Impact of Therapeutic Strategies on the Prognosis of Candidemia in the ICU

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Objectives: To determine the epidemiology of *Candida* bloodstream infections, variables influencing mortality, and antifungal resistance rates in ICUs in Spain.

Design: Prospective, observational, multicenter population-based study.

Setting: Medical and surgical ICUs in 29 hospitals distributed throughout five metropolitan areas of Spain.

Patients: Adult patients (≥ 18 yr) with an episode of *Candida* bloodstream infection during admission to any surveillance area ICU from May 2010 to April 2011.

Interventions: *Candida* isolates were sent to a reference laboratory for species identification by DNA sequencing and susceptibility testing using the methods and breakpoint criteria promulgated by the European Committee on Antimicrobial Susceptibility Testing. Prognostic factors associated with early (0–7 d) and late (8–30 d) mortality were analyzed using logistic regression modeling.

Measurements and Main Results: We detected 773 cases of candidemia, 752 of which were included in the overall cohort. Among these, 168 (22.3%) occurred in adult ICU patients. The rank order of *Candida* isolates was as follows: *Candida albicans* (52%), *Candida parapsilosis* (23.7%), *Candida glabrata* (12.7%), *Candida tropicalis* (5.8%), *Candida krusei* (4%), and others

(1.8%). Overall susceptibility to fluconazole was 79.2%. Cumulative mortality at 7 and 30 days after the first episode of candidemia was 16.5% and 47%, respectively. Multivariate analysis showed that early appropriate antifungal treatment and catheter removal (odds ratio, 0.27; 95% CI, 0.08–0.91), Acute Physiology and Chronic Health Evaluation II score (odds ratio, 1.11; 95% CI, 1.04–1.19), and abdominal source (odds ratio, 8.15; 95% CI, 1.75–37.93) were independently associated with early mortality. Determinants of late mortality were age (odds ratio, 1.04; 95% CI, 1.01–1.07), intubation (odds ratio, 7.24; 95% CI, 2.24–23.40), renal replacement therapy (odds ratio, 6.12; 95% CI, 2.24–16.73), and primary source (odds ratio, 2.51; 95% CI, 1.06–5.95).

Conclusions: Candidemia in ICU patients is caused by non-*albicans* species in 48% of cases, *C. parapsilosis* being the most common among these. Overall mortality remains high and mainly related with host factors. Prompt adequate antifungal treatment and catheter removal could be critical to decrease early mortality. (*Crit Care Med* 2014; XX:00–00)

Key Words: antifungal agents; candidiasis; epidemiology; intensive care units; mortality; treatment outcome

Candida bloodstream infections (BSIs) represent a severe healthcare-related complication in critically ill patients. The relevance of the disease in ICUs was recently underscored by the Extended Prevalence of Infection in Intensive Care (EPIC-II) study, which reported that 17% of ICU-acquired infections are caused by *Candida species* (1). Furthermore, the Hospitals in Europe Link for Infection Control through Surveillance (HELICS) project estimated that candidemia represented 6.3% of all ICU BSIs in 2004 and 2005 (2).

Despite the existence of effective antifungal drugs, recent studies continue to report high mortality rates, ranging from 40.2% to 56% (3–7). Attempts have been made to decrease the prevalence of candidemia with the use of antifungal prophylaxis or preemptive therapy in selected high-risk patients. However, these strategies could lead to an increased risk of fluconazole nonsusceptible isolates and contribute to the emergence of non-*albicans Candida* species (8, 9). In fact, the epidemiology of fungal infection can significantly differ between geographical regions owing to the influence of differing medical practice.

Numerous studies have focused on describing the current epidemiology and management of *Candida* BSI in the ICU setting (3, 5, 10–14). However, little effort has been dedicated to providing an in-depth understanding of the reasons for the poor prognosis of candidemia in ICU patients. In particular, few studies have assessed the risk factors for death in this population (6, 10, 15), and the benefit of modifiable therapeutic strategies has been mainly generalized from data provided by selected hospitals or studies that included patients who were not critically ill (16–18).

This study reports the candidemia episodes occurring in our ICU setting through analysis of the data from a population-based surveillance program conducted in five metropolitan areas of Spain.

The aims of the study were to describe the epidemiology of *Candida* BSI in Spanish ICUs, to determine the prevalence of antifungal drug resistance, and to identify predictors of death. In relation to this last objective, our hypothesis was that the potential effect of treatment-related variables had to be assessed in an early stage of the infection because of indications that the patient's outcome might be adversely affected by host factors (19).

MATERIALS AND METHODS

Design, Setting, and Study Population

The design of the Prospective Population Study on Candidemia in Spain study has been previously described (20). It was a prospective, population-based surveillance for *Candida* BSI conducted from May 2010 to April 2011 in five of the largest metropolitan areas of Spain: Barcelona, Bilbao, Madrid, Seville, and Valencia (population 9,498,980). Twenty-nine public and private hospitals participated, accounting for all ICUs that were representative of the Spanish healthcare system. We report here all cases of *Candida* BSI occurring in adults (≥ 18 yr) following admission to the medical or surgical ICU of any hospital in the surveillance area. Patients with a hospital stay less than or equal to 48 hours and candidemias that were already present at ICU admission were excluded.

Definitions

An incident case was the first positive *Candida* species blood culture in a surveillance area resident. Candidemias occurring more than 30 days after the incident episode or isolation of a different *Candida* species after the initial case were considered new episodes. Proven catheter-related candidemia was defined according to the following criteria: 1) evidence of catheter exit site exudate with the same *Candida* species that was isolated from the bloodstream; 2) semiquantitative catheter tip culture yielded greater than 15 colony-forming units (CFUs) of the same *Candida* species; or 3) simultaneously quantitative cultures of blood samples showed a ratio of 3:1 of CFU between blood samples obtained through a catheter and peripheral vein, or the differential time to positivity was greater than or equal to 2 hours (21). Secondary candidemias occurred after a potential origin of infection was identified based on the isolation of the same *Candida* species in blood culture and the presumed source of infection. In detail, abdominal origin required a positive culture from intra-abdominal space obtained during surgery or needle aspiration and the evidence of abdominal infection or abscess. Urinary source was identified by the isolation of *Candida* species from urine culture or tissue from affected site and the presence of urologic conditions (e.g., manipulation or obstruction of the urinary tract). Candidemia was classified as primary when there was no apparent infection at another site. Severity of illness was measured by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score on the day of candidemia (22) and the presence of severe sepsis or septic shock at presentation (23).

To assess the impact of therapeutic measures on outcome, antifungal therapy and central venous catheter (CVC) removal

were evaluated in accordance with the following definitions: 1) early, adequate antifungal treatment was the administration of the recommended dose of an antifungal drug within 48 hours after blood culture collection for a susceptible *Candida* isolate, according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints (24). Fluconazole at any dose was considered inappropriate for nonsusceptible *Candida* species, *Candida glabrata*, *Candida guilliermondii*, and *Candida krusei*. For species with no established EUCAST breakpoints to micafungin and caspofungin, we arbitrarily used the anidulafungin threshold to decide the adequacy of antifungal treatment; 2) early CVC removal was established when the catheter was removed within 48 hours after obtaining blood culture, and in patients with multiple CVCs, when at least the responsible CVC was removed within this timeframe (it was a retrospective judgment made once all necessary investigations had been performed); 3) early, appropriate combined treatment was defined as receiving adequate antifungal medication in addition to CVC removal within the first 48 hours. The outcome variables were early (≤ 7 d) and late (8–30 d) mortality.

Data Collection

Laboratory-based reporting of cases from the participating institutions went to regional study coordinators (i.e., specialists in infectious diseases or intensivists) who collected the data with the use of a standardized case report form. Demographic characteristics, predisposing risk factors within the preceding 30 days, clinical management, and 30-day follow-up period were recorded in a dedicated database created for the study. Information was then revised by one study collaborator (M.P.-A.) to verify data accuracy and completeness. Patient management was at the discretion of the attending physician. Laboratories were audited to ensure that all cases were reported. The institutional review board of each participating center approved the study protocol, and informed consent was obtained from patients.

Microbiological Methods

Candida isolates were centralized to the Mycology Reference Laboratory (MRL), National Center for Microbiology (Madrid, Spain), for species confirmation and antifungal susceptibility testing. Species identification was performed with molecular methodology by sequencing the internal transcribed spacer regions (ITS1 and ITS2) from ribosomal DNA. The identities of *Candida parapsilosis* sensu stricto, *Candida orthopsilosis*, and *Candida metapsilosis* isolates were confirmed as described by Tavanti et al (25, 26). Molecular reidentification of all *C. glabrata* sensu lato isolates into the species *C. glabrata* sensu stricto, *Candida nivariensis*, and *Candida bracarensis* was performed as described by Alcoba-Flórez et al (27). When MRL and submitted laboratory identifications differed, the MRL data were used. In vitro antifungal susceptibilities of isolates were evaluated according to the EUCAST-Antifungal Susceptibility Testing microdilution method (28, 29). *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258 were used as quality control strains for antifungal drug susceptibility testing.

Statistical Analysis

Descriptive data were presented per disease episodes or per patients depending on whether it was a characteristic of the episode of candidemia or the patient, respectively. Quantitative variables are reported as median and interquartile range (IQR), and categorical variables as counts (%). The chi-square test or Fisher exact test was used to compare the distribution of categorical variables, and the Student *t* test or Mann-Whitney *U* test for quantitative variables. Significance was set at a p value of less than 0.05. Only the first episode of candidemia recorded for an individual patient was considered for mortality analysis. The Kaplan-Meier curve was performed to show the relationship between therapeutic strategies and 30-day survival. Follow-up period was divided into early (0–7 d) and late (8–30 d) mortality to evaluate variables related to death. This division was based on the belief that mortality is highly determined by patients' baseline characteristics and may confuse the effect of potential modifiable factors such as therapeutic measures when assessed at 30 days. A univariate logistic regression model was fitted for each variable to test its relationship with mortality outcomes. Variables clinically relevant and statistically significant ($p < 0.1$) on univariate analysis were considered to build the multivariate regression model. Clinical interventions were maintained in the final model as a fixed variable. Variables that did not improve likelihood ($p < 0.10$) were excluded. Potential confounders of treatment strategies (APACHE II score) were tested. Significant interactions between variables were ruled out. Statistical analyses were performed with Microsoft SPSS-PC+, version 15.0 (SPSS, Chicago, IL).

RESULTS

A total of 773 episodes of candidemia were detected in the CANDIPOP study. Of these, 21 case-patients were excluded because they declined to participate. Within the remaining cohort, 264 (35.1%) occurred in hospitalized patients (> 48 hr) who were admitted to the ICU. Among them, 85 pediatric patients (≤ 18 yr) and 11 candidemias that were already present at ICU admission were excluded. Hence, this report is based on 168 episodes of candidemia identified in 164 patients.

At the time of candidemia, 79 case-patients (47.0%) were admitted in medical-surgical ICUs, 50 (29.8%) in surgical ICUs, and 39 (23.2%) in medical ICUs. The median length of hospitalization before *Candida* BSI was 19 days (IQR, 12–34 d). Ninety-five cases (56.5%) were previously colonized with the same *Candida* species, and 27 of them had multifocal colonization. Baseline characteristics of the study population are outlined in **Table 1**.

Microbiological Findings

There were five episodes where two *Candida* species were simultaneously isolated in the incident blood culture and three episodes where two different species were obtained on

TABLE 1. Characteristics of Patients Who Developed Candidemia and Description of All Episodes of *Candida* Bloodstream Infection Included in the Study

Variable	*n/N* (%)[a]
Patients admitted to ICU (*n* = 164)	
Males	108 (65.9)
Age in years, median (IQR)	63.0 (49.0–74.0)
Acute Physiology and Chronic Health Evaluation II score, median (IQR)	19 (14–25)
No. of days in hospital to candidemia onset, median (IQR)	19 (12–34)
Comorbidities	
Diabetes mellitus	40 (24.4)
Malignancy (active treatment within 1 yr)	33 (20.1)
Chronic obstructive pulmonary disease	17 (10.4)
Transplant recipient	14 (8.5)
Liver cirrhosis	6 (3.7)
HIV infection	4 (2.4)
Episodes of candidemia (*n* = 168)	
Risk factors for candidemia	
Previous antibiotic therapy (1 mo)	164 (97.6)
Central venous catheter	162/166[b] (97.6)
Intubation	120 (71.4)
Renal replacement therapy[c] (before or due to candidemia)	39 (23.2)
Previous surgery (3 mo)	111 (66.1)
Abdominal surgery	60/111 (54.1)
Parenteral nutrition	106 (63.1)
Previous *Candida* colonization	95 (56.5)
Previous hospitalization (3 mo)	67 (39.9)
Neutropenia at candidemia onset (< 1,000 cells/mm^3)	8 (4.8)
Previous corticosteroids (1 mo)[d]	65 (38.7)
Recent antifungal exposure (< 1 mo)	54 (32.1)
Azoles	36 (21.4)
Echinocandins	25 (14.9)
Source of candidemia	
Primary	93 (55.4)
Proven catheter-related	58 (34.5)
Abdominal	10 (6)
Urologic tract	2 (1.2)
Others	5 (3)
Clinical presentation of *Candida* bloodstream infection	
Septic shock or severe sepsis	98 (58.3)
Concomitant bacteremia	35 (20.8)
Initial antifungal therapy	
Echinocandin	84 (50)
Azole	60 (35.7)
Amphotericin B	12 (7.1)
Combination therapy[e]	3 (1.8)
No targeted antifungal treatment[f]	9 (5.4)

IQR = interquartile range.

[a]Values are reported as no./total no. (%) of patients or episodes unless otherwise indicated.

[b]Data regarding the presence of a central venous catheter was missing in two out of 168 cases.

[c]Hemodialysis or hemodiafiltration.

[d]More than 10 mg of systemic methylprednisolone per day (or equivalent) during ≥ 5 d.

[e]Combination therapy of an echinocandin plus azole was used in two cases and combination of amphotericin B plus azole was used in one case.

[f]One patient died while receiving voriconazole treatment due to isolation of *Aspergillus* species from bronchoalveolar lavage.

separate days during the 30-day follow-up period (at 1, 5, and 8 d, respectively). In addition, a bacterial pathogen was isolated in conjunction with *Candida* species in 35 cases (20.8%) (the most common: coagulase-negative staphylococci in 17, gram-negative rods in 6, and anaerobes in 5). Overall, 173 yeast strains were obtained from 168 episodes. *Candida albicans* was the leading agent (90; 52%), followed by *C. parapsilosis* (41; 23.7%), *C. glabrata* (22; 12.7%), *Candida tropicalis* (10; 5.8%), *C. krusei* (7; 4%), *C. guilliermondii* (1; 0.6%), *Candida kefyr* (1; 0.6%), and *C. orthopsilosis* (1; 0.6%). Species distribution varied substantially between areas. *C. albicans* was the causal species in 31.8–64.5% of cases and predominated in Barcelona (64.5%), Madrid (64.4%), and Seville (48.1%). In Bilbao and Valencia, however, *C. parapsilosis* was the most common isolate (45.5% and 35.3%, respectively).

The results of in vitro susceptibility testing are summarized in **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/A858). Overall, 79.2% of *Candida* isolates (137 of 173) were susceptible to fluconazole. Specifically, all *C. albicans* showed fluconazole susceptibility, but 12.2% of *C. parapsilosis* (5 of 41) and 10% of *C. tropicalis* (1 of 10) were intermediate or resistant (minimum inhibitory concentration [MIC] ≥ 4 mg/L). Resistance to anidulafungin was uncommon: 1.1% for *C. albicans* (1 of 90), 4.5% for *C.*

glabrata (1 of 22), and no resistance among *C. tropicalis* and *C. krusei*. However, the MIC_{90} of echinocandins against *C. parapsilosis* (2 mg/L) was higher than those recorded for the most common *Candida* species. All isolates were susceptible to amphotericin B.

Clinical Data and Candidemia Management

Severe sepsis or septic shock was the clinical presentation of candidemia in 98 cases (58.3), and 21 (12.5) required renal replacement therapy (RRT) (hemodialysis or hemodiafiltration) due to infection. Evidence of metastatic candidiasis was found in 9 episodes (5.4%): eight cases of endophthalmitis (one in the course of echocardiography-documented endocarditis and two in the context of concomitant septic thrombophlebitis) and one case of metastatic renal infection in a patient receiving corticosteroids.

Fifty-two cases (31%) were receiving an antifungal agent at candidemia onset (fluconazole in 25, 14.9%; anidulafungin in 11, 6.5%; caspofungin in 8, 4.8%; micafungin in 3, 1.8%; voriconazole in 3, 1.8%; and amphotericin B in 2, 1.2%). In these cases, the median time during which the antifungal drug had been given before positive blood culture was 7 days (IQR, 3–13 d). Interestingly, these episodes were more likely to be caused by *Candida* strains intermediate or resistant to fluconazole than those not exposed to antifungal agents (17 of 52, 32.7% vs 19 of 116, 16.4%; $p = 0.017$). In the remaining cohort, treatment was started after the blood sample was drawn, at a median of 2 days (IQR, 1–3 d). Overall, 159 cases (94.6%) received specific antifungal treatment for candidemia. Antifungal agents administered are shown in Table 1. Echinocandins were the initial antifungal agent most frequently used as a single drug (84 cases, 50%). Nine cases never received targeted antifungal therapy, and eight of them died before blood culture results became available.

With respect to CVC management, the indwelling catheter was investigated for the source of infection in 74.1% of cases (120 of 162), and early CVC removal was performed in 47.5% (77 of 162). Cases needing RRT before or after candidemia and those with severe sepsis or septic shock were less likely to have prompt catheter removal (30.8% vs 52.8%, $p = 0.016$, and 37.5% vs 62.1%, $p = 0.002$, respectively).

Regarding other care processes, follow-up blood samples were obtained in 115 of the 154 patients (74.7%) who survived more than 48 hours. Blood cultures were persistently positive for more than 3 days in 27% (31 of 115).

Outcome and Predictors of Mortality

Cumulative mortality at 7 and 30 days after the first episode of candidemia was 16.5% (27 of 164) and 47% (77 of 164), respectively. Median time from blood sample collection to death was 10 days (IQR, 4.5–19.5 d). The 30-day mortality according to the initiation time of therapeutic measures is shown in **Figure 1**. The Kaplan-Meier survival curves in **Figure 2** show that cases receiving appropriate combined therapy ($n = 59$) within the first 48 hours had a greater likelihood of 30-day survival compared to cases with delayed treatment or no combined intervention therapy ($n = 99$) ($p = 0.024$ by log-rank test).

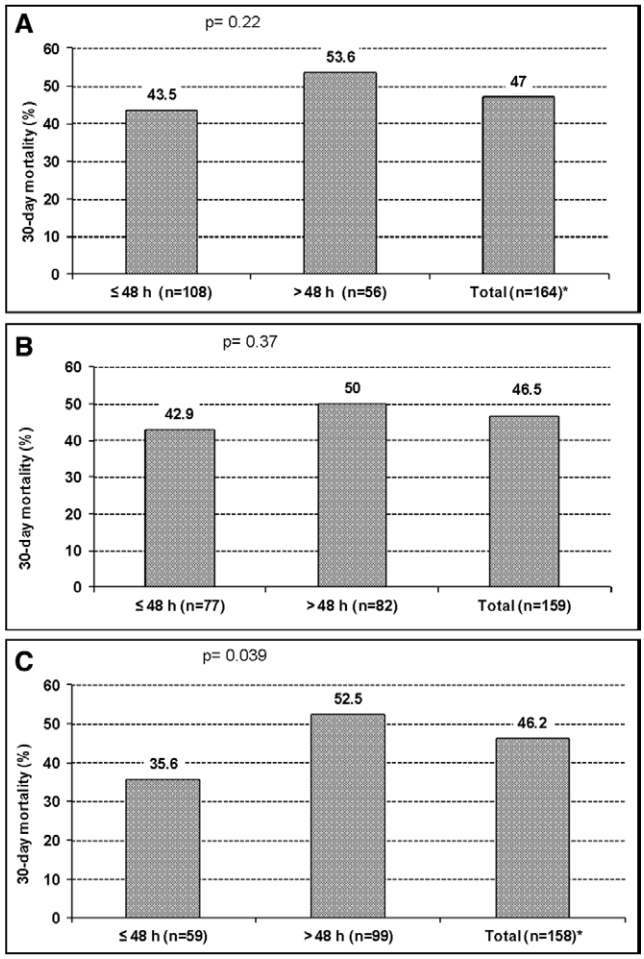

Figure 1. Overall 30-day mortality in relation to time of initiation of adequate antifungal therapy (**A**), time of central venous catheter removal (**B**), and time of initiation of appropriate combined treatment (**C**). *Data regarding time to starting antifungal treatment were missing in one patient.

To better understand the reason for the high mortality rates in ICU patients with *Candida* BSI and to elucidate the impact of therapeutic measures on death, we assessed predictors of mortality at two time points: early (≤ 7 d) and late (8–30 d) mortality. On multivariate analysis and controlling for APACHE II score, combined appropriate treatment (odds ratio [OR], 0.27; 95% CI, 0.08–0.91) and abdominal source (OR, 8.15; 95% CI, 1.75–37.93) were independently associated with early mortality (**Table 2**). Independent risk factors for late mortality were primary source (OR, 2.51; 95% CI, 1.06–5.95), host factors such as age (OR, 1.04; 95% CI, 1.01–1.07), and variables that categorized patients as more seriously ill (intubation and RRT) (**Supplemental Table 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/A859).

DISCUSSION

This is the first population-based description of candidemia specifically dedicated to the critical care setting in Spain, and

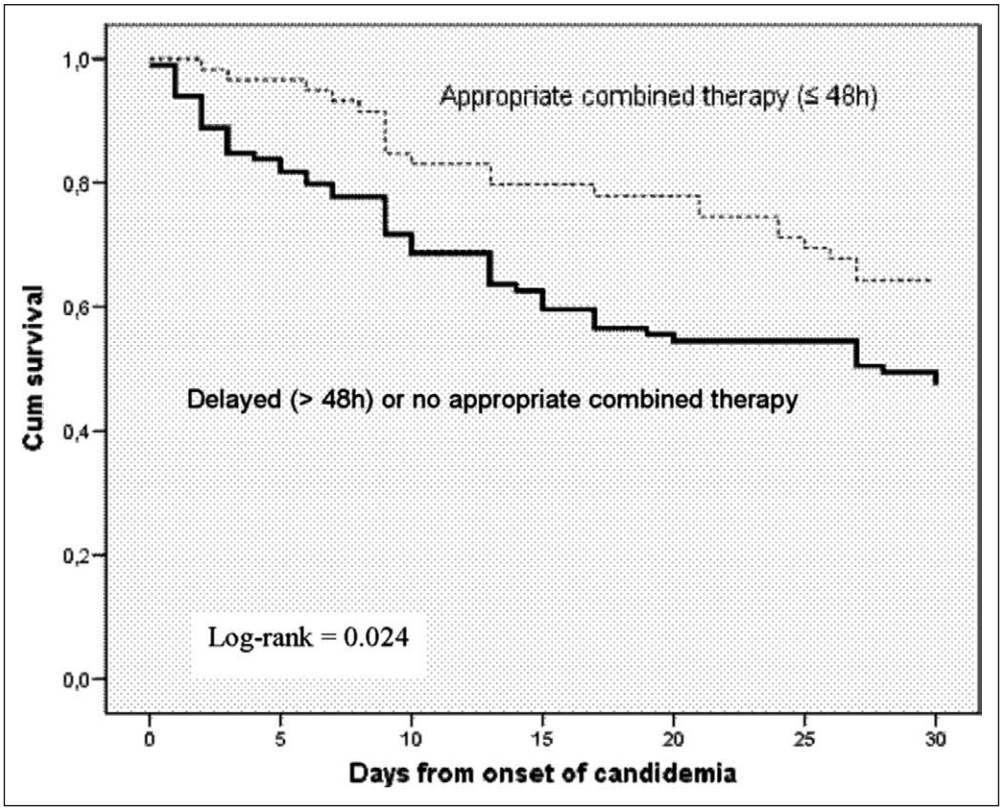

Figure 2. Kaplan-Meier 30-day survival curves according to appropriate combined therapy in the first 48 hr after candidemia diagnosis.

it is performed according to the methods used by Almirante et al (30) in the 2002–2003 Barcelona Candidemia Project. Our study indicates that the considerable mortality associated with *Candida* BSI is related with the severe comorbidities of affected patients and points out that updated epidemiological data are crucial for guiding empirical antifungal treatment.

During the last decade, there has been a shift toward an increasing prevalence of non-*albicans Candida* species, especially in critically ill patients (3, 10, 13). Our results confirm the importance of these microorganisms, which accounted for almost half the isolates in this setting. We observed that *C. parapsilosis* was the most frequent non-*albicans* species in our ICUs (23.7% of isolates), in keeping with the epidemiology described in a previous Spanish multicenter study (31) and Italian ICUs (3, 13). Nonetheless, it contrasts with data from France and the United States, where *C. glabrata* is the second cause of candidemia (8, 10, 11). The predominance of *C. parapsilosis* could be a positive factor, since this species has been associated with a better outcome (32). We believe that the high prevalence of *C. parapsilosis* in our study may be influenced by multiple factors. First, *C. parapsilosis* is commonly related to parenteral nutrition and catheter-related infection due to its capability to adhere to and form biofilms in foreign material. Both risk factors are particularly frequent in ICU patients. Second, although our distribution of *Candida* species better represents the regional epidemiology than series from single centers, further molecular studies would be needed to assess the possibility of institutional outbreaks (12). Lastly, current guidelines recommend empirical use of echinocandins in critically ill patients (33), a fact that may have contributed to increasing their use as first-line agent. Considering the increased frequency of *C. parapsilosis* after caspofungin exposure (34, 35), clinical practice changes could also justify our findings.

Another important finding is the relatively low percentage of *Candida* isolates that were susceptible to fluconazole (79.2%). This was related, in part, to lowering of the new EUCAST breakpoints and classification of *C. glabrata* as intermediate or resistant (24). The impact of decreased susceptibility to fluconazole on clinical outcomes remains uncertain. However, some reports have suggested a potentially increased risk of mortality if fluconazole is underdosed in less susceptible *Candida* isolates (36). This fact, together with the potential rise in fluconazole resistance, must be considered when deciding empirical treatment and supports the recommendation given in the latest European guidelines to use echinocandins as the first choice agent (37). However, for fluconazole-susceptible strains and for *C. parapsilosis*, the preferred treatment is fluconazole, since increasing use of echinocandins may also lead to emergence of resistant isolates (38, 39).

It is a cause of concern that candidemia remains associated with high mortality rates. Our study showed an overall 30-day mortality of 47%, similar to other contemporary reports (3–7). The multivariate model of early mortality highlighted the importance of the severity of illness (APACHE II score) and an abdominal source of infection to predict death, as well as the benefit of therapeutic strategies on outcome. However, the data analysis for late mortality clearly revealed the influence of host-related factors and the need for external support (e.g., intubation and RRT) as determinants of death. These results reinforce the idea that comorbid status at baseline may be strongly involved in the current high mortality rates of candidemia. In fact, previous reports have suggested that infection per se does not seem to be associated with an increase in either ICU- or hospital-attributable mortality (7, 19). To our knowledge, this is the first time that early and late mortality have been described separately in ICU patients with candidemia.

Over the last years, the combination of prompt antifungal therapy and catheter withdrawal has been the cornerstone of treatment for *Candida* BSI (33, 37), and the benefits of this

TABLE 2. Univariate and Multivariate Logistic Regression Analyses of Factors Influencing Early Mortality in Patients With *Candida* Bloodstream Infections in the ICUs

			Univariate Analysis		Multivariate Analysis	
Variable	**Alive (*n* = 137)**	**Died (*n* = 27)**	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Males	88 (64.2)	20 (74.1)	1.59 (0.63–4.03)	0.327		
Age, yr	62.7 (47.3–71.6)	69.6 (55.0–76.0)	1.03 (1.00–1.07)	0.039		
Acute Physiology and Chronic Health Evaluation II	18.0 (13.0–23.0)	23.0 (19.5–29.0)	1.10 (1.04–1.17)	0.001	1.11 (1.04–1.19)	0.002
Comorbidities and risk factors						
Diabetes mellitus	32 (23.4)	8 (29.6)	1.38 (0.55–3.45)	0.489		
Renal replacement therapy	30 (21.9)	8 (29.6)	1.50 (0.60–3.77)	0.386		
Malignancy (≤ 1 yr)	30 (21.9)	3 (11.1)	0.45 (0.13–1.59)	0.211		
Chronic obstructive pulmonary disease	10 (7.3)	7 (25.9)	4.45 (1.52–13.02)	0.007		
Transplant recipient	13 (9.5)	1 (3.7)	0.37 (0.05–2.93)	0.344		
Neutropenia (< 1,000 cell/mm^3)	6 (4.4)	2 (7.4)	1.75 (0.33–9.15)	0.509		
Liver cirrhosis	5 (3.6)	1 (3.7)	1.02 (0.11–9.05)	0.989		
Intubation	98 (71.5)	20 (74.1)	1.14 (0.45–2.90)	0.788		
Prior corticosteroids[a]	53 (38.7)	11 (40.7)	1.09 (0.47–2.53)	0.841		
Antifungal agent at incident blood culture	40 (29.2)	8 (29.6)	1.02 (0.41–2.52)	0.964		
Microbiology						
Candida albicans	75 (54.7)	15 (55.6)	1.03 (0.45–2.37)	0.938		
Candida parapsilosis	38 (27.7)	2 (7.4)	0.21 (0.05–0.92)	0.039	0.21 (0.04–1.04)	0.055
Candida glabrata	15 (10.9)	6 (22.2)	2.32 (0.81–6.67)	0.117		
Candida tropicalis	7 (5.1)	1 (3.7)	0.71 (0.08–6.05)	0.758		
Candida krusei	4 (2.9)	3 (11.1)	4.16 (0.87–19.76)	0.073		
Strains intermediate/ resistant to fluconazole	25 (18.2)	9 (33.3)	2.24 (0.90–5.57)	0.082		
Source of candidemia						
Primary	71 (51.8)	18 (66.7)	1.86 (0.78–4.43)	0.161		
Catheter-related	54 (39.4)	4 (14.8)	0.27 (0.09–0.82)	0.020		
Abdominal	5 (3.6)	5 (18.5)	6.00 (1.60–22.44)	0.008	8.15 (1.75–37.93)	0.008
Urologic	2 (1.5)	0 (–)	–	–		
Clinical severity						
Severe sepsis or septic shock	73 (53.3)	23 (85.2)	5.04 (1.66–15.35)	0.004		
Bacteria in incident culture	32 (23.4)	2 (7.4)	0.26 (0.06–1.17)	0.079		

(*Continued*)

TABLE 2. (*Continued*). Univariate and Multivariate Logistic Regression Analyses of Factors Influencing Early Mortality in Patients With *Candida* Bloodstream Infections in the ICUs

			Univariate Analysis		Multivariate Analysis	
Variable	Alive ($n = 137$)	Died ($n = 27$)	OR (95% CI)	*p*	OR (95% CI)	*p*
Therapeutic measures (≤ 48 hr)						
Central venous catheter removal[b]	69/133 (51.9)	8/26 (30.8)	0.41 (0.17–1.01)	0.054		
Adequate antifungal treatment[c]	92/136 (67.6)	15/27 (55.6)	0.60 (0.26–1.39)	0.230		
Appropriate combined treatment	55/132 (41.7)	4/26 (15.4)	0.26 (0.08–0.78)	0.017	0.27 (0.08–0.91)	0.035

OR = odds ratio. Dashes indicate appropriate combined therapy receiving adequate antifungal medication in addition to central venous catheter removal within the first 48 hr.

[a]More than 10 mg of systemic methylprednisolone per day (or equivalent) during ≥ 5 d.

[b]Considering episodes with central venous catheter as a risk factor for candidemia ($n = 159$).

[c]Data concerning time when adequate antifungal treatment was initiated were missing for one patient.

All data are given as *n*/*N* (%) or median (interquartile range) unless otherwise indicated. Only the first episode of candidemia is included for patients with multiple episodes.

approach were corroborated in our study. At least three recent reports (15, 16, 40) have demonstrated a close relationship between the combination measures and survival, especially in patients with septic shock (40). Nevertheless, catheter withdrawal remains a controversial issue: there are no data from randomized controlled trials, and some reports have failed to confirm the association between early CVC removal and survival (41). The conflicting results may result, in part, from limitations in the study designs and inability to properly control the analysis for severity of illness. However, there are other relevant aspects to consider. Garnacho-Montero et al (16) pointed out that the benefit of CVC withdrawal might be disputable when the source of candidemia is not the catheter. In our study, there were very few secondary candidemias, and we were unable to investigate whether CVC removal provides no benefit in this specific origin of infection. Nucci et al (41) found no clinical benefit of CVC removal in adults treated with an echinocandin or with liposomal amphotericin B, which have in vitro activity against biofilms. Such results have led recently published European guidelines to recommend the use of these antifungals when catheter removal is not possible (37). Based on the expert guidelines and our findings, we believe that CVC withdrawal should be attempted in all ICU patients. There is, however, sufficient evidence in the literature to support the strategy of early administration of antifungal therapy in patients with invasive candidiasis (42–45). In fact, several score systems and serum biomarkers (e.g., *Candida* score, β-D-glucan) (46) have been evaluated to reduce delays in treatment. Nonetheless, the potential interest of preemptive therapy was not the objective of our study.

Some limitations of this study should be mentioned. First, although this multicenter study includes five of the largest cities in Spain and is probably representative of the overall spectrum of ICU patients in our country, our epidemiology cannot be extrapolated to all settings. Second, patients who died before candidemia was diagnosed could not be excluded from the analysis of early mortality because sample size limited the ability to perform an accurate statistical evaluation. Although this might have introduced a bias favoring the benefit of therapeutic measures, the multivariate model was adjusted for potential outcome confounders, a fact that lends strength to the results. Finally, the frequency of *Candida* species colonization was probably underestimated because screening surveillance cultures were not systematically performed.

CONCLUSIONS

The present study confirms the high prevalence of non-*albicans Candida* species in ICU patients (nearly half of all isolates in our setting) and the presence of *C. parapsilosis* as the second most common species in Spain. A total of 20.8% of isolates were nonsusceptible to fluconazole and this finding should be taken into account when deciding empirical treatment. Thirty-day mortality remained high (47%), but late mortality was mainly related with host factors indicating the importance of comorbidities on death. Early mortality may be decreased with strict adherence to guidelines.

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