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Impact of empirical treatment with antifungal agents on survival of patients with candidemia

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ABSTRACT

Introduction. The objective of this study was to evaluate the impact of echinocandins and fluconazole) on mortality 7 and 30 days after candidemia onset and overall in-hospital mortality), in patients with candidemia at a Spanish tertiary hospital.

Methods. A retrospective study was conducted that enrolled all non-neutropenic adult patients diagnosed with candidemia at Hospital Clínico Universitario de Valladolid between 2007 and 2016. A total of 179 patients were evaluated, they were divided into two sub-groups: surviving patients (n = 92) and non-surviving patients (n = 87).

Results. The 7-day mortality was 25,1% (45), 30-day mortality was 46,9% (84), and overall in-hospital mortality was 48,6% (87). 40.8% of patients received no antifungal treatment (43.8% of surviving patients and 37.8% of non-surviving patients; p=0.15). A total of 106 (59.2%) patients were treated, of which 90 patients (50.3%) received empiric treatment. 19.6% and 47.8% of surviving patients were treated with echinocandins and fluconazole, respectively. By contrast, of non-surviving patients, 31.0% were treated with echinocandins and 47.1% received fluconazole. Survival for the first 7 days was significantly higher in treated with antifungal agents (log-rank = 0.029), however, there were not significant differences in 30-day survival. Factors linked to a significant increase in overall in-hospital mortality were age (OR 1.040), septic shock (OR 2.694) and need for mechanical ventilation > 48 h (OR 2.812).

Conclusion. Patients who received antifungal treatment, regardless of whether they received fluconazole or echinocandins, had a significantly lower mortality rate after 7 days than untreated patients, although no significant differences in 30-day mortality were seen.

Keywords: Candidemia, echinocandins, antifungal, mortality

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Impacto del tratamiento antifúngico empírico en la supervivencia de pacientes con candidemia

RESUMEN

Introducción. El objetivo del estudio es evaluar el impacto del tratamiento antifúngico en la mortalidad hospitalaria a los 7 y 30 días en pacientes con candidemia en un hospital terciario español.

Métodos. Se realizó un estudio retrospectivo que incluyó los pacientes adultos no neutropénicos diagnosticados de candidemia en el Hospital Clínico Universitario entre 2007 y 2016. Se evaluaron 179 pacientes, se dividieron en grupo de supervivientes (n=92) y no supervivientes (n=87).

Resultados. La mortalidad a 7 días fue 25,1% (45), a los 30 días 46,9% (84) y la hospitalaria 48,6% (87). El 40,8% no recibieron antifúngico (43,8% de supervivientes y 37,8% de no supervivientes; p=0,15). El 50,3% (90) recibieron tratamiento empírico. De los supervivientes el 19,6% y 47,8% se trataron con equinocandinas y fluconazol, respectivamente. De los no supervivientes el 31% recibió equinocandinas y el 47,1% fluconazol. La supervivencia a los 7 días fue significativamente mayor en los tratados (log-rank = 0.029), no hubo diferencias a los 30 días. Los factores asociados a mortalidad hospitalaria fueron edad (OR: 1.040), shock séptico (OR: 2.694) y ventilación mecánica> 48 h (OR: 2.812).

Conclusión. Los pacientes tratados con antifúngicos (ya sean equinocandinas o fluconazol) tienen una tasa de mortalidad inferior a los 7 días que los no tratados, sin embargo no hallamos diferencias a los 30 días.

Palabras clave: candidemia, mortalidad, equinocandinas, antifúngicos

INTRODUCTION

Candidemia, i.e. the presence of *Candida* species in the bloodstream, represents a common, serious complication in the hospital setting. Its incidence has increased in recent decades [1-3]. The United States has reported an incidence of approximately 0.28-0.42 cases per 1000 hospitalisations [4, 5]. Some European countries such as Italy and France have reported 1.73-6.7 cases per 1000 hospital admissions [6, 7]. Meanwhile, in Spain, a nationwide study in 2010, CANDIPOP study, conducted at 29 hospitals reported a total incidence of 8.1cases per 1,000 admissions [8].

The aetiology of the disease has also changed in recent years. In the 1970s, 90% of infections resulted from *Candida albicans*. Now, less than 50% of cases are linked to this species, and the prevalence of non-albicans species (*C. glabrata*, *C. tropicalis*, *C. parapsilosis* and *C. krusei*) has increased [9]. Nosocomial candidemia is associated with an increase in mortality, a prolonged hospital stay [10] and, as a result, an increase in healthcare expenditures [11].

Candidemia is usually detected late in the course of the disease [12]. This is because it has non-specific clinical signs or no clinical signs at all, and because the diagnostic procedures used are limited and non-specific as well.. If infection is suspected, while blood culture results to confirm this suspicion are pending, clinicians should make a decision on starting an empirical anti-fungal treatment to prevent fatal outcomes in critically ill hospitalised patients. The Candida score and the Ostrosky-Zeichner rule are useful diagnostic tools designed to identify patients who might benefit from early treatment with antifungal agents [13-17].

Echinocandins, fluconazole, voriconazole and amphotericin B are the main drugs prescribed as empirical antifungal treatment. Both the Infectious Diseases Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommend the use of echinocandins for critically ill patients not previously exposed to azoles or infected with a non-albicans species of *Candida*, as these medicines have a broader spectrum of action and a greater efficacy [18, 19]. The scientific evidence to date, though still limited, has suggested that empirical antifungal treatment reduces the early mortality rate (which is directly related to fungal infection) in critically ill patients [20, 21]. However, further data are needed to confirm this assumption. The objective of this study was to evaluate the impact of different antifungal strategies (echinocandins and fluconazole) on mortality, both early (7 days after candidemia is suspected) and late (30 days after candidemia is suspected), in ill patients diagnosed with candidemia and hospitalised at a Spanish tertiary hospital.

METHODS

Study design. A restrospective study was conducted from inpatients of Hospital Clínico Universitario of Valladolid (Spain), a tertiary-level medical center with 800 beds, between 2007 and 2016. During the period 257,525 patients were admitted (figure 1). All non-neutropenic patients admitted both in conventional hospital units and in critical care units (medical, coronary and postsurgical) who met the following criteria were enrolled: a) patients over 18 years of age and b) isolation of any *Candida* species in blood cultures (n=215). Patients with haematologic neoplasms and patients having undergone transplantation were excluded from the study (n=36). Considering the criteria described, a total of 179 patients were evaluated. For purposes of analysis, they were divided into two subgroups: surviving patients (n = 92) and non-surviving patients (n = 87). The study was approved by the Institutional Review Board and was conducted according to the guidelines established by the hospital ethics committee and in accordance with the Declaration of Helsinki.

Empirical antifungal treatment was prescribed at each physician's discretion. Given the retrospective nature of the study, it was not possible to clarify the physician's discretion. However, at the hospital where the study was conducted, treatment guidelines are governed by IDSA recommendations [18] and by published evidence for identifying risk factors for candidemia on the intensive care unit (ICU). This suggests that diagnostic methods such as the Candida score and the Ostrosky-Zeichner prediction rule were used [14-19, 22]. The Candida score determines the likelihood of candidiasis depending on the results obtained in a scoring system based on the presence or absence of each of the following variables: 1 × (total parenteral nutrition) + 1 × (ICU admission for surgery) + 1 × (multifocal colonisation by species of *Candida*) + 2 × (severe sepsis) [22]. The Ostrosky-Zeichner rule has been proposed as a tool capable of predicting the development of candidiasis in critically ill patients. It identifies as potential risk patients those treated with broad-spectrum antibiotics (1-3 days), those having undergone placement of a central venous catheter (1-3 days) and those with at least two of the following risk

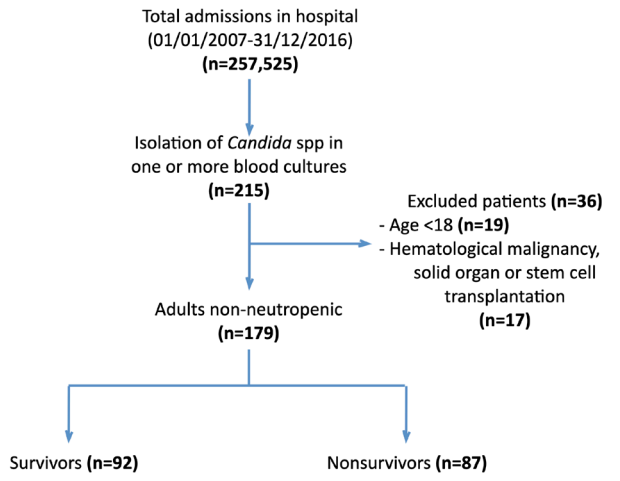

Figure 1 | **Flowchart of selection of study patients**

factors: total parenteral nutrition (1-3 days), any type of dialysis (1-3 days), major surgery (–7-0 days), pancreatitis (–7-0 days), corticosteroids (–7-3 days) or other immunosuppressant treatments (–7-0 days) [16].

In addition to the above, information on the following variables was obtained retrospectively from the patients' medical records: age, sex, comorbidities and Charlson comorbidity index, surgery prior to treatment (in the last month), development of septic shock, pancreatitis, ICU admissions, duration of hospitalisation, need for surgery, need for mechanical ventilation > 48 h, parenteral nutrition, central venous catheter, and renal replacement therapy. Furthermore, in-hospital mortality, both after 7 days and after 30 days, was evaluated. The start time was considered to be the time when sampling for blood culture was performed due to suspected candidemia.

Statistical analysis. Categorical variables were expressed in terms of absolute and relative frequencies (%). Continuous variables were expressed in terms of median plus standard deviation (SD). Comparisons between surviving patients and non-surviving patients were performed using the chi-squared test for categorical variables and Student's *t* test or the Mann–Whitney *U* test for continuous variables. The Kaplan–Meier survival analysis was performed by comparing treatment with echinocandins, treatment with fluconazole and no treatment. A stepwise logistic regression model (odds ratio [OR] and 95% confidence interval [95% CI]) was created to identify factors associated with in-hospital mortality. Statistical significance was set at $p \leq 0.05$. All procedures were performed with the SPSS 20.0 software program.

RESULTS

The total number of patients hospitalised at our hospital between 2007 and 2016 was 257,525. Of them, 215 (0.083%) were patients with candidemia, i.e. 0.008% per year and per 12,500 patients. Table 1 shows the baseline demographic and clinical characteristics of the study patients. Of the 179 patients evaluated, surviving patients (n = 92) slightly outnumbered non-surviving patients (n = 87). Non-surviving patients were significantly older than surviving patients (70.8 ± 11.7 vs 65.0 ± 16.0; p < 0.006, respectively). Furthermore, a higher percentage of non-surviving patients had undergone surgery prior to treatment (18.3% vs 8.6%). There were also significantly higher numbers of non-surviving patients who suffered from septic shock (88.5% vs 35.9%; p < 0.001), needed mechanical ventilation > 48 h (52.8% vs 25%; p = 0.001) and were admitted to ICU (72.4% vs 45.6%; p = 0.002).

No antifungal treatment group was 40.8% of patients (43.8% of surviving patients and 37.8% of non-surviving patients; p=0.15). 106 (59.2%) patients were treated. 90 patients (50.3%) received empiric treatment. 19.6% and 47.8% of surviving patients were treated with echinocandins and fluconazole, respectively. By contrast, of non-surviving patients, 31.0% were treated with echinocandins and 47.1% received fluconazole.

The species of *Candida* isolated and the clinical characteristics of the patients with candidemia, as well as the survival of these patients, are shown in table 2. The main species of *Candida* isolated were as follows: *C. albicans* (64.2% of patients), *C. glabrata* (13.9%), *C. parapsilosis* (12.8%) and *C. tropicalis* (5.0%). The factors that turned out to be significantly different between surviving patients and non-surviving patients were need for parenteral nutrition (23.4% vs 43.7%; p = 0.01), placement of a central venous catheter (68.8% vs 71.0%; p = 0.03), a Candida score ≥ 3 (34.7% vs 64.3%; p = 0.001) and fulfilment of the Ostrosky-Zeichner prediction rule (32.8% vs 52.3%; p < 0.001).

The 7-day mortality was 25.1% (45 patients), 30 day mortality was 46.9% (84 patients), and overall in-hospital mortality was 48.6% (87 patients). Regarding mortality, the survival analysis performed showed that survival for the first 7 days following the development of candidemia (t = 0 when sampling for blood culture due to suspected candidemia was performed) was significantly higher in patients treated with antifungal agents, regardless of treatment received, than in patients with no specific treatment (log-rank = 0.029). However, this same analysis also showed no significant differences in 30-day survival between patients who received echinocandins, patients who received fluconazole and patients who received no treatment (figure 2). Table 3 shows the multivariate analysis performed to identify risk factors associated with in-hospital mortality after 7 days and after 30 days, and with overall mortality during the development of candidemia. The factors linked to a significant increase in overall in-hospital mortality were age (OR 1.040; 95% CI 1.018-1.062; p < 0.001), septic shock (OR 2.694; 95% CI 1.271-5.709; p = 0.010) and need for mechanical ventilation > 48 h (OR 2.812; 95% CI 1.129-7.005, p = 0.026). Table 4 reflects microbiological isolates before and after candidemia found during hospital admission.

DISCUSSION

The most significant findings of our retrospective study were as follows: i) the incidence of candidemia in non-neutropenic critically ill patients was 0.083%; ii) of the species in blood culture, *C. albicans* was the most commonly isolated (64.2%), consistent with the scientific evidence; iii) approximately 41% of patients with candidemia received no treatment with antifungal agents; iv) 50% of patients received empirical treatment, within a suitable period of time; v) only 49.5% of patients had a Candida score ≥ 3, and just 32.05% of patients fulfilled the Ostrosky-Zeichner prediction rule; and vi) patients who received antifungal treatment, regardless of whether they received fluconazole or echinocandins, had a significantly lower mortality rate after 7 days than untreated patients, although no significant differences in 30-day mortality were seen.

The incidence reported in this study was consistent with the results published in the scientific literature. Our study obtained an incidence of 0.083 cases per 1,000 hospitalisations. The above-mentioned study published in 2010 with data from

Table 1 **Demographic and clinical characteristics of patients with candidemia regarding survival.**

	Total (N=179)	Survivors (N=92)	Nonsurvivors (N=87)	P
Age, mean years ± SD	67.81 ± 13.91	65.0 ± 16.0	70.8 ± 11.7	0.006
Sex male, n (%)	117 (65.3)	62 (67.4)	55 (63.2)	0.55
Main comorbidities, n (%)				
Solid organ cancer	37 (20.6)	17 (18.5)	20 (23)	0.74
Cardiac disease	31 (17.3)	17 (18.5)	14 (16.1)	0.67
Immunosuppression	22 (12.2)	11 (12.0)	11 (12.6)	0.88
Diabetes mellitus	52 (29)	25 (27.2)	27 (31.0)	0.57
Chronic renal failure	29 (16.2)	14 (15.2)	15 (17.2)	0.71
COPD	11 (6.1)	5 (5.4)	6 (6.9)	0.68
Liver disease	2 (1.1)	2 (2.2)	0 (0.0)	0.16
Dementia	10 (5.5)	6 (6.5)	4 (4.6)	0.57
Charlson comorbidity index, mean score ± SD	2 ± 1	2 ± 1	2 ± 1	0.11
Pre-treatment surgery, n (%)	24 (13.4)	8 (8.6)	16 (18.3)	
Septic shock, n (%)	110 (61.4)	33 (35.9)	77 (88.5)	<0.001
No scheduled surgery, n (%)	92 (51.3)	45 (48.9)	47 (54.0)	
Main scheduled surgery, n (%)	87 (48.6)	47 (51.1)	40 (46.0)	0.49
Abdominal Surgery	27 (15)	13 (14.1)	14 (16.1)	0.78
Vascular Surgery	24 (13.4)	14 (15.2)	10 (11.5)	
Cardiac Surgery	15 (8.3)	6 (6.5)	9 (10.3)	
Urology Surgery	9 (5)	6 (6.5)	3 (3.4)	
More than 1 surgery	52 (29)	29 (31.5)	23 (26.4)	0.73
Antifungal treatment, n (%)				
No receiving fluconazole or echinocandins	73 (40.8)	39 (43.8)	34 (37.8)	0.15
Receiving treatment	106 (59.2)	53 (57.6)	53 (60.9)	
Echinocandins	45 (25.1)	18 (19.6)	27 (31.0)	0.08
Caspofungin	31 (17.3)	15 (16.3)	16 (18.4)	0.71
Micafungin	6 (3.3)	2 (2.2)	3 (3.3)	0.48
Anidulafungin	10 (5.5)	1(1.1)	8 (9.2)	0.02
Fluconazole	85 (47.4)	44 (47.8)	41 (47.1)	0.92
Only fluconazole	63 (35.1)	37 (40.2)	26 (29.9)	0.14
Empiric treatment n (%)	90 (50.2)	44 (47.8)	46 (50)	0.82
Blood culture directed-therapy, n (%)	16 (8.9)	9 (9.8)	7 (10.3)	0,68
Mechanic ventilation > 48 h, n (%)	69 (38.5)	23 (25)	46 (52.8)	0.001
Patients admitted in the ICU, n (%)	105 (58.6)	42 (45.6)	63 (72.4)	0.002
Total stay in the ICU, days ± SD	52.2 ± 33	45 ± 37	60 ± 30	0.33
ICU stay >4 days, n (%)	88 (49.1)	35 (38)	53 (57.6)	0.009
Total stay at the hospital, mean days ± SD	80.6 ± 96	103 ± 137	54 ± 42	0.29

Table 2 **Clinical characteristics and species isolated associated with candidemia regarding survival of patients.**

	Total (N=179) n (%)	Survivors (N=92) n (%)	Nonsurvivors (N=87) n (%)	P
More than 7 days from admission to blood culture positive, n (%)	131 (73.2)	63 (68.5)	68 (78.2)	0.14
Candida colonization, n (%)				
0	102 (57)	58 (63.0)	44 (50.6)	0.22
1	47 (26.2)	20 (21.7)	27 (31.0)	
2 or more	30 (16.7)	14 (15.2)	16 (18.4)	
Pre-culture surgery, n (%)	76 (42.4)	39 (42.3)	37 (40)	0.18
Requiring parenteral nutrition, n (%)	46 (25.7)	15 (16)	31 (33.6)	0.01
Central venous catheter, n (%)	149 (83.2)	64 (69.5)	85 (92.3)	0.03
Renal replacement therapy, n (%)	32 (17.9)	12 (13)	20 (21.7)	0.19
Pancreatitis, n (%)	4 (2.2)	1 (11)	3 (3.2)	0.36
Candida Score ≥3, n (%)	88 (49.2)	32 (34.7)	56 (64.3)	0.001
Meeting Ostrosky-Zeichner prediction rule, n (%)	59 (33)	21 (22.8)	38 (41.3)	<0.001
***Candida* species,** n (%)				0.11
C. albicans	115 (64.2)	60 (65.2)	55 (63.2)	
C. parapsilosis	23 (12.8)	13 (14.1)	10 (11.5)	
C. glabrata	25 (14)	14 (15.2)	11 (12.6)	
C. krusei	0 (0)	0 (0.0)	0 (0.0)	
C. tropicalis	9 (5)	2 (2.2)	7 (8.0)	
C. lusitaniae	3 (1.7)	0 (0.0)	3 (3.4)	
C. famata	0 (0.0)	0 (0.0)	0 (0.0)	
C. guillliermondii	0 (0.0)	0 (0.0)	0 (0.0)	
Antibiotic therapy at the time of candidemia, n (%)	147 (82.1)	69 (75.0)	78 (89.7)	0.011
Betalactams	109 (60.9)	49 (53.3)	60 (69.0)	0.03
Quinolones	25 (14)	12 (13.0)	13 (14.9)	0.71
Glycopeptides	16 (8.9)	9 (9.8)	7 (8.0)	0.68
Aminoglycosides	15 (8.4)	6 (6.5)	9 (10.3)	0.35

40 Spanish tertiary hospitals indicated an incidence of 0.76-1.49 cases per 1,000 hospital admissions. However, its prospective nature, as well as its shorter duration, may have influenced the peak incidence rates it obtained [23]. Previously, a population-based study with the objective of determining the incidence of *Candida* infections in Spain reported 8.1 cases of candidiasis per 100,000 individuals [1, 8].

Regarding species of *Candida* isolated in Spain, studies have shown that, despite an increase in the prevalence of *non-albicans* species, *C. albicans* has been identified as the aetiological agent in the highest percentage of candidiasis cases (45.4%-51%) [1, 8,23]. Our study proved consistent with these results, since *C. albicans* was isolated in 64.2% of cases. This showed that the outcomes of daily clinical practice at our hospital are consistent with the up-to-date scientific evidence.

Regarding the clinical effect of treatment on the development of candidemia, an early start for empirical antifungal treatment is generally thought to be associated with a reduced risk of death. The scientific literature features some studies having obtained results indicating inappropriate use of antifungal therapy in this type of patient. In 2007, Parkins et al. published a study that enrolled 207 patients with invasive

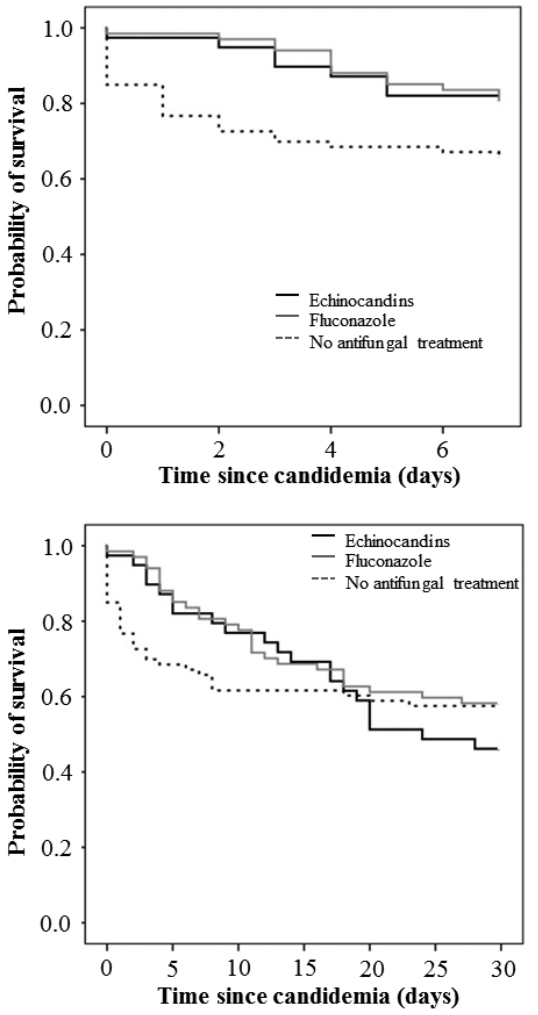

Figure 2 Probability of survival since candidemia

Table 3 Multivariate analysis for the identification of risk factors associated with 7-day, 30-days, and overall in-hospital mortality since the development of candidemia.

	Odds ratio	95% CI	P value
7-DAY MORTALITY			
Age	1.026	1.001 – 1.052	**0.038**
Sex male (versus female)	1.111	0.598 – 2.063	0.739
Charlson comorbidity index	1.105	0.941 – 1.298	0.223
Echinocandin treatment (versus no treatment)		0.177 – 0.974	**0.043**
Fluconazole (versus no treatment)	0.447	0.226 – 0.885	**0.021**
Septic shock (versus no septic shock)	4.435	1.962 – 10.024	**<0.001**
30-DAY MORTALITY			
Sex male (versus female)	1.068	0.673 – 1.694	0.780
Charlson comorbidity index	1.059	0.932 – 1.203	0.381
Echinocandin treatment (versus no treatment)	0.957	0.545 – 1.680	0.878
Fluconazole (versus no treatment)	0.839	0.498 – 1.414	0.510
Septic shock (versus no septic shock)	7.388	3.657 – 14.926	**<0.001**
OVERALL IN-HOSPITAL MORTALITY			
Age	1.040	1.018 – 1.062	**<0.001**
Sex male (versus female)	0.905	0.545 – 1.502	0.698
Charlson comorbidity index	1.068	0.923 – 1.235	0.378
Septic shock (versus no septic shock)	2.694	1.271 – 5.709	**0.010**
Meeting Ostrosky-Zeichner prediction rule	0.835	0.340 – 2.047	0.693
Requiring mechanical ventilation > 48 h	2.812	1.129 – 7.005	**0.026**

candidiasis and concluded that empirical antifungal treatment was effective in just 26% of patients. In the same vein, a study by Zilberberg et al. in a cohort of 90 patients with candidemia reported that antifungal therapy was inappropriate in 88.9% of patients, since there was a delay of more than 24 hours from the onset of candidemia. Consistent with these studies, the results of our study indicated that 40.8% of patients with confirmed candidemia did not receive antifungal treatment. In addition, of all patients evaluated, 48.9% received empirical antifungal treatment, within a suitable period of time. These data confirmed the difficulty of diagnosing invasive candidiasis in critically ill patients with a limited number of specific diagnostic tools. Antimicrobial stewardship increasingly receives worldwide attention for improving patient care by optimizing antifungal therapy. Antifungal stewardship programmes have the potential to optimize antifungal agent use and improve patient diagnosis and quality of care. In many centres, like in ours, antimicrobial stewardship tools are not readily available because of poor access to diagnostic tests with long turnaround times [24-26]. Although both the Candida score and the Ostrosky-Zeichner prediction rule have proven useful for identifying patients with candidemia [14-17,22], the results for our patient cohort with candidemia indicated that, of all patients, only 49.5% achieved a Candida score ≥ 3, while only 32.05% fulfilled the Ostrosky-Zeichner prediction rule. In addition, it should be noted that 19 patients received treatment with echinocandins (12 surviving patients and 7 non-surviving patients), regardless of not fulfilling the Ostrosky-Zeichner rule or having a Candida score < 3. There were 51 patients (28.4%) with Candida score ≥3 and meeting Ostroky-Zeichner rule, of these 28 (54.9%) received empiric treatment. All these results suggest that physicians, despite being familiar with the diagnostic tests described, started empirical antifungal therapy based on their clinical experience and did not follow the provisions of the current therapeutic guidelines.

Regarding impact on patient survival, which was the main objective of this study, the results demonstrated a significant decrease in 7-day mortality (since sampling for blood culture was performed) in the group of patients with antifungal treatment. However, no differences in 30-day mortality were seen between the group of patients having received antifungal treatment and the group of patients not having received anti-

Table 4 Microbiological findings before and after candidemia

	Total (N=179) n (%)	Survivors (N=92) n (%)	Nonsurvivors (N=87) n (%)	p value
PRECANDIDEMIA ISOLATIONS				
Any location				
Gram + cocci	98 (54.7)	47 (51.1)	51 (58.6)	0.31
Gram - bacilli	104 (58.1)	52 (56.5)	52 (59.8)	0.66
Gram + bacilli	4 (2.2)	1 (1.1)	3 (3.4)	0.27
Fungus	32 (17.9)	16 (17.4)	16 (18.4)	0.86
Urine				
Gram + cocci	11 (6.1)	6 (6.5)	5 (5.7)	0.82
Gram - bacilli	29 (16.2)	16 (17.4)	13 (14.9)	0.65
Fungus	41 (22.9)	20 (21.7)	21 (24.1)	0.7
Lung				
Gram + cocci	19 (10.6)	11 (12)	8 (9.2)	0.54
Gram - bacilli	41 (22.9)	14 (15.2)	27 (31)	0.012
Fungus	30 (16.8)	13 (14.1)	17 (19.5)	0.33
Mycobacteria	1 (0.6)	0 (0)	1 (1.1)	0.22
Blood				
Gram + cocci	55 (30.7)	25 (27.2)	30 (34.5)	0.28
Gram - bacilli	41 (22.9)	20 (21.7)	21 (24.1)	0.7
POSTCANDIDEMIA ISOLATIONS				
Any location				
Gram + cocci	56 (31.3)	30 (32.6)	26 (29.9)	0.69
Gram - bacilli	55 (30.7)	29 (31.5)	26 (29.9)	0.81
Fungus	28 (15.6)	15 (16.3)	13 (14.9)	0.8
Urine				
Gram + cocci	4 (2.2)	4 (4.3)	0 (0)	0.02
Gram - bacilli	42 (23.4)	25 (27.2)	17 (19.5)	0.22
Fungus	12 (6.7)	6 (6.5)	6 (6.9)	0.92
Lung				
Gram + cocci	6 (3.4)	3 (3.3)	3 (3.4)	0.94
Gram - bacilli	14 (7.8)	7 (7.6)	7 (8)	0.91
Fungus	12 (6.7)	5 (5.4)	7 (8)	0.48
Mycobacteria	1 (0.6)	0 (0)	1 (1.1)	0.22
Blood				
Gram + cocci	20 (11.1)	13 (14.1)	7 (8)	0.19
Gram - bacilli	15 (8.4)	9 (9.8)	6 (69)	0.48

fungal treatment. These data were consistent with some previously published studies. Bailly et al. published a retrospective study that enrolled 1491 non-neutropenic critically ill patients suspected of suffering from invasive candidiasis. Its results suggested that empirical antifungal systemic treatment had no effect on 30-day survival [27]. Similarly, Timsit et al. conducted a study in 260 non-neutropenic critically ill patients, with sepsis acquired in ICU, colonisation in multiple sites by species of *Candida* and multiple organ failure. They concluded that empirical treatment with micafungin did not increase infection-free survival on day 28 [28]. These results suggest that antifungal therapy may prevent early mortality, which is directly related to fungal infection. In addition, they underscore the need to start treatment empirically if candidemia is suspected in order to achieve the above-mentioned clinical benefit. In our study 39 patients survive without antifungal and we look for the explanation to this fact. Blot SI et al [29] reported in 2001 that in patients in ICU appearance of candidemia did not affect the prognosis. They attributed mortality to age, comorbidities and acute illness. These findings are concordant with those of our study, in which mortality risk factors are age, septic shock and need for mechanical ventilation. Empirical antifungal therapy would not prevent late mortality, as other factors deriving from the patient's clinical condition influence this outcome.

Regarding the suitability of using one drug or another, all updates to international guidelines recommend echinocandins as an empirical treatment in patients with a high risk of serious sepsis or septic shock [18,19]. In fact, the latest version of the IDSA guidelines increased their degree of recommendation to "strong recommendation; due to their demonstrated efficacy and broad spectrum of action [18]. However, to date, studies reporting the use of echinocandins in routine clinical practice are limited. The results of our study indicated that there are no significant differences in terms of survival between the use of echinocandins and the use of fluconazole. Therefore, in our opinion, based on the data obtained, an early fatal outcome promoted by candidemia may be prevented with empirical antifungal therapy, regardless of whether echinocandins or fluconazole are used.

One of the main limitations of the study was its retrospective nature, which meant that only variables with accessible information could be evaluated. In addition, the precise reasoning used by different physicians in making treatment decisions could not be determined. The fact that the prescription of antifungal agents was primarily based on the physician's discretion, which was not necessarily consistent with the current guidelines, represents another significant limitation of the study. This led to differences in the management of patients during their ICU stay, which means that differences in outcomes might have been attributable to factors other than the medicine used. This limitation is more substantial when the sample size of patients is small, as in this study. In any case, although we would agree that a higher number of centres would increase the precision and significance of the results, our data may be used with caution to get a current picture of the inci-

dence and treatment of candidemia in clinical practice. Future studies must be conducted with cohorts of older patients to corroborate these results.

In conclusion, patients who received antifungal treatment, regardless of whether they received fluconazole or echinocandins, had a significantly lower mortality rate after 7 days than untreated patients, although no significant differences in 30-day mortality were seen.

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CONFLICT OF INTEREST

None to declare

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