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Rodrigo Poves-Alvarez[1,2]
Beatriz Cano-Hernández[1,2]
Sara Balbás-Alvarez[1,2]
Patricia Román-García[1,2]
María Heredia-Rodríguez[1,2]
Esther Gómez-Sánchez[1,2]
Estefanía Gómez-Pesquera[1,2]
Mario Lorenzo-López[1,2]
Beatriz Martínez-Rafael[1,2]
María Fe Muñoz-Moreno[3]
José María Eiros[2,4]
Eduardo Tamayo[1,2]

Antifungal treatment with echinocandins : a 10-year clinical experience

[1]Anesthesiology and Surgical Critical Care Department, Clinic Universitary Hospital of Valladolid, Valladolid (Spain).
[2]Group of Biomedical Research in Critical Care Medicine (BioCritic), Clinic Universitary Hospital of Valladolid, Valladolid (Spain).
[3]Biomedic Investigation Unit, Clinic Universitary Hospital of Valladolid, Valladolid (Spain).
[4]Department of Microbiology, Faculty of Medicine, University of Valladolid, Valladolid (Spain).

ABSTRACT

Introduction. The number of studies evaluating the use of echinocandins, whether or not its indication meets international guidelines, in clinical practice is limited. The objective of the present study was to determine the use of echinocandins in a tertiary Spanish hospital in 10 years of clinical practice, and to evaluate its impact on prognosis.

Methods. This retrospective study involved adult non-neutropenic ill patients with suspicion of fungal invasion who started treatment with echinocandins between 2006 and 2015.

Results. The number of patients treated with echinocandins was 153, and candidemia was detected thereafter in 25.5%. Factors associated with in-hospital mortality in patients receiving echinocandins were: sex male, septic shock, Charlson comorbidity index, and total stay at the hospital. In-hospital mortality after 7, 30 and 90 days was 13.7%, 24.8%, and 56.8%, respectively. From patients receiving echinocandins, 98 did no show multifocal colonization, 50 had *Candida* score <2.5, and 49 did not meet Ostrosky-Zeichner prediction rule. A total of 19 patients did not show any of these 3 potential risk factors for candidemia.

Conclusions. The use of echinocandins in 10 years of clinical practice in our tertiary hospital has been performed according to international guidelines; however, candidemia was only diagnosed thereafter in only 25.5% of cases. Furthermore, according to our results, the adequate use of echinocandins seems not to be associated with reduced mortality rates. Further studies, involving a large cohort of patients and more hospitals, are required to corroborate these results.

KEYWORDS: Candidemia, antifungal, echinocandins, guidelines, mortality

Correspondence:
Rodrigo Poves Álvarez
Anesthesiology and Surgical Critical Care Department Clinic Universitary Hospital of Valladolid, Avenida Ramón y Cajal 3. 47003. Valladolid (Spain)
rodrigopoves@gmail.com

Tratamiento antifúngico con equinocandinas: 10 años de experiencia clínica

RESUMEN

Introducción. El número de estudios que evalúan la utilización de equinocandinas de acuerdo con las guías internacionales es limitado. El objetivo de este estudio es evaluar la utilización de equinocandinas en un hospital terciario español en los últimos 10 años y evaluar su impacto en el pronóstico del paciente.

Métodos. Este estudio retrospectivo incluye pacientes adultos no neutropénicos con sospecha de infección fúngica invasora a los que se indicaron equinocandinas entre 2006 y 2015.

Resultados. El número de tratados con equinocandinas fue 153, la candidemia se confirmó en un 25,5% de estos pacientes. La mortalidad hospitalaria a los 7, 30 y 90 días fue 13,7%, 24,8% y 56,8% respectivamente. De los pacientes a los que se indicó equinocandina 98 no sufrían colonización multifocal, 50 tenían un *Candida* score <2,5 y 49 no cumplían la regla de Ostrosky-Zeichner. En 19 pacientes no concurrían ninguno de estos 3 factores de riesgo de candidemia. Los factores de riesgo de mortalidad hospitalaria fueron: varón, shock séptico, índice de Charlson y estancia hospitalaria.

Conclusiones. El uso de equinocandinas durante 10 años en nuestro hospital terciario se realizó de acuerdo con las guías internacionales; sin embargo solo se detectó candidemia en un 25,5% de los pacientes. Incluso, de acuerdo a nuestros resultados la indicación adecuada de equinocandinas no se asocia con disminución de la mortalidad. Se requieren estudios multicéntricos que incluyan una cohorte más grande de pacientes para corroborar estos resultados.

Palabras clave: Candidemia, antifúngico, equinocandinas, guías, mortalidad

INTRODUCTION

In last decades, the frequency of candidemia, i.e. the presence of *Candida* species in the bloodstream, in hospitalized patients has increased significantly[1,2]. Some European countries present an incidence of up to 1.7 cases, in Italy, and 6.7 cases, in France, per 1,000 admissions. In Spain, overall incidence range from 1.1 cases per 1,000 admissions to 4.3 cases per 100,000 individuals, regarding respective studies[3,4]. Candidemia has been associated with increased mortality rates and longer hospital stay[5]. Risk factors that have been associated with the development of candidemia include prior antimicrobial treatment, previous fungal colonization, requiring mechanical ventilation, central venous catheter or parenteral nutrition, surgery (especially abdominal), neutropenia, solid organ malignancy[6-8]. International guidelines, such as IDSA or ESCMID, recommend the use of echinocandins for critically ill patients, with no prior azole exposure, or with a main infection by non-*albicans Candida* species[9,10]. Echinocandins are preferred over fluconazole in patients who are hemodynamically unstable, had previous exposure to azoles, or infection of *C. glabrata*. Early initiation of the antifungal therapy and removal of contaminated catheters have been associated with best clinical outcomes[11-13]. Nevertheless, the early diagnosis of candidemia is a difficult task due to: there are not specific manifestations; candidemia is frequently detected late in the course of infection; and diagnostic procedures are non-specifics and their accuracy is still limited[14]. Some diagnostic tools, such as the *Candida* score[15-17] or Ostrosky-Zeichner prediction rule[18-19], have been created to stratify the risk of candidiasis and to identify those patients who may benefit from early antifungal treatment. In our knowledge, the number of studies evaluating the use of echinocandins, whether or not its indication meets international guidelines, in clinical practice is limited. The objective of the present study was to determine the use of echinocandins in a tertiary Spanish hospital in 10 years of clinical practice (2006-2015), and to evaluate its impact on prognosis.

METHODS

Study design. This retrospective study involved clinical data from adult nonneutropenic ill patients with suspicion of fungal invasion who started antifungal treatment with echinocandins (caspofungin, micafungin or anidulafungin) at the Clinic University Hospital of Valladolid between 2006 and 2015. This is a 700-bed tertiary centre that provides health care for an urban population of approximately 300,000 inhabitants. The study was approved by the Institutional Review Board and conducted in concordance with guidelines established by the Hospital's Ethic Committee, and the Declaration of Helsinki.

Definitions. Candidemia was defined as the presence for a *Candida* species in the bloodstream. Time to adequate overall therapy was measured from the day of the culture to the administration of the first effective antifungal (the organism being fully susceptible)[20]. Delay in the initiation of the antifungal therapy was defined as the time (days) between the identification of *Candida* in culture and the initiation of the antifungal therapy. In-hospital mortality was measured since the administration of the first dose of echinocandin.

Echinocandin indication. The indication of the use of echinocandins was performed according to the criteria of the physician responsible, under suspicion of fungal infection (empirical therapy), or because a *Candida* sp. was isolated from blood or any other location. Guidelines followed in our hospital are based on recommendations from the Infectious Diseases Society of America (IDSA) and published data on relevant risk factors for candidemia in the intensive care unit (ICU), such as *Candida* score or Ostrosky-Zeichner prediction rule[15-19]. *Candida* colonization was screened by performing routine samples from tracheal aspirates, skin folds, pharynx, and urine. *Candida* score was calculated on presence (1 point) or absence (0 point) of the following variables: 1 × (total parenteral nutrition) + 1 × (surgery) + 1 × (multifocal *Candida* colonization) + 2 × (severe sepsis)[15-17]. Ostrosky-Zeichner prediction rule consisted in: "any systemic antibiotic (days 1–3) OR presence of a central venous catheter (days 1–3) and at least 2 of the following—total parenteral nutrition (days 1–3), any dialysis (days 1–3), any major surgery (days −7–0), pancreatitis (days −7–0), any use of steroids (days −7–3), or use of other immunosuppressive agents (days −7–0)"[18-19].

Study variable. The following data were obtained from clinical record of patients: age, sex, comorbidities, Charlson comorbidity index, pre-treatment surgery (within the last month), development of septic shock, pancreatitis, admissions in the ICU, length of hospitalization, scheduled surgery, antifungal treatment, time to adequate overall therapy, *Candida* colonization, and requirement of mechanic ventilation >48 h, parenteral nutrition, central venous catheter, or renal replacement therapy.

Statistical analysis. Categorical variables were expressed as absolute and relative (%) frequencies whereas continuous ones as the median and the standard deviation (SD). Comparisons between survival groups were performed by using the Chi-square test, for categorical variables, and the Student t-test or Mann-Whitney U-test, for continuous ones. A logistic forward stepwise regression analysis (Odd ratio, OR, and 95% confidence interval, 95% CI) was created to identify factors associated with survival among patients. Demographic and clinical variables, such as sex, age, Charlson comorbidity index, pancreatitis , requiring a surgery, septic shock, requiring parenteral nutrition, total stay in the hospital, *Candida* score, Ostrosky-Zeichner prediction rule, multifocal *Candida* colonization, were introduced in the regression analysis. Collinearity was evaluated among variables. The statistical significance was established for $P \leq 0.05$. All procedures were performed with SPSS 23.0 software.

RESULTS

The total number of patients admitted in our hospital

Table 1 **Socioeconomic and clinical characteristics of patients who received treatment with echinocandins regarding survival**

	Total (n=153)	Survivors (n=60)	Nonsurvivors (n=93)	P value
Age, mean years ± SD	66.1 ± 10.9	63 ± 11.9	68 ± 9.7	0.01
Sex male, n (%)	86 (56.2)	33 (55.0)	53 (57.0)	0.80
Main comorbidities, n (%)				
Solid organ cancer	52 (33.9)	20 (33.3)	32 (34.4)	0.89
Cardiac disease	41 (26.8)	12 (20.0)	29 (31.2)	0.12
Immunosuppression	38 (24.8)	15 (25.0)	23 (24.7)	0.97
Diabetes mellitus	36 (23.5)	14 (23.3)	22 (23.7)	0.96
Chronic renal failure	31 (20.2)	8 (13.3)	23 (24.7)	0.08
COPD	24 (15.7)	10 (16.7)	14 (15.1)	1.00
Liver disease	8 (5.2)	3 (5.0)	5 (5.4)	1.00
Charlson Index, mean ± SD	2.4 ± 1.6	2.24 ± 1.6	2.52 ± 1.6	0.312
Pre-treatment surgery, n (%)	96 (62.7)	38 (63.3)	58 (62.4)	0.90
Abdominal surgery	44 (28.7)	17 (28.3)	27 (29.0)	
Cardiac surgery	29 (18.9)	9 (15.0)	20 (21.5)	
Vascular surgery	29 (18.9)	3 (5.0)	4 (4.3)	
Urologic surgery	5 (3.3)	2 (3.3)	3 (3.2)	
ORL	4 (2.6)	4 (6.7)	0 (0.0)	
Others (NCR, TRA, CTO, GIN)	4 (2.6)	4 (6.7)	1 (1.1)	
More than one surgery	33 (21.6)	14 (23.3)	19 (20.4)	0.76
Previous antibiotic treatment, n (%)	153 (100.0)	60 (100.0)	93 (100.0)	1.00
β-lactam antibiotics	127 (83.9)	48 (80.0)	79 (84.9)	0.42
Quinolones	39 (25.5)	12 (20.0)	27 (29.0)	0.21
Glycopeptide antibiotics	19 (12.4)	11 (18.3)	8 (8.6)	0.07
Aminoglycosides	16 (10.5)	7 (11.7)	9 (9.7)	0.69
Severity of symptoms, n (%)				0.005
Sepsis	23 (15.0)	16 (26.7)	7 (7.5)	
Severe sepsis	56 (36.6)	20 (33.3)	36 (38.7)	
Septic shock	74 (48.3)	24 (40.0)	50 (53.8)	
Patients admitted in the ICU, n (%)	130 (85.0)	44 (73.3)	86 (92.5)	0.005
Clinical outcomes				
Prolonged mechanical ventilation, n (%)	110 (73.3)	33 (56.9)	77 (83.7)	0.001
Total stay at the hospital, mean days ± SD	54.0 ± 58.3	71.7 ± 80.8	42.6 ± 33.1	0.01
Total stay in the ICU, mean days ± SD	28.7 ± 22.9	28.6 ± 26.1	28.8 ± 21.1	0.96

SD, standard deviation; COPD, chronic obstructive pulmonary disease.

between 2006 and 2015 was 257,525. During this study period, the number of patients treated with echinocandins was 209: 153 nonneutropenic adults, 37 neutropenic adults, and 19 children younger than 18 years. Socioeconomic and clinical characteristics of the non-neutropenic adult patients who received treatment with echinocandins regarding survival are shown in table 1. Briefly, 56.2% of patients were male, with a mean age of 66.1 ± 10.9 years. The cause of hospital admission was due to medical condition in 37.3% and to scheduled surgery (pre-treatment) in 62.7% of patients. Main scheduled

Table 2 | **Clinical characteristics of patients and risk factors associated with candidemia regarding survival**

	Total (n=153)	Survivors (n=60)	Nonsurvivors (n=93)	P value
Requiring parenteral nutrition, n (%)	76 (49.7)	23 (38.3)	53 (57.0)	0.02
Requiring scheduled surgery, n (%)	96 (62.7)	38 (63.3)	58 (62.4)	0.74
Pancreatitis, n (%)	9 (5.9)	3 (5.0)	6 (6.5)	0.680
Previous antifungal treatment with fluconazole, n (%)	43 (28.1)	16 (26.7)	27 (29.0)	0.751
Culture-proven candidemia, n (%)	39 (25.5)	14 (23.3)	25 (26.9)	0.62
Multifocal Candida colonization, n (%)	55 (35.9)	23 (38.3)	32 (34.4)	0.56
Meeting Ostrosky-Zeichner prediction rule, n (%)	103 (67.3)	32 (54.2)	71 (79.8)	0.001
***Candida* Score ≥3,** n (%)	103 (67.3)	30 (51.7)	73 (79.3)	<0.001
Time to adequate overall therapy, n (%)	28 (18.3)	10 (16.7)	18 (19.4)	0.675
Antifungal treatment delay, mean days ± SD	9.3 ± 9.5	15.7 ± 11.7	5 ± 4.9	0.163

surgeries included: abdominal (28.7% of total). The mean value of Charlson comorbidity index was 2.4 ± 1.6. A total of 36.6% and 48.3% of patients experienced severe sepsis and septic shock, respectively, and 85% were admitted in the ICU. All patients received a previous antibiotic therapy, including mainly β-lactam antibiotics (83.0% of patients). The mean total stay at the hospital was 54.0 ± 58.3 days. In-hospital mortality after 7, 30 and 90 days was 13.7%, 24.8%, and 56.8%, respectively. Clinical characteristics of patients associated with candidemia and regarding survival are shown in table 2. Parenteral nutrition was required by 49.7% of patients. Candidemia was detected in 25.4% of total patients, in 23.3% of survivors and in 26.9% of nonsurvivors. Echinocandins time to adequate overall therapy for 18.3%. Multifocal *Candida* colonization was found in 38.3% of survivors and 34.4% of nonsurvivors, respectively. The percentage of patients who met Ostrosky-Zeichner prediction rule was lower in survivors (54.2%) than nonsurvivors (79.8%; P=0.001). Similarly, patients with *Candida* score ≥ 3 was lower in survivors (51.7%) than in nonsurvivors (79.3%; P<0.001). Clinical and demographic characteristics of patients with culture-proven candidemia regarding survival are shown in table 3. From these patients, the percentage of patients with septic shock was lower in survivors (35.7%) than nonsurvivors (96.0%; P<0.001). *Candida* score ≥ 3 was also lower in survivors (46.2%) than nonsurvivors (96.0%; P<0.001). At the time of starting treatment with echinocandins, *C. albicans* was isolated from 79.5% of patients, *C. parapsilosis* from 10.3%, *C. glabrata* from 7.7%, and *C. tropicalis* from 2.5%. The difference between survivors and nonsurvivors regarding *Candida* score ≥ 3, Ostrosky-Zeichner prediction rule, and multifocal colonization is shown in figure 1. From patients receiving echinocandin treatment, 98 did no show multifocal colonization, 50 had *Candida* score <2.5, and 49 did not meet Ostrosky-Zeichner prediction rule (figure 2). A total of 19 patients, did not show any of these 3 potential risk factors for candidemia. Independent factors associated with in-hospital mortality in patients receiving antifungal treatment with echinocandins and culture-proven candidemia were as follows: sex male (OR 2.70, 95% CI 1.14 – 6.39, P = 0.023), septic shock (OR 3.70, 95% CI 1.47 – 9.31, P = 0.006), Charlson comorbidity index (OR 0.73, 95% CI 0.54 – 0.97, P = 0.030), and total stay at the hospital (OR 1.01, 95% CI 1.00 – 1.02, P = 0.090; table 4).

DISCUSSION

The present study was aimed to evaluate the use of echinocandins in nonneutropenic adults in 10 years of clinical practice, and to determine its impact on prognosis. According to current international guidelines "Empiric antifungal therapy should be considered in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever and should be based on clinical assessment of risk factors, surrogate markers for invasive candidiasis, and/or culture data from nonsterile sites"[9,10] however, criteria for starting the therapy in ICU patients are poorly defined[14]. A Spanish nationwide study of 2010, involving 984 patients with candidemia from 40 tertiary care hospitals, reported that only 5 (0.5%) were receiving echinocandins[4]. However, another recent study, aimed to compare the efficacy of fluconazole and echinocandins for the treatment of candidemia in clinical practice, showed that 37.3% (118 out of 316) of non-neutropenic patients received echinocandins as empiric antifungal therapy (if administered before susceptibility tests), and 41.1% (173 out of 421) as targeted therapy[21]. In our study, the antifungal treatment with echinocandins was administered to 153 patients (0.059% of total of admissions), and from them, 25.5% showed candidemia.

Candida score or Ostrosky-Zeichner predictive rule are useful diagnostic tools aimed to identify patients who may benefit from early antifungal treatment[15-19]. A prospective study of 2011 have demonstrated a linear association between increasing values of *Candida* score and rates of invasive can-

Table 3 | **Clinical and demographic characteristics of patients with candidemia regarding survival**

	Total (n=39)	Survivors (n=14)	Nonsurvivors (n=25)	P value
Age, mean years ± SD	63 ± 11	59 ± 10	66 ± 10	0.055
Sex male, n (%)	13 (33.3)	3 (21.4)	10 (40.0)	0.304
Main comorbidities, n (%)				
Cardiac disease	5 (12.8)	0 (0.0)	5 (20.0)	0.139
Diabetes mellitus	8 (20.5)	2 (14.3)	6 (24.0)	0.686
Immunosuppression	7 (17.9)	4 (28.6)	3 (12.0)	0.225
Chronic renal failure	4 (10.3)	0 (0.0)	4 (16.0)	0.277
Peripheral vascular disease	4 (10.3)	1 (7.1)	3 (12.0)	0.720
COPD	5 (12.8)	2 (14.3)	3 (12.0)	0.930
Solid organ cancer	8 (20.5)	3 (21.4)	5 (20.0)	0.430
Liver disease	1 (2.6)	0 (0.0)	1 (4.0)	0.390
AIDS	1 (2.6)	0 (0.0)	1 (4.0)	0.390
Charlson Index, mean ± SD	2 ± 1	2 ± 1	2 ± 2	0.113
Pre-treatment surgery	24 (61.5)	8 (57.1)	16 (64.0)	0.673
Abdominal surgery	7 (17.9)	3 (21.4)	4 (16.0)	
Vascular surgery	3 (7.7)	1 (7.1)	2 (8.0)	
Urologic surgery	3 (7.7)	1 (7.1)	2 (8.0)	
Neurosurgery	0 (0.0)	0 (0.0)	0 (0.0)	
Cardiac surgery	8 (20.5)	1 (7.1)	7 (28.0)	
Traumatology	2 (5.1)	1 (7.1)	1 (4.0)	
ORL	0 (0.0)	0 (0.0)	0 (0.0)	
Others (NCR, TRA, CTO, GIN)	1 (2.6)	1 (7.1)	0 (0.0)	
Septic shock, n (%)	29 (74.4)	5 (35.7)	24 (96.0)	<0.001
Requiring mechanic ventilation >48h, n (%)	28 (73.7)	7 (53.8)	21 (84.0)	0.062
Central venous catheter, n (%)	36 (94.7)	11 (84.6)	25 (100.0)	0.111
Renal replacement therapy, n (%)	9 (23.7)	0 (0.0)	9 (36.0)	0.016
Pancreatitis, n (%)	1 (2.6)	0 (0.0)	1 (4.0)	1.000
Requiring parenteral nutrition, n (%)	20 (52.6)	5 (38.5)	15 (60.0)	0.207
***Candida* Score,** n (%)				0.007
0	9 (23.1)	0 (0.0)	0 (0.0)	
1	4 (10.5)	4 (30.8)	0 (0.0)	
2	3 (7.9)	2 (15.4)	1 (4.0)	
3	11 (28.9)	3 (23.1)	8 (32.0)	
4	10 (26.3)	1 (7.7)	9 (36.0)	
5	9 (23.7)	2 (15.4)	7 (28.0)	
Stay in the UCI ≥ 4 days, n (%)	31 (79.5)	9 (64.3)	22 (88.0)	0.109
Total stay at the hospital, mean days ± SD	72.1 ± 90.6	103.8 ± 137.7	54.3 ± 42.4	0.298
***Candida* species,** n (%)				
C. albicans	31 (79.5)	12 (85.8)	19 (76.0)	
C. parapsilosis	4 (10.3)	1 (7.1)	3 (12.0)	
C. glabrata	3 (7.7)	1 (7.1)	2 (8.0)	
C. tropicalis	1 (2.5)	0 (0.0)	1 (4.0)	
C. krusei, C. lusitaniae, C. famata, C. guillliermondii	0 (0.0)	0 (0.0)	0 (0.0)	

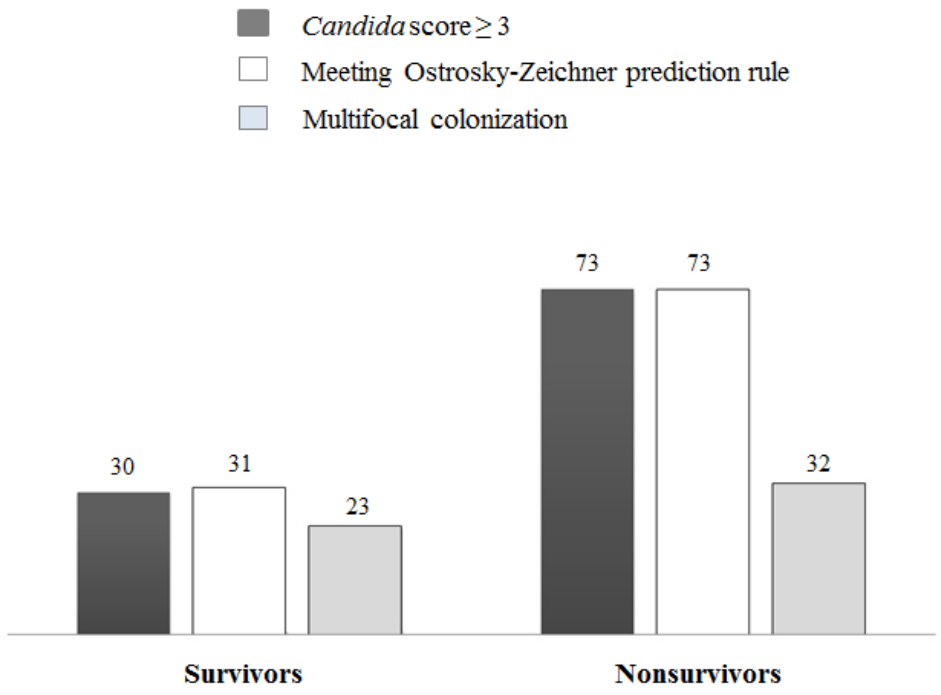

Figure 1 Difference between number of survivors and nonsurvivors regarding risk factors, such as *Candida* score ≥ 3, Ostrosky-Zeichner prediction rule, and multifocal colonization

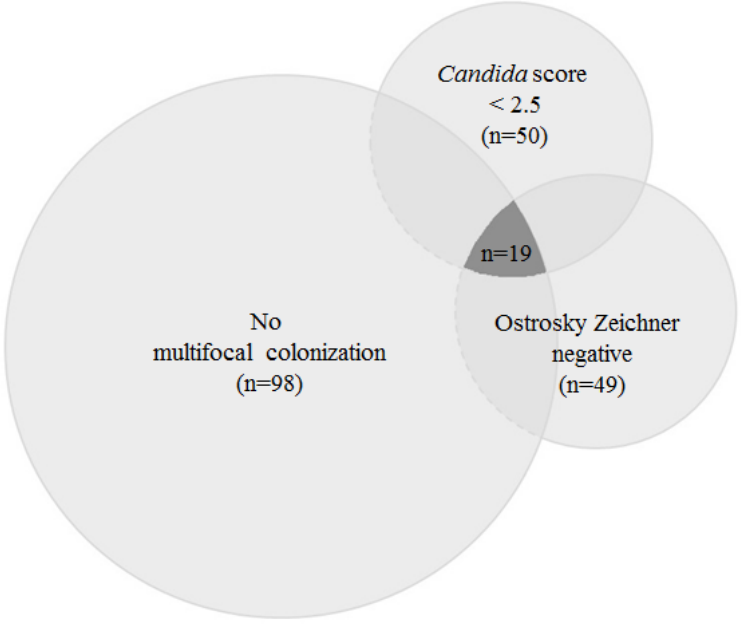

Figure 2 Representation of the number of patients who did not meet some risk factors associated with the development of candidemia (*Candida* score <3, multifocal colonization, or Ostrosky-Zeichner predictive rule). The number of individuals who did not meet any of the three risk factors is indicated in dark grey.

Table 4 | **Multivariate analysis for the identification of risk factors associated with in-hospital mortality in patients with candidemia**

	Odds ratio	95% CI	P value
Sex male	2.70	1.14 – 6.39	0.023
Septic shock	3.70	1.47 – 9.31	0.006
Charlson comorbidity index	0.73	0.54 – 0.97	0.030
Total stay at the hospital	1.01	1.00 – 1.02	0.090

didiasis; with no invasive candidiasis occurring with a *Candida* score ≤ 3[17]. In our study, 103 patients (68.7% of total) who received treatment with echinocandins had *Candida* score ≥ 3. Moreover, multifocal colonization was found in 35.9% of patients, and Ostrosky-Zeichner predictive rule was met by 67.3% of patients. However, 8 patients (5.2% of total) showed a *Candida* score of 0, and a total of 19 patients (12.5%) showed none of the risk factors associated with the development of candidemia, i.e *Candida* score <3, multifocal colonization or Ostrosky-Zeichner predictive rule. These observations demonstrate that physicians, despite knowing the importance and usefulness of *Candida* score or other risk factors, initiate the empirical antifungal treatment in critically ill patients on the base of individual experiences, under a scenario of poor clinical evolution, and with the aim of avoiding fatal outcomes.

Despite the increase of *non-albicans* species in last decades[22,23], in Spain *C. albicans* are the most isolated fungi from patients with candidemia (reported between 44% and 51% of cases), followed by *C. parapsilosis* (between 20.7% and 24.5%), *C. glabrata* (8.0–13.6%), *C. tropicalis* (7,6–10.8%), and *C. krusei* (1,9–5.0%)[3,4,24]. In our study, the distribution of *Candida* species was in concordance with literature; *C. albicans* in 79.5% of patients, *C. parapsilosis* in 10.3%, *C. glabrata* in 7.7%, and *C. tropicalis* in 2.5%. It is interesting to note that *C. krusei* was isolated in none of patients.

Candidemia is frequently detected late in the course of the infection[14]. Delaying the empiric antifungal treatment until positive blood culture has been also identified as a potential factor associated with in-hospital mortality[11,12]. However, the need for starting the antifungal treatment as earliest as possible has been intrinsically accompanied with the possibility of administering the treatment to patients who finally did not require it. Although still limited, there are studies that report the inappropriate use of antifungal treatment under this scenario. In a study of 2007, 32% of patients received antifungal therapy between the time of culture draw and reporting the positive culture, and in 26% of patients the treatment was adequate[20]. Patients who received an adequate treatment had a significant decrease in mortality. Indeed, the use of adequate empirical therapy was identified as an independent factor associated with a decreased risk for death. In another retrospective study of 2010, the inappropriate use of antifungal therapy was reported in 88.9% of patients, defined as the delay of the antifungal treatment in more than 24 hours from candidemia onset (95.0% of patients) or inadequate dose (26.3%)[25]. Authors also found that hospital mortality was greater among patients with an adequate antifungal treatment. In a prospective study of 2014 in a teaching medical ICU, 51 patients received an echinocandin based on their decision rule, and from them, candidemia was subsequently diagnosed in 9[26]. Mortality in patients receiving empirical and definitive antifungal treatment was similar (64.1% versus 75.0%, respectively). In concordance with previous studies, the treatment with echinocandins in our study was adequate in a reduced proportion of patients. In our study, from 153 patients receiving echinocandins, candidemia was identified in 39 patients (25.5%). In 28 patients (18.3%) the empiric treatment was adequate, and it was delayed in 11 (7.2%). In-hospital mortality after 7, 30 and 90 days was 13.7%, 24.8%, and 56.8%, respectively. Sex male, septic shock, Charlson comorbidity index, and total stay at the hospital were identified as risk factors associated with in-hospital mortality in patients with candidemia receiving echinocandins. Adequacy of the treatment was not associated with a reduced mortality risk. One possible explanation may derive from the delay in the initiation of the antifungal treatment (9.3 ± 9.5 days).

Finally, the use of echinocandins has increased dramatically in last decade, despite being expensive. The cost of the treatment of candidemia or invasive candidiasis with echinocandins is approximately €6,000[27]. In our study, a total of 114 patients (74.5%) receiving echinocandin treatment had no fungal infection. Therefore, assuming the huge associated cost, a total of €684,000 could be saved. Taking this information into account, it seems crucial to design better diagnostic and treatment guidelines and to identify more accurate tools (apart from *Candida* score, Ostrosky-Zeichner, or multifocal colonization) for predicting fungal infection, ,although biomarkers as galactomann or 1-3-β-d-glucan and PCR fungal identification have improved this field in the last years.

Two of the most important limitations of the study were its retrospective nature, analysing only the information that we could collect, and that data from patients came from one tertiary hospital. Furthermore, the number of patients was reduced for evaluating the risk factors associated with in-hospital mortality. Although we agree that a higher number of centres and patients would improve the strength of the results, we believe that our data may be cautiously used to report the incidence of candidemia and its treatment in clinical practice.

In conclusion, the use of echinocandins in 10 years of clinical practice in our tertiary hospital has been performed according to international guidelines; however, candidemia was only diagnosed thereafter in only 25.5% of cases. Furthermore, according to our results, the adequate use of echinocandins seems not to be associated with reduced mortality rates. Further studies, involving a large cohort of patients and more hospitals, are required to corroborate these results.

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CONFLICT OF INTEREST

None to declare

ETHICAL APPROVAL

The study was approved by the Institutional Review Board and conducted in concordance with guidelines established by the Hospital's Ethic Committee, and the Declaration of Helsinki.

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