Initial Use of Echinocandins Does Not Negatively Influence Outcome in Candida parapsilosis Bloodstream Infection: A Propensity Score Analysis

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(See the Editorial Commentary by Reboli on pages 1422–3.)

Background. Concerns have arisen regarding the optimal antifungal regimen for Candida parapsilosis bloodstream infection (BSI) in view of its reduced susceptibility to echinocandins.

Methods. The Prospective Population Study on Candidemia in Spain (CANDIPOP) is a prospective multicenter, population-based surveillance program on Candida BSI conducted through a 12-month period in 29 Spanish hospitals. Clinical isolates were identified by DNA sequencing, and antifungal susceptibility testing was performed by the European Committee on Antimicrobial Susceptibility Testing methodology. Predictors for clinical failure (all-cause mortality between days 3 to 30, or persistent candidemia for ≥72 hours after initiation of therapy) in episodes of C. parapsilosis species complex BSI were assessed by logistic regression analysis. We further analyzed the impact of echinocandin-based regimen as the initial antifungal therapy (within the first 72 hours) by using a propensity score approach.

Results. Among 752 episodes of Candida BSI identified, 200 (26.6%) were due to C. parapsilosis species complex. We finally analyzed 194 episodes occurring in 190 patients. Clinical failure occurred in 58 of 177 (32.8%) of evaluable episodes. Orotracheal intubation (adjusted odds ratio [AOR], 2.81; P = .018) and septic shock (AOR, 2.91; P = .081) emerged as risk factors for clinical failure, whereas early central venous catheter removal was protective (AOR, 0.43; P = .040). Neither univariate nor multivariate analysis revealed that the initial use of an echinocandin-based regimen had any impact on the risk of clinical failure. Incorporation of the propensity score into the model did not change this finding.

Conclusions. The initial use of an echinocandin-based regimen does not seem to negatively influence outcome in C. parapsilosis BSI.

Keywords. Candida parapsilosis; bloodstream infection; echinocandin; treatment; propensity score.

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Echinocandins for C. parapsilosis BSI • CID 2014:58 (15 May) • 1413
Candida parapsilosis represents one of the leading causes of bloodstream infection (BSI) due to non–Candida albicans species [1–5]. Compared with other species, C. parapsilosis shows a number of distinct features, such as its capability to develop biofilms on intravascular devices, high affinity for parenteral nutrition, or relevance as neonatal pathogen [6–9]. A further matter of concern lies on its susceptibility profile to the echinocandin class of antifungals. Candida parapsilosis has a naturally occurring polymorphism at the hotspot region 1 of the FKS1 gene, leading to higher minimum inhibitory concentration (MIC) values for all echinocandins than those observed in other species [10, 11]. This finding has raised an ongoing debate on whether echinocandins may be deemed appropriate for treating invasive disease due to C. parapsilosis.

Pivotal randomized controlled trials (RCTs) conducted with echinocandins did not find significant differences in the success rates for C. parapsilosis infection between treatment arms, although these studies were not powered to assess subgroup differences according to specific species [12–15]. The Infectious Diseases Society of America (IDSA) guidelines clearly state a preference for fluconazole in the setting of C. parapsilosis BSI [16], whereas the European guidelines are less explicit in their recommendation [17]. Of note, a majority of clinical isolates belonging to the C. parapsilosis complex are susceptible to echinocandins according to Clinical and Laboratory Standards Institute (CLSI) criteria [11, 18–21]. Nevertheless, European Committee on Antimicrobial Susceptibility Testing (EUCAST) documents indicate that C. parapsilosis should not be regarded as a good target for echinocandins [22]. Finally, although all the above-mentioned RCTs were designed as noninferiority studies, echinocandins have demonstrated superiority over comparators in post hoc analyses [23, 24].

Not infrequently, clinicians dealing with a preliminary blood culture showing the growth of yeast-like fungal pathogens are not provided with Candida species identification until after the first 48–72 hours of therapy. Our study was aimed at analyzing the impact of such initial treatment on the outcome of C. parapsilosis BSI and, specifically, at assessing whether the use of an echinocandin entails a worse outcome compared withazole-based regimens.

PATIENTS AND METHODS

Study Setting
The present study constitutes a subanalysis of the Prospective Population Study on Candidemia in Spain (CANDIPOP; ClinicalTrials.gov number NCT01236261), a prospective, multicenter, population-based surveillance program on Candida BSI conducted from May 2010 to April 2011 in 29 hospitals located in 5 of the largest municipal areas of Spain (Barcelona, Bilbao, Madrid, Seville, and Valencia). These centers serve an overall population of 9,498,980 inhabitants (2011 national census).

The methodology and main results of the CANDIPOP Study have been previously described [25]. In brief, all consecutive cases of Candida BSI diagnosed at the participating institutions were deemed eligible for inclusion. The refusal to participate in the study was the only exclusion criterion. Cases were identified by local laboratories and reported to study coordinators, who collected clinical data using a standardized case report form. Patients were managed according to routine clinical care, and no specific recommendations were provided on systematic screening for Candida colonization, treatment, or microbiological follow-up. Regular internal audits were performed to ensure that all cases had been properly reported. The study was approved by the local institutional review boards at each center, and written informed consent was obtained from each patient (or legal representative) before enrollment.

Definitions and Data Collection
An incident episode was defined as the first positive blood culture drawn from a peripheral vein yielding a species belonging to the C. parapsilosis complex. Those episodes in which a second non–C. parapsilosis species was simultaneously isolated (mixed candidemia) were excluded. The subsequent isolation of C. parapsilosis in the same patient beyond 30 days from the incident blood culture was deemed to be a new episode. Neonatal episodes were defined as those occurring in the first year of life. Episodes detected beyond 48 hours of hospital admission were considered to be hospital acquired. Proven catheter-related C. parapsilosis BSI was defined as previously described [26]. Other secondary episodes required microbiological documentation of an alternative source of infection. Episodes without apparent portal of entry were considered as primary. A breakthrough episode was defined as the occurrence of C. parapsilosis BSI in a patient previously receiving at least 72 hours of systemic antifungal therapy for any reason. Severity of infection and Pitt bacteremia score were recorded on the day of blood culture sampling [27]. The Acute Physiology and Chronic Health Evaluation (APACHE) II score was also determined for patients admitted to the intensive care unit at the onset of BSI. Initial antifungal therapy was that provided within the first 72 hours of administration of systemic antifungals for an incident episode of BSI. We established 4 categories: azole-based, echinocandin-based, amphotericin B–based, or combination regimens. Early central venous catheter (CVC) removal was defined as removal of the line within the first 48 hours from the incident BSI. In patients with multiple CVCs, removal of all catheters within this time frame was required, regardless of the type of vascular access.

Study Design
The primary study outcome was clinical failure, defined as (1) all-cause mortality between days 3 and 30 from the initial
positive blood culture, or (2) persistent C. parapsilosis BSI for ≥72 hours after the initiation of antifungal therapy. This composite variable was based on the Mycoses Study Group and European Organization for Research and Treatment of Cancer consensus criteria [28]. Patients who died within the first 72 hours were excluded from the analysis of outcome predictors to ensure that the potential impact of therapeutic strategies could be properly evaluated. We also analyzed 30-day all-cause mortality as secondary outcome. Those episodes without 30-day follow-up were considered missing when evaluating these outcomes.

Microbiological Studies
Candida species isolates were processed at participating hospitals using local routine methods. All the strains were then forwarded to the mycology reference laboratory at the Spanish National Center for Microbiology (Majadahonda, Madrid) for species confirmation and susceptibility testing. Internal transcribed spacer regions 1 and 2 from ribosomal DNA were directly amplified by polymerase chain reaction from yeast suspensions and sequenced using universal primers. When identification was discordant, the mycology reference laboratory data were used. Susceptibility to antifungal drugs was assessed according to the protocols and clinical breakpoints (CBPs) proposed by EUCAST [29, 30]. Due to significant interlaboratory variations, CBPs for caspofungin have not yet been established [31].

Statistical Analysis
Quantitative data were shown as the mean ± standard deviation (SD) or the median with interquartile ranges (Q1–Q3). Qualitative variables were expressed as absolute and relative frequencies. Categorical variables were compared using the χ² test, whereas Student t test or Mann-Whitney U test were applied for continuous variables. MIC results were showed as geometric means.

We analyzed the impact of initial treatment strategy on the primary study outcome by 2 different approaches. First, predictors for clinical failure were assessed in the entire study population by using a backward stepwise logistic regression model. Both the type of initial antifungal therapy and the early CVC removal were forced into the final model regardless of their significance level on univariate analysis. The Hosmer-Lemeshow test was used to measure the goodness of fit of the model. Associations are given as odds ratios (ORs) with 95% confidence intervals (95% CIs).

In a second analysis, we calculated the propensity to receive an echinocandin or an azole as the initial antifungal drug given the patient’s observed pretreatment characteristics. We limited this analysis only to nonneonatal episodes of C. parapsilosis BSI, and also excluded those in which amphotericin B or combination regimens were used. The propensity score was estimated using a backward stepwise logistic regression model including variables with P values ≤0.1 in the univariate analysis. Eight variables were finally included into the model (Supplementary Table 1), the fit of which was assessed by the Hosmer-Lemeshow test (P = .978). The estimated propensity score was then used as a covariate in a multivariate analysis to adjust for potential confounding by factors associated with initial antifungal therapy [32, 33]. Sensitivity analyses were performed by repeating the propensity score approach with different methods (matching with replacement and stratification). All the significance tests were 2-tailed. Statistical analysis was performed using SPSS, version 15.0 (IBM SPSS, Chicago, Illinois) and R software, version 3.0.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Incidence Rate
We identified 773 episodes of Candida BSI during the surveillance period. Twenty-one patients declined to participate. Of the remaining 752 episodes, 200 (26.6%) were due to C. parapsilosis species complex, with 191 (95.5%) strains identified as C. parapsilosis sensu stricto, 7 (3.5%) as C. orthopsilosis, and 2 (1.0%) as C. metapsilosis. The crude annual incidence rate was 2.10 cases per 10⁵ population. A second non-parapsilosis Candida species was simultaneously isolated in the incident blood culture in 6 episodes. Therefore, we finally analyzed 194 episodes occurring in 190 patients.

Underlying Conditions, Clinical Presentation, and Outcome
The characteristics of the study population are detailed in Table 1. Forty episodes (20.6%) were considered breakthrough BSI that occurred while receiving azoles (21 cases [52.5%]), echinocandins (11 cases [27.5%]), or amphotericin B (8 cases [20.0%]). Six episodes were lost to follow-up after a median of 11 days (Q1–Q3 range, 3.5–22.3), whereas repeated BCs yielded a second non-parapsilosis Candida species in another 2 (at 2 and 6 days from the onset of the incident episode). Follow-up blood cultures were performed beyond the first 48 hours of antifungal therapy in 131 episodes (75.3% of eligible cases). Overall, 32.8% (58/177) of evaluable episodes met the criteria for clinical failure (primary study outcome), whereas the 30-day all-cause mortality was 24.2%.

Therapeutic Approaches
Early CVC removal was performed in 64 of 163 episodes (39.3%) in patients with a CVC in place. Systemic antifungal therapy was administered in 174 episodes (89.7%). After excluding the 42 episodes in patients already receiving antifungal drugs at the onset of infection, median interval until initiation of therapy was 2.0 days (Q1–Q3 range, 1.0–3.0). Initial antifungal therapy consisted of an azole-based regimen in...
73 episodes (42.0%; 70 fluconazole and 3 voriconazole), an echinocandin-based regimen in 43 (24.7%; 23 caspofungin, 12 anidulafungin, and 8 mica fungin), an amphotericin B–based regimen in 33 (19.0%), and a combination regimen in 25 (14.4%) (Table 2).

### Antifungal Susceptibility

The results of antifungal susceptibility testing are depicted in Table 3. The rates of resistance to micafungin (1.1%), fluconazole, and voriconazole (0.6% each) were very low, whereas no isolates showed resistance to anidulafungin. All these resistant isolates were further identified as *C. parapsilosis sensu stricto*. These low rates of in vitro resistance precluded further analyses on the relationship between clinical failure and MIC values.

### Predictors of Clinical Failure

Univariate and multivariate analysis for predictors of clinical failure are shown in Table 4. We found no differences in outcome according to each of the *C. parapsilosis* complex species.
Orotracheal intubation at diagnosis (adjusted OR, 2.81; 95% CI, 1.19–6.65; \( P = .018 \)) and, with borderline significance, septic shock (adjusted OR, 2.91; 95% CI, .88–9.64; \( P = .081 \)) emerged as risk factors, whereas early CVC removal exerted a protective effect (adjusted OR, 0.43; 95% CI, .19–.96; \( P = .040 \)). Neither univariate nor multivariate analyses (adjusted OR, 1.73; 95% CI, .66–4.54; \( P = .265 \)) revealed that the initial use of an echinocandin-based regimen had any impact on the risk of clinical failure.

Outcome in Episodes Treated With Echinocandin-Based or Azole-Based Regimens

We then focused on the 103 nonneonatal episodes initially treated with either an echinocandin-based or an azole-based regimen. Episodes in the former group occurred in patients more severely ill and in those more likely to have been previously admitted to an intensive care unit, to have a history of underlying renal failure, and to present with septic shock. On the
other hand, more episodes in the azole group were deemed as catheter-related BSI (Supplementary Table 1). The time to initiation of antifungal therapy (median, 2.2 vs 2.0 days; \( P = .711 \)) and the rate of early CVC removal (41.5% vs 33.3%; \( P = .448 \)) were similar in both groups. As detailed in Table 5, we found no significant differences in the primary study outcome (clinical failure), nor in the rate of persistent BSI or 30-day all-cause mortality. The lack of impact of using an echinocandin-based regimen as initial antifungal therapy on the primary study outcome was confirmed after entering the propensity score into the logistic regression model (marginal OR, 1.23; 95% CI, .43–3.45; \( P = .691 \)). The consistency of this result was confirmed by repeating the propensity score analyses by 2 additional methods: 1:1 matching with replacement and a caliper of 0.25, and quintile stratification (data not shown).

### DISCUSSION

Various studies have assessed the risk factors for and mortality associated with C. parapsilosis BSI [2, 4, 6, 34–36]. However, there is a relative scarcity of data on the specific predictors for unfavorable outcome in this entity [24, 37, 38], as most of the authors did not separately analyze the outcome according to the isolated Candida species. The 30-day mortality in our experience was consistent with that reported in the literature, which ranges from 23% [6] to 30.8% [34]. Although attribution of cause of death in patients with candidemia is challenging, mortality in these populations often results from conditions seemingly unrelated to fungal infection. Accordingly, orotracheal intubation at infection onset—a clear surrogate marker for illness severity—emerged as independently associated with poor outcome in our cohort. Therefore, all-cause mortality—the only outcome assessed in most of the previous studies—may lack enough sensitivity and specificity to accurately define clinical failure in patients with C. parapsilosis BSI, and documented clearance of candidemia should constitute a requirement for a successful outcome [28].

To date, only 1 RCT has compared an echinocandin to an azole for the treatment of invasive candidiasis, concluding that anidulafungin was noninferior to fluconazole [13]. The

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**Table 4. Univariate and Multivariate Logistic Regression Analyses of Prognostic Factors for Clinical Failure**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Ototracheal intubation at diagnosis</td>
<td>4.67</td>
<td>2.32–9.38</td>
</tr>
<tr>
<td>Septic shock</td>
<td>7.17</td>
<td>2.63–19.56</td>
</tr>
<tr>
<td>Hematogenous dissemination</td>
<td>6.75</td>
<td>1.32–34.56</td>
</tr>
<tr>
<td>Early CVC removal (≤48 h)</td>
<td>0.41</td>
<td>0.20–0.86</td>
</tr>
<tr>
<td>Initial antifungal therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azole-based regimen</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Echinocandin-based regimen</td>
<td>1.34</td>
<td>.60–2.97</td>
</tr>
<tr>
<td>Amphotericin B–based regimen</td>
<td>0.99</td>
<td>.40–2.45</td>
</tr>
<tr>
<td>Combination regimen</td>
<td>0.86</td>
<td>.31–2.36</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CVC, central venous catheter; OR, odds ratio.

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**Table 5. Outcomes in 103 Nonneonatal Episodes of Candida parapsilosis Bloodstream Infection Treated With an Echinocandin- or Azole-Based Regimen as Initial Antifungal Therapy (First 72 Hours)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Azole-Based Regimen (( n = 64 ))</th>
<th>Echinocandin-Based Regimen (( n = 39 ))</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical failure(^a)</td>
<td>20/62 (32.3)</td>
<td>13/37 (35.1)</td>
<td>.769</td>
</tr>
<tr>
<td>Persistent BSI for ≥72 h of therapy(^b)</td>
<td>14/48 (29.2)</td>
<td>6/26 (23.1)</td>
<td>.573</td>
</tr>
<tr>
<td>30-day all-cause mortality(^c)</td>
<td>14/63 (22.2)</td>
<td>10/37 (27.0)</td>
<td>.587</td>
</tr>
<tr>
<td>Early (&lt;72 h)</td>
<td>1/64 (1.6)</td>
<td>0/39 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Nonearly (days 3–30)</td>
<td>13/63 (20.6)</td>
<td>10/37 (27.0)</td>
<td>.463</td>
</tr>
</tbody>
</table>

Abbreviation: BSI, bloodstream infection.

\(^a\) Four episodes (3.9%) did not meet the criteria for evaluation of clinical failure due to incomplete follow-up data (3 episodes) or death within the first 72 hours (1 episode).

\(^b\) Follow-up blood cultures were obtained beyond the first 48 hours of treatment in 74 episodes (72.5% of those in which antifungal therapy was administered and patient survived for ≥72 hours).

\(^c\) Three episodes (2.9%) did not have 30-day follow-up data.
numbers of *C. parapsilosis* isolates in both treatment arms were insufficient to draw any conclusion. As previously pointed out, this drawback is shared by the remaining RCTs on echinocandins [12, 14, 15]. Notwithstanding this, it should be noted that Mora-Duarte et al reported a higher number of episodes of persistent *C. parapsilosis* BSI in the caspofungin arm than in the amphotericin B deoxycholate arm [12], whereas a numerically lower eradication rate was found in the RCT by Reboli et al in the anidulafungin arm [13]. Such low-degree evidence, linked to the intrinsically higher MICs to echinocandins exhibited by *C. parapsilosis*, led to IDSA guidelines to favor fluconazole over the echinocandin-class drugs for treatment of *C. parapsilosis* infection [16]. Interestingly, this recommendation seems to have had a limited impact on daily practice, as suggested by the fact that half of the 531 patients with *C. parapsilosis* BSI enrolled in a registry received an echinocandin at some time [35].

We have found no impact of the type of initial antifungal treatment on the risk of clinical failure, nor even after adjusting for baseline imbalances between patients treated with echinocandins and those treated with azoles by a propensity score analysis. A recent patient-level quantitative review of RCTs found no effect of the antifungal therapy on 30-day mortality or treatment response in the *C. parapsilosis* subgroup either [24]. On the other hand, and despite the steady increase in echinocandin use over the last years, the resistance rates for micafungin and anidulafungin by applying the EUCAST species-specific CBPs in our cohort were negligible and in the range of those reported by other studies using the CLSI methods [18–21]. These results suggest that the presumed impact of the increased MIC values for echinocandins in *C. parapsilosis* should be carefully balanced against the advantages of this class of agents over the azoles (i.e., fungicidal activity, favorable safety profile, and low potential for drug interactions) when choosing the optimal antifungal therapy.

Additionally, we found that early CVC removal exerted a protective effect on the odds of clinical failure. The impact of CVC management on the outcome of candidemic patients has been extensively investigated [24, 37, 39, 40], and consensus guidelines strongly support removal of vascular catheters when feasible [16, 17]. However, few studies have examined the impact of CVC management across individual *Candida* species. *Candida parapsilosis* has higher ability for biofilm formation and lower pathogenicity than other species [8, 37]. In addition, patients with *C. parapsilosis* BSI usually have lower APACHE II scores [24] and lower prevalence of high-risk sources of candidemia [3, 6, 35]. Therefore, it is more likely that the independent impact of early CVC removal emerges in this form of candidemia than in those due to more virulent *Candida* species, and it could be hypothesized whether this intervention might have obscured, to some extent, the differential effect of antifungal regimens on outcome.

The present study has some limitations. First, serial follow-up blood cultures were not systematically performed, so the rate of persistent BSI could have been underestimated. Nevertheless, we found no differences in patients’ underlying conditions or outcome between episodes with or without microbiological follow-up (data not shown), and it may be argued that most physicians would have obtained repeated blood cultures in the presence of clinical signs suggestive of unfavorable evolution. Second, the allocation to the different groups of antifungal therapy was not random, but based on physicians’ choice. As expected, patients prescribed an echinocandin-based regimen were more critically ill than those prescribed an azole, a difference that a priori could have favored this latter therapy. In an attempt to control for such imbalances, we performed a propensity score analysis that provided further adjustment for selection bias. However, propensity analysis can only adjust for known measured variables, so we are unable to exclude the potential effect of other confounders. Finally, we did not apply this statistical approach to compare the outcome of those episodes treated with amphotericin B, because we believed that the high number of neonates among the latter would preclude comparability between treatment groups. In addition, sample size limitations precluded any subgroup analysis according to the specific echinocandin agent used.

In conclusion, we have not found that the use of an echinocandin-based regimen for the first 72 hours of therapy negatively influences the outcome of *C. parapsilosis* BSI, despite the lower in vitro activity of this class of antifungals compared to azoles. Our findings provide a preliminary basis for reviewing the current recommendations on antifungal therapy in that setting, particularly in the light of the expected benefits from the use of an echinocandin in critically ill patients in terms of reduced mortality and higher treatment success.

**Supplementary Data**

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

**Notes**

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