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Comparative effectiveness of echinocandins versus fluconazole therapy for the treatment of adult candidaemia due to *Candida parapsilosis*: a retrospective observational cohort study of the Mycoses Study Group (MSG-12)

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Objectives: A polymorphism in the gene encoding β-1,3-glucan synthase, the target of the echinocandin class of antifungals, results in increased *in vitro* MICs of the echinocandins. This has resulted in controversy surrounding use of the echinocandins for treatment of *Candida parapsilosis* candidaemia. We aimed to compare 30 day mortality in adults with *C. parapsilosis* candidaemia treated with echinocandins versus fluconazole.

Methods: This is a retrospective observational cohort study. We used the Premier Perspective Database to identify adult patients with *C. parapsilosis* candidaemia treated with only fluconazole or only an echinocandin as definitive therapy. The primary outcome was 30 day mortality. Propensity scores were derived to estimate the probability the patient would have received either an echinocandin or fluconazole. Inverse probability of treatment weighting (IPTW) was used in a weighted logistic regression to calculate odds of 30 day mortality.

Results: There were 307 unique patients with *C. parapsilosis* candidaemia. One hundred and twenty-six (41%) received fluconazole and 181 (59%) received an echinocandin. Age, gender, race, year of admission, need for ICU resources in the week prior to candidaemia onset, and receipt of vasopressors on the day of candidaemia onset were included in the propensity score model used to calculate inverse probability of treatment weights. Weighted logistic regression demonstrated no difference in 30 day mortality between patients receiving an echinocandin as compared with fluconazole (OR 0.82, 95% CI 0.33–2.07).

Conclusions: Our result supports the 2016 IDSA invasive candidiasis guidelines, which no longer clearly favour treatment with fluconazole over an echinocandin for *C. parapsilosis* candidaemia.

Introduction

Infections due to *Candida* species are associated with mortality of around 30%. Compared with azoles and polyenes, patients treated with echinocandins appear to have a lower risk of mortality across a range of illness severities and causative species.[1] This has in part been attributed to the fungicidal activity of the echinocandins via inhibition of β-1,3-glucan synthase, the enzyme that catalyses the assembly of glucan, a principle component of the fungal cell wall.[2] *Candida parapsilosis*, which accounts for ~10%–15% of invasive candidiasis,[1,3] has a polymorphism in the *fks1* gene encoding β-1,3-glucan synthase, resulting in higher *in vitro* MICs of the echinocandins.[2] Consequently, there has been concern about the use of echinocandins as primary therapy for *C. parapsilosis*, and prior versions of the IDSA candidiasis treatment guidelines recommended fluconazole over an echinocandin for this reason.[4]

However, a recent observational cohort study of 103 non-neonatal candidiasis episodes did not find a difference in clinical failure between initial treatment with an azole versus an

echinocandin.[5] Based on these new data, considered in context of existing data,[1,6,7] the 2016 IDSA invasive candidiasis guidelines no longer clearly support fluconazole over echinocandin, though a paucity of clinical data precludes a more definitive statement of equivalence.[8] We therefore aimed to compare the effectiveness of fluconazole with echinocandins in a US cohort of adults with *C. parapsilosis* candidaemia to provide additional clinical data to guide the choice of a definitive therapeutic agent in this clinical setting.

Patients and methods

Data source, study design and cohort assembly

Patients were identified using The Premier Perspective™ Database (PPD, Charlotte, NC, USA), which contains patient level and microbiological data from 115 US hospitals. Prior to inclusion in the PPD, data supplied from the member hospitals undergo numerous reliability and validity checks.[9] This database has previously been used for comparative effectiveness research.[10]

We performed a retrospective observational cohort study of adult (>17 years of age) inpatients admitted between 1 January 2009 and 31 December 2013 who had at least one blood culture positive for monomicrobial *C. parapsilosis*, survived for at least 4 days after the positive culture was obtained, and received initial definitive therapy with only fluconazole or only an echinocandin. Only index episodes of *C. parapsilosis* candidaemia were included. Admissions originating as transfers from other institutions were excluded.

Ethics

Institutional Review Board exemption was granted for this work.

Definitions, exposure and outcome

The primary exposure of interest was administration of at least 1 day of definitive therapy with only an echinocandin (anidulafungin, caspofungin or micafungin) or only fluconazole. Definitive therapy was defined *a priori* as the antifungal agent the patient received on the third day after the positive blood culture was drawn. Illness severity was reflected by resource utilization, including receipt of vasopressors on the day of candidaemia onset as well as need for ICU resources in the week prior to candidaemia onset. ICU level resource utilization was defined as ICD-9 procedure code and/or billing charge for vasopressors, mechanical ventilation, haemodialysis, intracranial pressure monitoring, arterial/Swan–Ganz catheter insertion, cardiopulmonary resuscitation or defibrillation. Hospital-onset infections were defined as those cultures drawn >3 days after admission. Antifungal prophylaxis was defined as receipt of any antifungal agent in the 7 days prior to the blood culture being drawn and empirical therapy was defined as receipt of any antifungal agent on the day the blood culture was drawn and up to 2 days after. The primary outcome was 30 day all-cause inpatient mortality. Patients discharged prior to 30 days were coded as alive unless discharged to palliative care, in which case they were coded as an inpatient death.

Statistical analysis

The antifungal agent administered on day 3 after the blood culture was drawn was deemed the definitive therapy for intention-to-treat exposure assignment for our primary analysis. As the treating clinician's choice of definitive therapy may be influenced by patient factors present at the time of or prior to therapy initiation, propensity scores informed by measured baseline covariates were generated to model the probability of a patient receiving definitive therapy with an echinocandin. The following variables were considered for inclusion in the propensity score model: year of admission, Charlson comorbidity index, need for ICU resources in the week prior to candidaemia onset, vasopressor exposure on the day of candidaemia onset, hospital-onset infection, length of stay prior to candidaemia onset, and receipt of antifungal prophylaxis or empirical therapy. Age, gender, race and any variable associated with receipt of echinocandin with $P<0.10$ on univariate analysis were included in the final propensity score model.

Inverse probability of treatment weights were then calculated using these propensity scores to reflect the inverse of the probability that the patient would have received the treatment they ultimately did. Weighted logistic regression using inverse probability of treatment weighting (IPTW) was then used to compare 30 day mortality in patients treated with an echinocandin versus fluconazole. All analyses were performed using Stata 13.1 (Stata Corporation, College Station, TX, USA).

Results

Demographic and clinical data

There were 307 unique patients with *C. parapsilosis* candidaemia surviving for at least 4 days after the blood culture was drawn. Of these, 126 (41%) received fluconazole and 181 (59%) received an echinocandin. Table 1 summarizes demographic and clinical characteristics by treatment group.

Thirty day inpatient mortality

Overall, the crude 30 day mortality rate for this cohort of patients with *C. parapsilosis* candidaemia was 9.8%. In the echinocandin group, the mortality rate was 9.9% versus 9.5% in the fluconazole group (OR 1.05, 95% CI 0.49–2.26).

Propensity scores derived from a multivariate model including age, race, gender, year of admission, need for ICU resources in the week prior to candidaemia onset, and receipt of vasopressors on the day of candidaemia onset were used to calculate inverse probability of treatment weights. Following IPTW, standardized differences between treatment groups were substantially reduced (Table 1) for those variables included in the propensity score derivation model. Weighted logistic regression was then performed to compare odds of 30 day mortality. There was no statistically significant difference in 30 day mortality between patients receiving an echinocandin as compared with fluconazole (OR 0.82, 95% CI 0.33–2.07).

Discussion

We examined the effect of fluconazole versus an echinocandin as definitive therapy for *C. parapsilosis* candidaemia and found no increase in 30 day mortality in a comparative model standardized by IPTW. Our finding complements the earlier work of Fernandez-Ruiz *et al.*,[5] which showed no difference in 30 day mortality in patients treated with either agent (OR 1.23, 95% CI 0.43–3.45). Additionally, a pooled analysis of randomized trials evaluating various therapeutic agents in adult candidaemia found no difference in mortality with empirical echinocandin therapy in the subgroup of patients with *C. parapsilosis*.[1] These data suggest that, compared with fluconazole, echinocandins are similarly effective therapy for *C. parapsilosis* candidaemia with regard to overall mortality, as suggested by the 2016 IDSA invasive candidiasis guidelines.[8]

It is notable that in the aforementioned pooled analysis the mortality benefit observed with echinocandin therapy for other

Candida species was not observed in the subset of patients with *C. parapsilosis*.[1] Furthermore, echinocandin use may be associated with persistent candidaemia compared with both fluconazole and amphotericin B in subgroup analyses of randomized trials restricted to patients with *C. parapsilosis*.[6,7] Although these analyses are underpowered to draw definitive conclusions, it does raise the possibility that time to resolution of candidaemia is longer in echinocandin-treated patients. Further investigation is needed to confirm this finding and assess the ultimate impact on morbidity and mortality. Unfortunately, evaluation of persistent candidaemia was problematic in our study design because clearance of candidaemia may have occurred prior to or soon after definitive therapy was started on day 3 from the initial blood culture, our *a priori*-defined exposure of interest. More complex modelling, such as a marginal structural model, would have allowed us to account for the effect of time-varying antifungal therapy exposure on such an outcome, but our sample size was insufficient to utilize this approach.[11] Furthermore, the frequency at which repeat blood cultures are obtained will vary by institution, resulting in artificial differences in duration of candidaemia. Unfortunately, adjustment for hospital level variation in blood culture practice was not possible in this analysis given the small sample size relative to the number of institutions.

Other limitations of our analysis are worthy of specific discussion. Despite utilization of IPTWs, there remains unmeasured as well as residual confounding. One important unmeasured confounder is central venous catheter (CVC) management, which is not available in the PPD. While CVC retention has been associated with increased mortality, prior studies have also suggested that CVCs are more often retained in patients with greater illness severities.[1,12,13] In our cohort, illness severity was greater in the echinocandin-treated patients and thus it is expected that CVCs would be more often retained in this group. Failure to adjust for this covariate would therefore result in bias towards a conclusion of fluconazole superiority.

A patient's clinical status prior to and at the time of candidaemia onset may also confound the association of the initial antifungal choice and subsequent mortality.[1,12,13] Our propensity score model incorporated utilization of specific resources (i.e. vasoactive agents) as proxy measures to adjust for potential variation in illness severity across the two treatment groups. The reduction in standardized differences after IPTW (Table 1) suggests that this approach appropriately accounted for illness severity differences at baseline between the two treatment groups. There was, however, residual imbalance in receipt of vasopressors on the day of candidaemia onset, with a standardized mean difference between groups of 11.9, exceeding the conventional threshold of <10% to be considered negligible imbalance.[14] However, we would expect this imbalance to also bias towards a conclusion of fluconazole superiority. This approach to adjusting

Table 1. Demographic and clinical characteristics by treatment group before and after IPTW

	Fluconazole (*N*=126)	Echinocandin (*N*=181)	Standardized difference before IPTW	Standardized difference after IPTW
Age (years), median (IQR)[a]	60 (46, 69)	60 (50, 75)	11.4	2.4
Male, *n* (%)[a]	61 (48.4)	115 (63.5)	−30.7	0.5
Black race, *n* (%)[a]	33 (26.2)	39 (21.6)	−10.9	−4.6
Need for ICU resources the week prior to candidaemia onset, *n* (%)[a]	53 (42)	101 (56)	27.7	5.1
Need for vasopressors the day of candidaemia onset, *n* (%)[a]	28 (22)	67 (37)	32.7	11.9
Year of candidaemia onset, *n* (%)[a]			24.6	2.7
2009	35 (55)	29 (45)	—	—
2010	34 (44)	43 (56)	—	—
2011	23 (31)	51 (69)	—	—
2012	17 (35)	32 (65)	—	—
2013	17 (40)	26 (60)	—	—
Charlson comorbidity score, median (IQR)	2 (1, 4)	2 (1, 4)	NA	NA
LOS, median (IQR), days	18 (8, 37)	21 (10, 34)	NA	NA
LOS prior to candidaemia onset, median (IQR), days	3 (0, 16)	5 (0, 19)	NA	NA
Receipt of antifungal prophylaxis, *n* (%)	20 (15.9)	33 (18.2)	NA	NA
Healthcare-onset candidaemia, *n* (%)	67 (53.2)	98 (54.1)	NA	NA
Empirical antifungal, *n* (%)	109 (86.5)	162 (89.5)	NA	NA

LOS, length of stay; NA, not applicable.
[a]Variable included in final propensity score model.

for illness severity was selected over APACHE II scores as APACHE II scores are only measured during the first 24 h of ICU stay and therefore would not have applied to a significant proportion of our study population. Also, the PPD does not contain APACHE II scores.

Our approach of an intention-to-treat analysis based on defining 'definitive' therapy as the agent the patient received on the third day after the culture was obtained assumes that the prescribing clinician knew the culture was positive and the identity of the causative organism at this time. While this assumption has the potential to introduce misclassification, it is based on available literature that suggests that most cultures will be positive by this timepoint.[15] Additionally, our model only considers the choice of therapy on day 3 and does not consider time-varying antifungal therapy choices after day 3. To do so would require utilization of a marginal structural model, which was unfortunately not an option in this study, given the limited sample size.[11] Finally, we do not have information regarding dosing of either fluconazole or echinocandin, nor do we have information about whether patients received loading doses with either agent; inadequate dosing could result in increased mortality in either group, so we anticipate that this unmeasured confounding would be non-differential and therefore bias towards the null hypothesis.

The 9.8% mortality rate in our study is significantly lower than the 20%–25% mortality rates reported in other studies, likely due to the exclusion of patients who died within 3 days of blood culture acquisition.[1,5] Exclusion of these patients is appropriate given our clinical question of whether choice of definitive therapy affects 30 day mortality, though the reduced event rate resulted in a relatively wide confidence interval around the point estimate (OR 0.82, 95% CI 0.33–2.07). As the lower and upper bounds of the confidence interval range from 0.33 and 2.07 we cannot completely exclude the possibility that echinocandins are either superior or inferior to fluconazole for *C. parapsilosis*.

In conclusion, our study provides additional comparative effectiveness data evaluating the use of either echinocandin or fluconazole in the treatment of candidaemia due to *C. parapsilosis*. Noting the limitations discussed above, we found no difference in 30 day mortality between echinocandin- and fluconazole-treated patients.

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