Fluconazole versus an echinocandin for *Candida glabrata* fungaemia: a retrospective cohort study

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Received 7 September 2012; returned 8 October 2012; revised 31 October 2012; accepted 3 November 2012

**Objectives:** We studied whether fluconazole or echinocandin treatment of *Candida glabrata* fungaemia results in superior outcomes.

**Methods:** A multicentre, retrospective study was performed with 224 adult patients who received ≥5 days of therapy with either fluconazole or an echinocandin as their first antifungal treatment after collection of a blood culture that grew *C. glabrata*. The primary outcome was day 14 complete response.

**Results:** Patients in the echinocandin group were generally more ill, both at baseline and at the time of the index culture. Day 14 complete response was obtained in 58/127 (46%) and 50/97 (52%) of the fluconazole and echinocandin patients, respectively \(P = 0.383\). Logistic regression found intensive care unit admission to be associated with failure \(OR \ 0.456 \ (0.217–0.957), P = 0.038\) and echinocandin therapy to be associated with day 14 complete response \(OR 2.305 \ (1.124–4.727), P = 0.023\). Twenty-eight day survival was similar between the fluconazole and echinocandin groups and logistic regression did not reveal antifungal therapy choice to be independently predictive of mortality. For patients treated with fluconazole, a dose:MIC ratio >12.5 (when compared with a ratio ≤12.5) was associated with a significantly higher day 14 complete response \(4/20 \ (20\%) \leq 12.5 \text{ versus } 50/102 \ (49\%) >12.5, P = 0.025\).

**Conclusions:** Severity of illness and choice of antifungal predict response in patients with *C. glabrata* fungaemia. Antifungal choice, however, does not influence mortality. In addition, new CLSI *C. glabrata* fluconazole susceptibility breakpoints are predictive of response when fluconazole is dosed appropriately.

**Keywords:** pharmacodynamics, breakpoints, ICU

**Introduction**

In the USA, *Candida* species are the fourth most common cause of nosocomial bloodstream infections and are associated with the highest crude mortality.1 With the introduction of the echinocandins, clinicians may choose from three classes of antifungals to treat invasive candidiasis. Individual clinical trials have largely demonstrated non-inferiority rather than superiority of any antifungal therapy,2 leading to debate over which agent(s) should be preferred. A recent review of seven randomized controlled trials of the treatment of invasive candidiasis concluded that treatment with an echinocandin was associated with decreased mortality.2 However, only one study comparing fluconazole with an echinocandin (anidulafungin) was included.3

The 2009 Infectious Diseases Society of America (IDSA) guidelines recommend echinocandins empirically for patients with moderate-to-severe infection or those with recent azole exposure. The recommendation, given an evidence grade of A-III (i.e. based on expert opinion), is founded on the safety, drug interaction profile and broad-spectrum fungicidal activity of the echinocandins.4 However, despite its fungistatic activity, fluconazole is a relatively non-toxic agent that demonstrates several
pharmacokinetic advantages over echinocandins; it penetrates the CNS, vitreous body and urine and is highly bioavailable when administered orally.4

Further complicating the issue of which antifungal therapy is preferred is that much research has approached the treatment of Candida as a singular entity. However, it is possible that outcomes and treatment differences may differ depending on the specific Candida species causing infection. Indeed, data have confirmed differences in outcome, which are probably due in part to a combination of host factors and differences in virulence between species.5 For example, Candida krusei is more commonly associated with haematological malignancy and neutropenia than is Candida parapsilosis,5 and, in animal models, Candida albicans is significantly more virulent than C. parapsilosis.6 However, it is not known whether the optimal antifungal therapy differs depending on Candida species.

The incidence of Candida glabrata as a cause of fungaemia compared with other Candida species is increasing in the USA.7 In most USA-based surveys, C. glabrata ranks second only to C. albicans as a cause of bloodstream infection.7 However, there are very few data comparing outcomes in patients treated with an echinocandin versus fluconazole. As such, we studied whether fluconazole or echinocandin treatment of C. glabrata fungaemia results in superior outcomes. We also assessed whether new CLSI susceptibility breakpoints appropriately predict fluconazole efficacy.

**Methods**

**Study design**

This was a retrospective, multicentre study of adult patients with C. glabrata fungaemia from 1 January 2002 to 30 December 2011. Patients were identified by queries of microbiology databases. For patients with multiple episodes of C. glabrata fungaemia, only the first episode was included. Patients were included if they received at least 5 consecutive days of therapy with either fluconazole or an echinocandin as their first antifungal therapy after collection of the index blood culture (for C. glabrata). Patients were excluded if they received the same antifungal for >48 h immediately prior to culture collection or if blood cultures within 24 h of the index culture grew other pathogens (excluding coagulase-negative staphylococci). The study was approved by the institutional review board at all centres.

**Data collection**

Data collected included demographics, past medical history, markers of severity of illness at the time the index culture was drawn and central venous catheter (CVC) presence (at the time the index culture was drawn) and removal (within 48 h of the index culture). Fluconazole susceptibility testing was independently performed at each centre. Antifungal therapy, including agent, dose and time to initiation, was also collected. As all APACHE II variables were not available for all patients, a modified acute physiology score (mAPS) was calculated. This score excludes variables that are frequently absent from non-intensive care unit (ICU) patients (Glasgow coma score and oxygenation parameters), thus standardizing collected variables across the entire patient population.9 Likewise, as arterial pH was not available in all patients, serum bicarbonate levels were substituted.9

**Outcomes/definitions**

The primary outcome was complete response at day 14. The primary outcome definition was derived from the Mycoses Study Group and European Organization for Research and Treatment of Cancer consensus criteria and was defined as a composite of clinical success (resolution of fever, leucocytosis and no need for vasopressor support), microbiological success (sterilization of blood) and survival.10 Secondary outcomes included day 7 and 28 complete response, survival at days 7, 14 and 28 and 12 weeks, microbiological success at days 7, 14 and 28, and clinical success at days 7, 14 and 28.

The ratio of free-drug area under the curve to MIC (FAUC:MIC) has been correlated with fluconazole treatment success.11 For fluconazole, AUC is virtually equivalent to daily dose in adults with normal function.21 As such, to determine whether pharmacodynamic variables affected fluconazole outcomes, a renal function-normalized dose to MIC (dose:MIC) ratio was calculated for each patient. If the estimated creatinine clearance was <50 mL/min (calculated using the Cockcroft and Gault equation12), the recorded dose of fluconazole was doubled.21

**Statistics**

Patients who received fluconazole were compared with those who received an echinocandin. Nominal baseline variables between groups were compared using Pearson’s χ² test or Fisher’s exact test, as appropriate, and continuous data were compared using Student’s t-test. Univariate analysis was performed to evaluate the association between each primary and secondary outcome with treatment groups. Time to event variables were analysed by the log-rank test. All tests were two-tailed and P<0.05 was considered statistically significant.

A multivariable logistic regression was performed to evaluate the independent effects of the treatment groups on the primary outcome measure and 28 day mortality after adjustments for baseline discrepancies between groups. All baseline differences with P<0.05 were entered into the multivariable analyses. It was decided a priori that CVC removal within 48 h of the index culture would be forced into the model, given the potential that early catheter removal may be associated with improved clinical outcomes and survival.5 If variables exhibited collinearity between each other with a correlation coefficient >0.4, separate models were created where the collinear variables were individually introduced. The variable that had a more significant effect on the model, as assessed by a greater R² value, was included. All variables were entered into the model as a best subset as specified by the selection criteria listed above. The Hosmer–Lemeshow goodness-of-fit test was used to test the power of the model. A statistical software program (SPSS, version 15.0 for Windows; SPSS Inc., Chicago, IL, USA) was used to perform all analyses.

**Results**

**Demographics**

Two hundred and twenty-four patients were eligible for inclusion from five medical centres (89 from the University of Michigan Hospital, 60 from the Cleveland Clinic, 44 from the National Taiwan University Hospital, 17 from Shands at the University of Florida and 14 from the University of Pittsburgh Medical Center). One hundred and twenty-seven patients received fluconazole, while 97 received an echinocandin (11 anidulafungin, 30 caspofungin and 56 micafungin). Baseline characteristics and severity of illness determinants at the time of fungaemia are presented in Table 1. Patients in the echinocandin group were generally more ill, both at baseline and at the time of the index culture. Significantly more patients in the echinocandin
group had a history of solid organ transplant and end-stage renal disease. At the time of positive blood culture, significantly more patients who received an echinocandin were in an ICU and required renal replacement therapy. Time to initiation of antifungal therapy did not significantly differ between patients treated with fluconazole versus an echinocandin (data not shown). If present at the time of fungaemia, CVCs were removed within 48 h in 36/82 (44%) and 22/67 (33%) of fluconazole and echinocandin patients, respectively (P=0.168).

**Complete response**
Outcomes are presented in Table 2. Overall, 108/224 patients (48%) met the criteria for complete response at day 14. At day 14, clinical and microbiological success rates were 135/224 (60%) and 177/224 (79%), respectively. There were no significant differences in outcomes between patients treated with an echinocandin versus fluconazole. The primary outcome of day 14 complete response was 58/127 (46%) and 50/97 (52%) for the fluconazole and echinocandin groups, respectively (P=0.383). Logistic regression found ICU admission to be associated with failure [OR 0.456 (0.217–0.957), P=0.038] and echinocandin therapy to be associated with success for the primary outcome (day 14 complete response) [OR 2.305 (1.124–4.727), P=0.023] (Table 3).

There were trends to suggest that fluconazole (but not echinocandin) efficacy was dependent on the severity of illness characteristics. Fluconazole response appeared to vary depending on ICU status [13/39 (33%) in ICU patients versus 45/88 (51%) in non-ICU patients, P=0.063], while echinocandin response did not [24/46 (52%) versus 26/51 (51%), respectively, P=0.907]. Fluconazole also trended towards being less efficacious in patients with mAPSs above versus below the median [26/66 (39%) versus 32/61 (53%), respectively, P=0.140], while echinocandins did not [23/44 (52%) versus 27/53 (51%), respectively, P=0.896].

**Mortality**
Mortality data are presented in Table 2. Overall survival was 205/224 (92%) and 176/224 (79%) at 14 and 28 days, respectively. Day 28 survival was 100/127 (79%) and 76/97 (78%) for fluconazole and echinocandins, respectively. Day 28 survival was similar for fluconazole versus echinocandin therapy in ICU patients [29/39 (74%) versus 33/61 (53%), respectively, P=0.491] and non-ICU patients [71/88 (81%) versus 43/53 (84%), respectively, P=0.591]. Logistic regression for 28 day mortality did not reveal any factors to be independently associated with death (Table 3).

**Fluconazole pharmacodynamics**
One hundred twenty-two of the 127 patients treated with fluconazole had MIC data available. Fifty-six (46%), 49 (40%) and 17 (14%) were infected with isolates with MICs of ≤8, 16–32 and ≥64 mg/L, respectively. Adjusting doses for renal function, 18/122 (15%), 61/122 (50%) and 43/122 (35%) patients were dosed at ≤800 mg/day, 201–400 mg/day and >400 mg/day, respectively. Day 14 complete response rates were 23/56 (41%), 27/49 (55%) and 4/17 (24%) for MICs ≤8, 16–32 and ≥64 mg/L,
respectively. When comparing patients who received fluconazole at a doseMIC ratio ≤ 12.5, administration of fluconazole at a doseMIC ratio > 12.5 was associated with a significantly higher day 14 complete response in all patients (4/20 (20%) versus 50/102 (49%) in patients with doseMIC ratios of ≤ 12.5 or > 12.5, respectively, P = 0.025) and in ICU patients only (0/9 (0%) versus 13/30 (43%), respectively, P = 0.018). While there was a trend towards increased 28 day survival with the same doseMIC cut-off, this result did not reach statistical significance [13/20 (65%) ≤ 12.5 versus 84/102 (82%) > 12.5, P = 0.079].

Discussion

Our study does not crown a clear ‘king’ in the treatment of C. glabrata fungaemia. Crude outcomes were strikingly similar between fluconazole and echinocandin treatment groups. However, patients who received echinocandins were more ill and, when a multivariable analysis was performed to adjust for such differences, echinocandin therapy was independently associated with complete response. This does not, however, rule out a role for fluconazole. We found some trends to suggest that fluconazole efficacy may be optimized if utilized in less ill patients. However, these results should be interpreted cautiously, as they were not statistically significant. Crucially, antifungal choice did not influence mortality, whether in univariate or multivariable analyses.

Only one randomized, controlled trial has compared fluconazole with an echinocandin for the treatment of invasive candidiasis. Rates of successful global response at the end of intravenous therapy (56% anidulafungin versus 50% fluconazole, P = 0.75) were not significantly different between groups in patients infected with C. glabrata. However, only 38 cases of C. glabrata infection were available for evaluation. Our primary outcome results, using a similar measure (complete response at 14 days), but including significantly more patients (n = 224), very closely resemble those of Reboli et al. (52% echinocandin versus 46% fluconazole, P = 0.383). Our findings are also consistent with the review by Andes et al., who found echinocandin therapy to be independently associated with treatment success, but not survival, in invasive candidiasis due to C. glabrata.

Our finding that a fluconazole doseMIC ratio > 12.5 was significantly correlated with complete response (and a trend towards improved survival) is consistent with that of Pai et al. and Baddley et al. Pai et al. reported that the weight-normalized fluconazole doseMIC values were significantly higher in survivors versus non-survivors (13.3 versus 7.0, respectively, P = 0.03). Similarly, Baddley et al. used classification and regression tree analysis to determine that a fluconazole AUC/MIC < 11.5 or an MIC > 64 mg/L was associated with increased patient mortality (P ≤ 0.09). However, whereas those studies included very few isolates with elevated MICs, our dataset included the largest number of isolates with MICs of 16–32 mg/L and > 64 mg/L that we are aware of (49 and 17, respectively). In addition, the prior studies grouped Candida species together, while we solely assessed C. glabrata. This is an important distinction, since new CLSI fluconazole clinical breakpoints are different for C. glabrata than for other Candida species. Our data lend support to these C. glabrata breakpoints of ≤ 32 mg/L (susceptible dose dependent) and > 64 mg/L (resistant), as a dose of 800 mg in adults with normal renal function would achieve a doseMIC ratio > 12.5 for MICs as high as 32 mg/L, while doses > 800 mg would be required for MICs > 64 mg/L.

Our data are subject to several limitations. Given the nature of retrospective reviews, we were not able to collect information on long-term complications such as endocarditis or endophthalmitis. In addition, susceptibility results were drawn largely from the patient charts. As such, it is not known whether differences in susceptibility testing techniques over time and across centres may have impacted our pharmacodynamic relationships. Finally, since we collected data from patients treated over a 9 year period and the echinocandins were not preferentially recommended until the 2009 IDSA guidelines, it is possible that advances in medical care may have influenced our findings. However, we did not observe any outcome trends when segregated by year (data not shown).

In conclusion, we found that the severity of illness and choice of antifungal predicted response in patients with C. glabrata fungaemia. However, mortality was not influenced by the choice of antifungal therapy. Our data also lend support to CLSI C. glabrata fluconazole susceptibility breakpoints and dosing recommendations. Further research is necessary to delineate optimal therapy choices in fungaemia due to other Candida species.
Acknowledgements
We would like to thank Lloyd G. Clarke, Chih-Min Fu, Philip Kong, Diana L. Pakstis and Tess Lin for their assistance in this study.

Funding
This study was carried out as part of our routine work. R. K. S. is supported by the National Institutes of Health through grant numbers KL2 RR024154 and KL2TR000146 and investigator-initiated grants received from Astellas and Merck.

Transparency declarations
P. L. C. has received grants from Merck and Astellas. C. J. C. has received research funding from Pfizer and Merck. M.-H. N. has received research funding from Viracor-IBT Laboratories and grant support from Pfizer and Merck. All other authors: none to declare.

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