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Propensity Score Analysis of the Role of Initial Antifungal Therapy in the Outcome of *Candida glabrata* Bloodstream Infections

M. Puig-Asensio,[a] M. Fernández-Ruiz,[b] J. M. Aguado,[b] P. Merino,[c] D. Lora-Pablos,[d,e] J. Guinea,[f] P. Martín-Dávila,[g] M. Cuenca-Estrella,[h] B. Almirante,[a] on behalf of the CANDIPOP Project, GEIH-GEMICOMED (SEIMC), and REIPI

Infectious Diseases Department, Hospital Universitari Vall d'Hebron, Medicine Department, Universitat Autònoma de Barcelona, Barcelona, Spain[a]; Unit of Infectious Diseases, Hospital Universitario 12 de Octubre, Instituto de Investigación Hospital 12 de Octubre (i+12), Medicine Department, Universidad Complutense, Madrid, Spain[b]; Clinical Microbiology Department, Hospital Universitario Clínico San Carlos, Madrid, Spain[c]; Clinical Research Unit, Instituto de Investigación Hospital 12 de Octubre (i+12), Madrid, Spain[d]; CIBER de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain[e]; Clinical Microbiology and Infectious Diseases Department, Hospital General Universitario Gregorio Marañón, Universidad Complutense de Madrid, Madrid, Spain[f]; Infectious Diseases Department, Hospital Ramón y Cajal, Instituto Ramón y Cajal de Investigaciones Sanitarias (IRYCIS), Madrid, Spain[g]; Department of Mycology, Spanish National Centre for Microbiology, Instituto de Salud Carlos III, Madrid, Spain[h]

Candida glabrata **isolates have reduced *in vitro* susceptibility to azoles, which raises concerns about the clinical effectiveness of fluconazole for treating bloodstream infection (BSI) by this *Candida* species. We aimed to evaluate whether the choice of initial antifungal treatment (fluconazole versus echinocandins or liposomal amphotericin B [L-AmB]-based regimens) has an impact on the outcome of *C. glabrata* BSI. We analyzed data from a prospective, multicenter, population-based surveillance program on candidemia conducted in 5 metropolitan areas of Spain (May 2010 to April 2011). Adult patients with an episode of *C. glabrata* BSI were included. The main outcomes were 14-day mortality and treatment failure (14-day mortality and/or persistent *C. glabrata* BSI for ≥48 h despite antifungal initiation). The impact of using fluconazole as initial antifungal treatment on the patients' prognosis was assessed by logistic regression analysis with the addition of a propensity score approach. A total of 94 patients with *C. glabrata* BSI were identified. Of these, 34 had received fluconazole and 35 had received an echinocandin/L-AmB-based regimen. Patients in the echinocandin/L-AmB group had poorer baseline clinical status than did those in the fluconazole group. Patients in the fluconazole group were more frequently (55.9% versus 28.6%) and much earlier (median time, 3 versus 7 days) switched to another antifungal regimen. Overall, 14-day mortality was 13% (9/69) and treatment failure 34.8% (24/69), with no significant differences between the groups. On multivariate analysis, after adjusting for baseline characteristics by propensity score, fluconazole use was not associated with an unfavorable evolution (adjusted odds ratio [OR] for 14-day mortality, 1.16, with 95% confidence interval [CI] of 0.22 to 6.17; adjusted OR for treatment failure, 0.83, with 95% CI of 0.27 to 2.61). In conclusion, initial fluconazole treatment was not associated with a poorer outcome than that obtained with echinocandins/L-AmB regimens in patients with *C. glabrata* BSI. (This study has been registered at ClinicalTrials.gov under registration no. NCT01236261.)**

Candida glabrata has emerged as one of the most common non-*albicans Candida* species causing invasive candidiasis. The incidence of this infection is increasing, particularly in the United States, Canada, and Northern Europe, where *C. glabrata* accounts for 13% to 29% of all episodes of *Candida* bloodstream infection (BSI) (1–8).

The choice of optimal antifungal therapy for treating these patients and, particularly, whether fluconazole use is appropriate remain uncertain. According to current microbiological criteria, *C. glabrata* wild-type strains are considered intermediate or susceptible dose dependent to fluconazole, which means that prescribing fluconazole without confirmation of isolate susceptibility would not be recommended. Based on this evidence, the latest European and American guidelines have relegated the use of fluconazole to a step-down strategy for managing *C. glabrata* infection, favoring echinocandins as first-line empirical therapy (9, 10). Nonetheless, evidence from observational studies suggests that the maximum fluconazole dose (800 mg/day, or an amount equivalent to 12 mg/kg of body weight/day adjusted for renal failure) may achieve clinical success in infections caused by *C. glabrata* isolates with MIC values of ≤32 mg/liter (11).

Clinical efficacy analyses related to the choice of initial antifungal drug have been rarely performed in recent series of patients with *C. glabrata* infection (12). Thus, the aim of this study was to analyze the impact of initial antifungal treatment on the outcome of *C. glabrata* BSI and to determine whether initial use of fluconazole is associated with a poorer outcome than that obtained with echinocandin/liposomal amphotericin B (L-AmB)-based regimens.

MATERIALS AND METHODS

Study design, setting, and patients. The CANDIPOP study (ClinicalTrials.gov number NCT01236261) is a prospective, multicenter, population-based candidemia surveillance program (29 hospitals from 5 metro-

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Address correspondence to B. Almirante, balmirante@vhebron.net.

M.P.-A. and M.F.-R. contributed equally to the manuscript.

politan areas) conducted in Spain between May 2010 and April 2011. Complete details on the study design and its main results have been published elsewhere (13). Briefly, blood cultures positive for *Candida* spp. were identified by the microbiology laboratories of the participating hospitals and reported to regional study coordinators, who obtained clinical data from the patients' medical records using a standardized case report form. Pertinent demographic, clinical, treatment, and 30-day follow-up data were compiled.

The choice of antifungal drug used and the timing of follow-up blood cultures to confirm candidemia clearance were left to the discretion of the attending physicians. Written informed consent was obtained from all patients, according to the requisites of the local institutional review boards.

The present report includes adult patients (≥16 years of age) diagnosed with *C. glabrata* BSI. Episodes in which two different *Candida* species were simultaneously identified were excluded. Only the first episode of *C. glabrata* BSI per patient was included in the analysis. This analysis was reported in accordance with the STROBE recommendations (14).

Microbiology. Isolates were forwarded to the Spanish National Microbiology Centre (Instituto de Salud Carlos III, Majadahonda, Madrid, Spain), where *Candida* species were definitively identified by sequencing the internal transcribed spacer 1 (ITS1) and ITS2 regions from ribosomal DNA (rDNA). Antifungal susceptibility testing was carried out according to the EUCAST (E.Def7.1 and E.Def7.2) (15, 16) and CLSI M27-A3 (17) broth microdilution methods. The second procedure was performed at Hospital General Universitario Gregorio Marañón (Madrid, Spain). Both these methods were used because previous microbiological data from the CANDIPOP study showed that the CLSI method offers higher MIC values for fluconazole in our *C. glabrata* strains than the EUCAST method (18). MICs of azoles and echinocandins were obtained after 24 h of incubation at 35°C and were defined as the antifungal drug concentration producing 50% growth inhibition relative to that of drug-free control growth. MICs by the CLSI method were additionally read at 48 h to avoid misclassification of borderline-resistant isolates because of a MIC shift (19). The CLSI (20) and EUCAST species-specific clinical breakpoints, published in the EUCAST website (http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/AFST/Clinical_breakpoints/Antifungal_breakpoints_v_8.0_November_2015.pdf), were applied to categorize isolate susceptibilities. The presence of *FKS1* or *FKS2* gene mutations was investigated in isolates showing phenotypic resistance to one or more echinocandins. The hotspot 1 and 2 regions were amplified as previously described (18).

Outcomes and definitions. We aimed to evaluate potential differences in therapy response between patients initially treated with fluconazole (fluconazole group) and those treated with an echinocandin and/or L-AmB (echinocandin/L-AmB group). The primary study outcome was 14-day all-cause mortality, starting from the time of the first positive blood culture. The secondary outcome was treatment failure, defined as the composite variable of 14-day all-cause mortality and/or persistent *C. glabrata* BSI for ≥48 h despite antifungal initiation. To be included in the evaluation of these outcomes, patients had to receive at least 2 consecutive days of therapy with either fluconazole or an echinocandin and/or L-AmB as initial antifungal therapy after blood culture collection (except for patients who died within the first 48 h, who had to receive at least 1 complete day of therapy for inclusion). As an approach to study the pharmacokinetic/pharmacodynamic (PK/PD) parameters that best correlated with fluconazole efficacy, we also investigated potential correlations between the patient's prognosis and the fluconazole daily dose/MIC ratio as a surrogate marker of the area under the concentration-time curve/MIC ratio (11).

Episodes occurring after 2 days of hospitalization were considered hospital acquired. Breakthrough candidemia was defined as development of *C. glabrata* BSI in patients who had been receiving antifungal drugs for >3 days. The criteria for proven catheter-related candidemia have been described elsewhere (21). Secondary foci required isolation of the same *Candida* species in the presumed source of infection. Adequate source control included removal of all central venous catheters (CVC) within the first 24 h after initiation of antifungal treatment or drainage of intra-abdominal abscesses if a collection was present. Episodes occurring in patients without an intravascular device or potentially drainable source were considered as having adequate source control. On the day of blood sample extraction, the Pitt bacteremia score (22) and the acute physiology and chronic health evaluation II (APACHE II) score for intensive care unit (ICU) patients (23) were recorded to estimate disease severity. In detail, the Pitt bacteremia score was calculated based on oral temperature (35.1 to 36.0°C or 39.0 to 39.9°C, 1 point; ≤35 or ≥40°C, 2 points), blood pressure (hypotension, 2 points), mental status (disorientation, 1 point; stupor, 2 points; coma, 4 points), respiratory status (mechanical ventilation, 2 points), and cardiac status (cardiac arrest, 4 points).

Statistical analysis. Quantitative variables are reported as the median (interquartile range [IQR]) and qualitative variables as absolute numbers and relative frequencies. The chi-square test or Fisher's exact test was used for comparisons of categorical variables, and the Student *t* test was used for continuous variables. The Mann-Whitney *U* test was applied in variables with a nonnormal distribution.

Determinants of 14-day mortality and treatment failure were analyzed by logistic regression analysis. Given the limited sample size and imbalances between the baseline characteristics of the treatment groups, a propensity score-based approach was used to minimize the risk of confounding by indication. The probability of receiving fluconazole or an echinocandin/L-AmB was estimated using a penalized logistic regression model that included variables with *P* values of <0.2 in the univariate analysis. Specifically, the full model was developed by using a penalized maximum likelihood estimation to directly correct for overfitting (i.e., a small data set with a large number of candidate predictors in relation to the number of events). It was further simplified by decreasing the number of predictors based on recommendations in the related literature (24, 25). Ultimately, 4 variables were included in the final model (age, ICU admission, immunosuppressive therapy, and prior surgery). The propensity score model obtained showed an area under the receiving operating characteristic (ROC) curve of 0.795, thus suggesting good predictive ability. The propensity score was then entered as a covariate into the multivariate models analyzing the primary and secondary outcome measures to adjust for the effects of confounding factors (26, 27). In addition, the center effect was controlled by performing a sensitivity analysis on outcome variables (14-day mortality and treatment failure) by using multilevel models according to the participating center. Because the APACHE II score was not available for all patients, a composite variable reflecting disease severity was created to adjust for this potential host confounder of mortality. Patients were classified as having *high severity of illness* when they met any of the following criteria: APACHE II score of ≥15, Pitt score of ≥3, or severe renal failure, defined as dependence on renal replacement therapy at candidemia onset. Statistical analyses were performed with Microsoft SPSS-PC+, version 15.0 (SPSS, Chicago, IL, USA), and R software package, version 3.0.3 (R Project for Statistical Computing, http://www.r-project.org/).

RESULTS

In total, 773 episodes of *Candida* BSI were identified during the 1-year study period. Twenty-one case-patients declined to participate, resulting in 752 evaluable episodes. Of these, 103 (13.4%) were caused by *C. glabrata*, yielding an annual incidence of 1.08 episodes per 100,000 inhabitants, 0.56 episodes per 1,000 admissions, and 0.93 episodes per 10,000 patient-days.

Patient characteristics of the entire cohort. Among the 103 episodes of *C. glabrata* BSI, 94 different patients-episodes met the inclusion criteria and were ultimately analyzed (Fig. 1). The median age of the patients was 71.8 (IQR, 59.1 to 79.2) years, and 24 patients (25.5%) were hospitalized in the ICU at the time of BSI onset. The most common comorbidities and predisposing risk

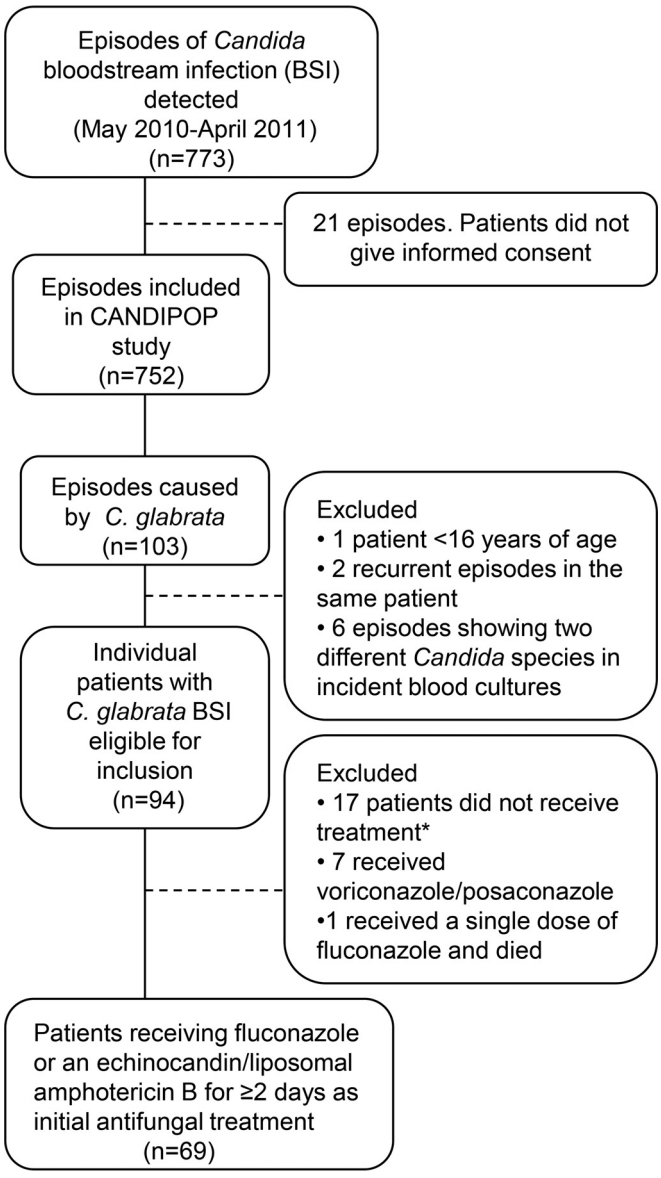

FIG 1 Flow chart of patients included in the study. *Reasons for not receiving antifungal treatment: death within the first 72 hours before knowledge of positive blood culture ($n = 7$), severe baseline medical conditions leading to limitation of treatment ($n = 7$), discharge from the emergency department before knowledge of positive blood culture ($n = 1$), and unknown reasons ($n = 2$).

factors for candidemia were the presence of malignancy in 41 (43.6%), CVC placement in 63 (67%), and prior gastrointestinal surgery in 34 (36.2%) patients.

Treatment groups. Seventy-seven (81.9%) patients received antifungal therapy for the episode, and 69 were eligible for the clinical outcome evaluation: 34 (49.3%) in the fluconazole group and 35 (50.7%) in the echinocandin and/or L-AmB group (Fig. 1).

In the fluconazole group, 1 patient (2.9%) received 200 mg/day, 28 patients (82.4%) received 400 mg/day, and 5 patients (14.7%) received 800 mg/day (or equivalent doses after adjusting by renal function). In the echinocandin/L-AmB group, 30 patients (85.7%) received echinocandins, 4 (11.4%) L-AmB, and 1 (2.9%) a combination of caspofungin and L-AmB. All antifungal agents were dosed according to universally accepted dosing regimens (9, 10).

Demographic and clinical characteristics of the patients by treatment group are shown in Table 1. Compared to fluconazole-treated patients, patients in the echinocandin/L-AmB group were more likely to be receiving immunosuppressive therapy (25.7% versus 5.9%, $P = 0.024$), be admitted to the ICU at diagnosis (37.1% versus 17.6%, $P = 0.070$), or have a CVC in place (82.9% versus 64.7%, $P = 0.086$). There were no significant differences in the source of candidemia, the median time to receive antifungal therapy, or the rate of adequate source control. However, a higher percentage of patients in the echinocandin/L-AmB had follow-up blood cultures after starting antifungal treatment (91.4% [32/35] versus 58.8% [20/34], $P = 0.002$).

Duration of initial antifungal regimen. Median duration of the initial antifungal regimen was shorter in the fluconazole group than in the echinocandin/L-AmB group (5 days [IQR, 3 to 14] versus 13 days [IQR, 7 to 22], $P = 0.001$). Nineteen patients (55.9%) in the fluconazole group were switched to other antifungal regimens after a median of 3 days (range, 2 to 20): 17 to echinocandins, 1 to L-AmB, and 1 to voriconazole. Ten patients (28.6%) in the echinocandin/L-AmB group were transitioned to fluconazole (8 patients) or voriconazole (2 patients) after a median of 7 days (range, 3 to 39). None of the aforementioned antifungal changes were due to drug-related adverse events.

Antifungal susceptibility testing. Antifungal susceptibility results for all 94 isolates are shown in Table 2. In the subset of 69 episodes evaluable for clinical outcome, fluconazole resistance was found in 5.8% of isolates according to the EUCAST method and in 11.6% by the CLSI procedure after 24 h of incubation. Regarding the CLSI technique, identical resistance rates were found when MICs were additionally determined at 48 h. The EUCAST and 24-h CLSI methods agreed on identification of a single isolate resistant to all echinocandins in the overall cohort. It should be noted, however, that EUCAST has not yet established clinical breakpoints for caspofungin; hence, isolates that were susceptible to anidulafungin as well as micafungin were considered susceptible to caspofungin. The single echinocandin-resistant strain was harboring a deletion of the F659 amino acid in the *FKS2* gene (18). All isolates were susceptible to L-AmB, and none of the fluconazole-resistant isolates were also resistant to any echinocandin.

Outcomes and fluconazole pharmacodynamics. Overall, 14-day mortality was 13% (9/69) and treatment failure 34.8% (24/69), with no significant differences between the groups (Table 1). None of the patients had evidence of hematogenous dissemination of *C. glabrata* (e.g., endophthalmitis, endocarditis) within 30 days after the first positive blood culture.

To explore whether patients who had an early switch from fluconazole to another antifungal regimen may have benefitted from this change, the 11 patients who received a short duration of initial fluconazole treatment (≤3 days) were compared with those who were switched later or those who did not change the initial fluconazole therapy ($n = 23$). In this analysis, no differences in 14-day mortality (9.1% [1/11] versus 13% [3/23], $P = 1$) or treatment failure (27.3% [3/11] versus 34.8% [8/23], $P = 1$) were found between the two cohorts.

Because of the low 14-day mortality (4 of 34, 11.8%) and treatment failure (11 of 34, 32.4%) rates in the fluconazole group, we

TABLE 1 Comparison between patients who received fluconazole or an echinocandin and/or liposomal amphotericin B as initial treatment for *C. glabrata* bloodstream infection[a]

Variable	Initial antifungal therapy		*P* value
	Fluconazole ($n = 34$)	Echinocandin and/or L-amphotericin B ($n = 35$)	
Demographics			
Age (yr)	75.4 (57.8–82.3)	65.6 (55.2–73.2)	0.118
Male sex	20 (58.8)	22 (62.9)	0.731
Hospital-acquired candidemia	27 (79.4)	29 (82.9)	0.714
Time (days) in hospital to candidemia onset	18 (11–35)	25 (14.5–38.5)	0.409
In ICU at diagnosis	6 (17.6)	13 (37.1)	0.070
APACHE II score	21.5 (14.8–25)	19 (14–25)	0.970
Comorbidities			
Charlson index score	2 (1–4)	2 (1–3)	0.407
Hematologic malignancy	0 (0)	4 (11.4)	0.114
Diabetes mellitus	9 (26.5)	11 (31.4)	0.650
Chronic renal failure	4 (11.8)	5 (14.3)	1.000
Renal replacement therapy	2 (5.9)	3 (8.6)	1.000
HIV infection	0 (0)	2 (5.7)	0.493
Liver cirrhosis	1 (2.9)	1 (2.9)	1.000
Predisposing risk factor			
Central venous catheter	22 (64.7)	29 (82.9)	0.086
Previous surgery (3 mo)	22 (64.7)	17 (48.6)	0.176
Gastrointestinal surgery	18 (52.9)	12 (34.3)	0.118
Total parenteral nutrition	14 (41.2)	19 (54.3)	0.276
Immunosuppressive treatment[e]	2 (5.9)	9 (25.7)	0.024
Prior antibiotic therapy (1 mo)	31 (91.2)	34 (97.1)	0.356
Prior azole exposure (1 mo)	6 (17.6)	6/34 (17.6)	1.000
Breakthrough candidemia	3 (8.8)	7/34 (20.6)	0.171
Clinical data at candidemia onset			
Septic shock	5 (14.7)	7 (20)	0.562
Intubation	5 (14.7)	9 (25.7)	0.256
Neutropenia ($<$500 cells/mm^3)	0 (0)	1 (2.9)	1.000
Pitt score	1 (0–4)	1 (0–4)	0.902
Bacteria in incident blood culture	5 (14.7)	6 (17.1)	0.782
Source of infection			
Primary	18 (52.9)	16 (45.7)	0.548
Catheter related	10 (29.4)	8 (22.9)	0.535
Abdominal	2 (5.9)	5 (14.3)	0.428
Urologic	4 (11.8)	4 (11.4)	1.000
Others	0 (0)	2 (5.7)	0.493
Therapeutic strategies			
Time (days) to receiving antifungal therapy[b]	2 (0–3)	2 (1–3)	0.391
CVC removal ($\leq$48h)[c]	13/22 (59.1)	17/29 (58.6)	0.973
Adequate source control	28 (82.4)	27 (77.1)	0.591
Outcomes			
14-day all-cause mortality	4 (11.8)	5 (14.3)	1.000
Persistent candidemia[d]	7/20 (35)	10/32 (31.3)	0.779
Treatment failure at 14 days	11 (32.4)	13 (37.1)	0.676

[a] Unless noted otherwise, values represent the absolute no. (%) of patients in the category; continuous variables are expressed as the median (interquartile range). IQR, interquartile range; ICU, intensive care unit; CVC, central venous catheter.
[b] Data missing for 1 patient.
[c] Considering patients with central venous catheter as a risk factor for candidemia ($n = 51$).
[d] Follow-up blood cultures were obtained after start of antifungal treatment in 52 of 69 patients (74.5%) at a median of 3.5 days (IQR, 2 to 7), with no significant differences between the groups.
[e] Includes corticosteroid therapy equivalent to $\geq$10 mg methylprednisolone per day for at least 5 days, chemotherapy, and other immunosuppressive drugs.

TABLE 2 Antifungal susceptibility testing of 94 *C. glabrata* isolates by CLSI and EUCAST broth microdilution methods after 24 h of incubation[a]

Antifungal agent	EUCAST method results				CLSI method results			
	GM	MIC_{90} (mg/liter)	MIC range (mg/liter)	Resistance rate, *n*/*N* (%)	GM	MIC_{90} (mg/liter)	MIC range (mg/liter)	Resistance rate, *n*/*N* (%)
Anidulafungin	0.031	0.03	0.03–0.5	1 (1.1)	0.032	0.06	0.007–1	1 (1.1)
Caspofungin	0.44	1	0.25–1	NA	0.15	0.25	0.007 to >2	1 (1.1)
Micafungin	0.031	0.03	0.03–1	1 (1.1)	0.016	0.03	0.007–2	1 (1.1)
Fluconazole	3.19	16	0. 5 to >64	6 (6.4)	10.26	64	1 to >64	10 (10.6)
Voriconazole	0.13	0.5	0.015–8	NA	0.12	0.5	0.003 to >2	NA

[a] Abbreviations: GM, geometric mean; MIC_{90}, 90% MIC; NA, not applicable; *n*/*N*, ratio of resistant isolates to total isolates.

did not perform correlation analyses between fluconazole MIC values or fluconazole pharmacodynamic parameters (fluconazole dose/MIC ratio) and outcomes. However, 29 of the 34 patients (85.3%) had a daily fluconazole dose/24-h CLSI MIC ratio of ≥25, which is a reported predictor of treatment success (11). Of note, 2 patients with fluconazole-resistant isolates survived despite receiving inadequate initial treatment (400 mg of fluconazole/day or a dose/MIC ratio of 3.125 assuming an average weight of 70 kg). These patients had prompt source control, were not admitted to the ICU, and were not categorized as having high severity of illness at presentation.

Predictors of mortality and clinical failure. On univariate analysis, several host- and infection-related factors were associated with 14-day mortality and treatment failure (Table 3). We were unable to construct a single multivariate model including all potential confounders of treatment outcome (e.g., disease severity, infection source, and source control). That analysis would have overfitted the model with an excessive number of variables compared to the number of events (9 deaths and 24 treatment failures). As an alternative, we created a number of different multivariate models in which only one covariate was added at a time to fluconazole use and the propensity score. After adjusting the model for baseline characteristics with the propensity score, use of fluconazole or an echinocandin/L-AmB as initial antifungal therapy was not significantly related to the risk of death or response to treatment (adjusted OR for 14-day mortality, 1.16, with 95% CI of 0.22 to 6.17; adjusted OR for treatment failure, 0.83, with 95% CI of 0.27 to 2.61). Further multilevel adjustment for participating center did not meaningfully modify these results (Fig. 2).

In addition, because current guidelines consider voriconazole as an alternative agent for treating candidemia and all triazole classes have decreased activity against *C. glabrata*, we repeated the same analyses comparing patients who received any triazole as initial antifungal therapy (fluconazole [34 patients], voriconazole [6 patients], or posaconazole [1 patient]) with those who received an echinocandin-based/L-AmB regimen (35 patients). Again, no association was found between the initial antifungal treatment and either outcome measure (adjusted OR for 14-day mortality, 1.04, with 95% CI of 0.21 to 6.15; adjusted OR for treatment failure, 0.98, with 95% CI of 0.36 to 2.71).

DISCUSSION

In this observational study, the choice of initial antifungal agent (fluconazole versus echinocandin/L-AmB-based regimens) had no apparent impact on the risk of 14-day mortality or treatment failure in patients with *C. glabrata* BSI. Although patients initially receiving echinocandin/L-AmB were in poorer baseline condition than those receiving fluconazole, there were no significant differences in the outcomes of the two groups after adjusting by the propensity score and disease severity. These findings are clinically relevant. Fluconazole is still the most commonly prescribed antifungal in hemodynamically stable patients who are not hospitalized in ICUs (13, 28), and published data on its effectiveness for *C. glabrata* BSI treatment are scarce and a matter of debate. The results found here do not support initial use of fluconazole for all cases of candidemia and in all settings, but rather, they suggest that fluconazole may be a valid option as initial treatment for less severely ill patients who have not been exposed to azoles, even when *C. glabrata* cannot be ruled out. This clinical approach may decrease overuse of echinocandins as first-line agents, thereby reducing hospital expenditure and limiting the emerging risk of echinocandin-resistant strains (29).

To date, only one randomized clinical trial has compared fluconazole at a standard dose of 400 mg/day and anidulafungin for invasive candidiasis (30). The treatment response in the echinocandin arm was not inferior to that of fluconazole. However, this study was not designed to assess treatment differences between subgroups of *Candida* species, and only 38 patients with *C. glabrata* were evaluated for overall treatment response; hence, definitive conclusions could not be drawn for this species. Two more recent studies that focused on *C. glabrata* BSI demonstrated that echinocandin therapy was associated with greater treatment success but not with increased survival (12, 31). The first of these, a retrospective observational study by Eschenauer et al. found no differences in 28-day mortality between patients with *C. glabrata* BSI initially treated with fluconazole for ≥5 days and patients receiving echinocandins (12). Nonetheless, fluconazole tended to be less effective in the ICU population, thus supporting preferred use of echinocandins in more severely ill patients. Similarly, a patient level quantitative review of randomized clinical trials found no influence of antifungal therapy on 30-day mortality when the subgroup of 104 episodes of *C. glabrata* was analyzed (31). Notwithstanding this, both investigations differ from our results in showing that echinocandins were predictors of treatment success. It is possible that the lower frequency of blood sampling in our fluconazole group may have influenced the evaluation of treatment response and limited the capacity to detect real differences in microbiological eradication between treatment groups. However, our data lend support to previous studies that have also failed to demonstrate an association between antifungal choice and mortality in *C. glabrata* BSI.

Another matter under discussion is the optimal fluconazole dosing for *C. glabrata* infection. Given the decreased susceptibility of *C. glabrata* to fluconazole, current guidelines recommend the

TABLE 3 Univariate logistic regression analyses of prognostic factors for 14-day all-cause mortality and treatment failure in patients with *C. glabrata* bloodstream infection receiving fluconazole or echinocandin/liposomal-amphotericin B-based regimens as initial treatment[a]

	Mortality (primary outcome)				Treatment failure (secondary outcome)			
Variable	Alive ($n = 60$)	Died ($n = 9$)	OR (95% CI)	*P* value	Success ($n = 45$)	Failure ($n = 24$)	OR (95% CI)	*P* value
Age (yr)	68.8 (51.4–77.2)	78.0 (64.9–83.5)	1.05 (0.99–1.12)	0.088	70.6 (51.9–78.7)	69.9 (63.0–77.9)	1.01 (0.98–1.03)	0.749
Male sex	36 (60)	6 (66. 7)	1.33 (0.30–5.85)	0.703	26 (57.8)	16 (66.7)	1.46 (0.52–4.11)	0.472
Comorbidities and risk factors								
Charlson index score	2 (1–4)	2 (1–3)	0.77 (0.49–1.20)	0.247	2 (1–4)	2 (1–3)	0.83 (0.62–1.10)	0.190
Malignancy (≤1 yr)	30 (50)	0 (0)			22 (48.9)	8 (33.3)	0.52 (0.19–1.47)	0.217
Immunosuppressive treatment	11 (18.3)	0 (0)			10 (22.2)	1 (4.2)	0.15 (0.02–1.27)	0.082
Neutropenia (<500 cells/mm^3)	1 (1.7)	0 (0)			1 (2.2)	0 (0)		
Gastrointestinal surgery	26 (43.3)	4 (44.4)	1.05 (0.26–4.29)	0.950	18 (40)	12 (50)	1.5 (0.55–4.07)	0.426
Prior RRT	2 (3.3)	3 (33.3)	14.5 (2.01–104.68)	0.008	1 (2.2)	3 (12.5)	8.8 (0.92–83.84)	0.059
Intubation	9 (15)	5 (55.6)	7.08 (1.59–31.54)	0.010	5 (11.1)	9 (37.5)	4.80 (1.38–16.65)	0.013
Antifungal agent at blood culture collection	10/59 (16.9)	4 (55.6)	6.13 (1.39–26.91)	0.016	7/44 (15.9)	8 (33.3)	2.64 (0.82–8.53)	0.104
Source of infection								
Primary	28 (46.7)	6 (66.7)	2.29 (0.52–10.00)	0.272	22 (48.9)	12 (50)	1.05 (0.39–2.82)	0.930
Catheter related	18 (30)	0 (0)			13 (28.9)	5 (20.8)	0.65 (0.20–2.10)	0.470
Abdominal	4 (6.7)	3 (33.3)	7.00 (1.26–38.99)	0.026	2 (4.4)	5 (20.8)	5.66 (1.01–31.80)	0.049
Urologic	8 (13.3)	0 (0)			7 (15.6)	1 (4.2)	0.24 (0.03–2.04)	0.190
Others	2 (3.3)	0 (0)			1 (2.2)	1 (4.2)	1.91 (0.11–32.01)	0.652
Clinical data at candidemia onset								
High severity of illness	20 (33.3)	8 (88.9)	16.0 (1.87–136.95)	0.011	16 (35.6)	12 (50)	1.81 (0.66–4.96)	0.247
Septic shock	8 (13.3)	4 (44.4)	5.20 (1.15–23.56)	0.032	7 (15.6)	5 (20.8)	1.43 (0.40–5.10)	0.583
Therapeutic strategies								
Fluconazole	30 (50)	4 (44.4)	0.80 (0.20–3.27)	0.756	23 (51.1)	11 (45.8)	0.81 (0.30–2.19)	0.676
Echinocandins-L-AmB	30 (50)	5 (55.6)	1.25 (0.31–5.11)	0.756	22 (48.9)	13 (54.2)	1.24 (0.46–3.34)	0.676
CVC removed within 24 h after[b] starting antifungal treatment	31/44 (70.5)	2/7 (28.6)	0.168 (0.03–0.98)	0.047	24/32 (75)	9/19 (47.4)	0.30 (0.09–1.00)	0.050
Adequate source control	49 (81.7)	6 (66.7)	0.45 (0.10–2.08)	0.306	39 (86.7)	16 (66.7)	0.31 (0.09–1.03)	0.056
Time (days) to receiving antifungal therapy	2 (1–3)	0 (0–3)	0.75 (0.46–1.22)	0.248	2 (1–3)	1 (0–3)	0.81 (0.59–1.12)	0.197

[a] Unless noted otherwise, values represent the absolute no. (%) of patients in the category; continuous variables are expressed as the median (interquartile range). Abbreviations: IQR, interquartile range; RRT, renal replacement therapy; CVC, central venous catheter.

[b] Considering patients with CVC as a risk factor for candidemia ($n = 51$).

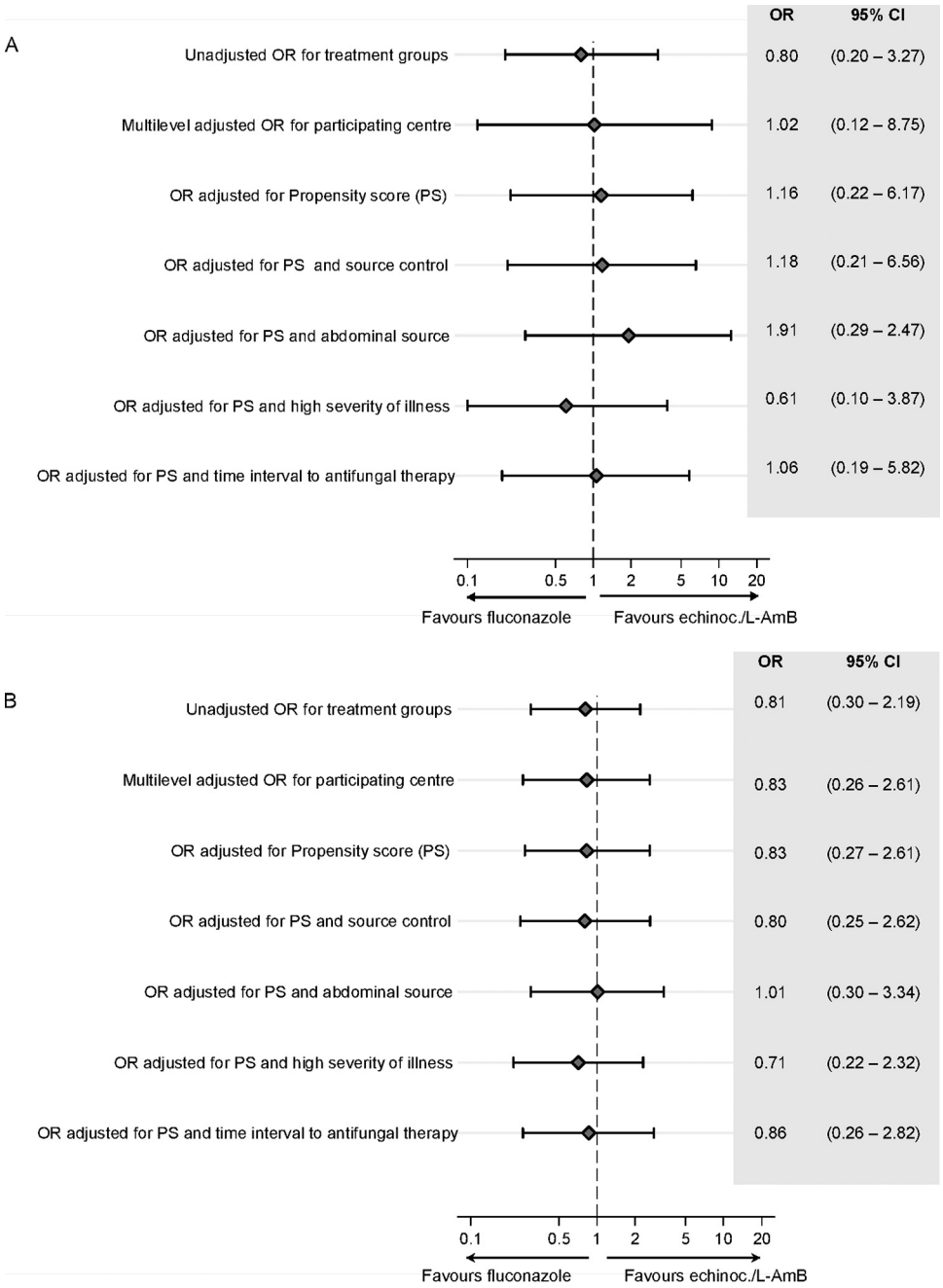

FIG 2 Adjusted odds ratios for 14-day mortality (A) and treatment failure (B) according to initial antifungal therapy (fluconazole or echinocandin/liposomal amphotericin B).

maximum dose of 800 mg/day (or 12 mg/kg/day) for treating these infections (10). However, 65% of patients in Eschenauer's study and most of our patients received an inadequate fluconazole dose according to this criterion, mainly because antifungal treatment was prescribed before the *Candida* species had been identified. Nevertheless, we stress that initial use of fluconazole was not associated with a poorer prognosis, even in these circumstances. These findings suggest that suboptimal fluconazole doses may still exert a certain activity against *C. glabrata* strains. Current recommendations for high-dose fluconazole in *C. glabrata* infection are based on studies that have analyzed treatment success or cure rates rather than mortality as the endpoint (11). However, previous pharmacokinetic/pharmacodynamic analyses have demonstrated a clear relationship between fluconazole dose, MIC values, and response to antifungal treatment (32). Thus, we believe that when fluconazole is used as initial treatment for candidemia and *C. glabrata* infection cannot be ruled out, a prudent approach would be administration of the maximum dose of 800 mg/day. With this clinical strategy, more than 85% of susceptible dose-dependent *C. glabrata* isolates would be covered in settings with low rates of resistance to fluconazole, such as Spain, some areas of the United States, Northern Europe, and South America (8, 18, 33, 34).

To further complicate the evaluation of the response to antifungal treatment, other factors apart from microbiological aspects seem to come into play and should be considered. Two patients in the fluconazole group in our study survived, even though the *C. glabrata* strains isolated were resistant to fluconazole. This means that despite the relevance of MIC values and susceptibility testing to estimate drug activity, they are only a part of the picture. Source control, underlying host immune status, and baseline disease severity also have an impact on treatment success or failure and should be included in the decision of the initial antifungal therapy to be used. Additionally, drug distribution to the site of the infection is also a relevant factor. In particular, fluconazole is preferred over echinocandins in cases of *C. glabrata* urinary tract infection because it can reach urine concentrations that exceed the MIC for susceptible dose-dependent strains, whereas echinocandins do not (35).

This study has some limitations. First, because of its observational nature, the choice of initial antifungal drug was not randomized and patients with a poorer baseline status were more frequently given an echinocandin/L-AmB regimen than fluconazole. However, a propensity score analysis was performed and the multivariate model was adjusted by factors and confounders known to be associated with therapy choice, treatment response, and mortality. Second, the reasons why the initial antifungal drug was changed are unknown. It is true that patients in the fluconazole group were more frequently and much earlier switched to another antifungal regimen, but this strategy does not necessarily reflect patients' unfavorable evolution. It might also highlight the influence of current guidelines favoring the use of echinocandins for infections caused by *C. glabrata*. Third, follow-up blood cultures were not performed for all patients. This could have led to an underestimation of the true incidence of persistent candidemia and introduced bias in the analysis of treatment failure. However, paired blood cultures are typically repeated in patients who are not responding to treatment and those with signs of an unfavorable clinical course. Furthermore, the clinical relevance of persistent candidemia on a patient's final outcome has not been well established (36). Finally, the sample size was too small to enable a single multivariate analysis including all confounding factors, thus limiting the statistical power of the study. Therefore, our results should be interpreted with caution, especially when dealing with severely ill patients.

In conclusion, this multicenter study based on patients with *C. glabrata* BSI found that initial treatment with fluconazole was associated with 14-day all-cause mortality and treatment failure similar to those who received echinocandin/L-AmB-based regimens. These results suggest that in settings with low rates of fluconazole-resistant *C. glabrata* strains, this agent may be still a reasonable option for treating stable patients with candidemia before the *Candida* species is identified. Further clinical studies are needed to better understand the role of fluconazole as an optional treatment for *C. glabrata* BSI.

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