016) Recent developments in the management of invasive fungal infections in patients with oncohematological diseases. Ther Adv Hematol SAGE Publ 7(6): 345–359
19. Clancy CJ, Nguyen MH (2013) Finding the "missing 50%" of invasive candidiasis: how nonculture diagnostics will improve understanding of disease spectrum and transform patient care. Clin Infect Dis 56(9):1284–1292
20. Li W-S, Chen Y-C, Kuo S-F, Chen F-J, Lee C-H (2018) The impact of biofilm formation on the persistence of candidemia. Front Microbiol 9:1196
21. Monfredini PM, Souza ACR, Cavalheiro RP, Siqueira RA, Colombo AL (2017) Clinical impact of *Candida* spp. biofilm production in a cohort of patients with candidemia. Med Mycol 56(7): 803–808
22. Lin K-Y, Chen P-Y, Chuang Y-C et al (2018) Effectiveness of echinocandins versus fluconazole for treatment of persistent candidemia: a time-dependent analysis. J Inf Secur 77(3):242–248
23. Muñoz P, Agnelli C, Guinea J et al (2018) Is biofilm production a prognostic marker in adults with candidaemia? Clin Microbiol Infect 24(9):1010–1015
24. Hamdy RF, Zaoutis TE, Seo SK (2017) Antifungal stewardship considerations for adults and pediatrics. Virulence 8(6):658–672
25. Nucci M, Anaissie E, Betts RFF et al (2010) Early removal of central venous catheter in patients with candidemia does not improve outcome: analysis of 842 patients from 2 randomized clinical trials. Clin Infect Dis 51(3):295–303
26. Garnacho-Montero J, Diaz-Martin A, Garcia-Cabrera E, Ruiz Perez de Pipaon M, Hernandez-Caballero C, Lepe-Jimenez JA (2013) Impact on hospital mortality of catheter removal and adequate antifungal therapy in *Candida* spp. bloodstream infections. J Antimicrob Chemother 68(1):206–213
27. Caccese R, Carfagna P, Pistilli N, Massetti AP, Falcone M, Venditti M (2012) Candidal thrombophlebitis of central veins: case report and review. Med Mycol 50(3):299–304
28. Mahmood M, Kendi AT, Ajmal S, et al (2017) Meta-analysis of 18F-FDG PET/CT in the diagnosis of infective endocarditis. J Nucl Cardiol. Advance online publication. https://doi.org/10.1007/s12350-017-1092-8
29. Sharma P, Mukherjee A, Karunanithi S, Bal C, Kumar R (2014) Potential role of 18 F-FDG PET/CT in patients with fungal infections. Am J Roentgenol American Roentgen Ray Society 203(1): 180–189
30. Kauffman C (2015) Complications of candidemia in ICU patients: endophthalmitis, osteomyelitis, endocarditis. Semin Respir Crit Care Med. Thieme Medical Publishers 36(05):641–649
31. Fernández-Cruz A, Cruz Menárguez M, Muñoz P et al (2015) The search for endocarditis in patients with candidemia: a systematic recommendation for echocardiography? A prospective cohort. Eur J Clin Microbiol Infect Dis 34(8):1543–1549
32. Safdar A, Bannister TW, Safdar Z (2004) The predictors of outcome in immunocompetent patients with hematogenous candidasis. Int J Infect Dis 8(3):180–186
33. Velasco E, Bigni R (2008) A prospective cohort study evaluating the prognostic impact of clinical characteristics and comorbid conditions of hospitalized adult and pediatric cancer patients with candidemia. Eur J Clin Microbiol Infect Dis 27(11):1071–1078
34. Phillips P, Shafran S, Garber G et al (1997) Multicenter randomized trial of fluconazole versus amphotericin B for treatment of candidemia in non-neutropenic patients. Canadian Candidemia Study Group. Eur J Clin Microbiol Infect Dis 16(5):337–345
35. Chen C-Y, Huang S-Y, Tsay W et al (2012) Clinical characteristics of candidaemia in adults with haematological malignancy, and antimicrobial susceptibilities of the isolates at a medical centre in Taiwan, 2001–2010. Int J Antimicrob Agents 40(6):533–538
36. Bassetti M, Righi E, Montravers P, Cornely OA (2018) What has changed in the treatment of invasive candidiasis? A look at the past 10 years and ahead. J Antimicrob Chemother 73(suppl_1):i14–i25
37. Puig-Asensio M, Padilla B, Garnacho-Montero J et al (2014) Epidemiology and predictive factors for early and late mortality in *Candida* bloodstream infections: a population-based surveillance in Spain. Clin Microbiol Infect 20(4):O245–O254