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Initial treatment and outcome of *Candida glabrata* versus *Candida albicans* bloodstream infection☆

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Abstract

Candida glabrata is a common cause of bloodstream infection (BSI) and exhibits decreased susceptibility to fluconazole. We sought to determine whether patients with *C. glabrata* infection were at increased risk of inappropriate initial therapy and mortality compared with the more fluconazole-susceptible species *Candida albicans* by performing a matched case-control study using the Prospective Antifungal Therapy Alliance registry of invasive fungal infections. *C. glabrata* BSI patients were matched to those with *C. albicans* BSI by age, sex, and underlying illness after screening all *C. glabrata* patients entered into the registry from March 2004 through September 2007. Of 161 patients with *C. glabrata* BSI included and matched to 161 *C. albicans* patients, those with *C. glabrata* were less likely to receive an adequate dose of fluconazole as initial therapy (12% versus 52%, $P < 0.05$) and more likely to receive an echinocandin (44% versus 26%, $P < 0.05$) or inadequately dosed fluconazole (32% versus 8%, $P < 0.05$) as initial therapy. Although time to initiation of therapy did not differ by species ($P = 0.2$), time to receipt of adequate therapy was longer for those with *C. glabrata* BSI ($P < 0.001$). Overall, *C. glabrata* patients were more likely to receive inadequate initial therapy (34% versus 11%, $P < 0.05$), but 4-week mortality was no different between groups (30% for *C. glabrata* versus 29% for *C. albicans*, $P = 0.80$). We found hematologic malignancy, age greater than 60, the presence of a central venous catheter at diagnosis, mechanical ventilation, and dialysis dependence to be independent predictors of 4-week mortality. The lack of difference in mortality between species may reflect the overriding importance of host variables and/or a difference in virulence by species: further study is needed to investigate these hypotheses.

Keywords: Candida; Antifungal therapy

1. Introduction

Candida ranks as the 4th most common cause of nosocomial bloodstream infection (BSI) in the United States (Wisplinghoff et al., 2004), and mortality remains high for the past 20 years despite advances in antifungal therapy (Gudlaugsson et al., 2003). Recent reports have shown that early initiation of therapy can reduce mortality in patients with *Candida* BSI (Garey et al., 2006; Morrell et al., 2005), but the severity of underlying illness in these patients likely plays a significant role in the high risk of death that remains. Previous work has shown that patients with *Candida* BSI were at high risk for inadequate empiric therapy for infection, and that this may contribute to increased mortality rates (Ibrahim et al., 2000).

Candida glabrata, a species with reduced susceptibility to azole antifungal drugs, has emerged as the 2nd most common cause of candidemia in the United States (Trick et al., 2002). The rise to prominence of this species in recent decades has been postulated to be due to the

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increasing use of azoles such as fluconazole; however, several other factors such as patient age and the use of antimicrobials from other classes may play a role (Lin et al., 2005; Pfaller and Diekema, 2004). The reduced susceptibility to azoles of *C. glabrata* may increase the risk of patients receiving inadequate initial therapy because of the frequent use of fluconazole in this setting. We examined the incidence of inadequate antifungal therapy use in patients with *C. glabrata* BSI and the impact of antifungal therapy on outcome using data from a large registry of invasive fungal infections.

2. Materials and methods

2.1. Study design

The Prospective Antifungal Therapy (PATH) Alliance is a prospective, multicenter, observational registry that collects data on the epidemiology, diagnosis, treatment, and outcomes of invasive fungal infections from 23 medical centers in North America. The details of the study design, including patient inclusion criteria, data collection methods, and initial descriptive results, have been previously published (Horn et al., 2007). The study was approved by the institutional review boards of all participating centers.

In September of 2007, we obtained data for all patients with *C. glabrata* and *Candida albicans* BSI entered in the PATH Alliance registry between March 2004 and September 2007. First, *C. glabrata* BSI patients were excluded if they were also infected with another fungal pathogen (including another *Candida* spp.), if outcome at 4 weeks was not known, if patients were treated with blinded therapy as part of another study, if the patient died within 1 day of culture draw, or if a suitably close match with a *C. albicans* BSI patient could not be accomplished. The remaining patients with *C. glabrata* BSI were matched 1:1 with *C. albicans* patients by sex, age within 5 years, and underlying illness variables.

2.2. Definitions

Prior antifungal therapy was defined as receipt of antifungal treatment within 30 days before the date of culture. Adequate initial therapy was defined as appropriate treatment by *Candida* spp. with recommended doses of amphotericin B (deoxycholate or lipid formulation), an echinocandin, fluconazole, or voriconazole on the day of culture or later (Pappas et al., 2004). Regarding fluconazole dosing, treatment of *C. albicans* BSI was considered adequate at a dose of 400 mg daily, and for *C. glabrata*, at 800 mg daily, with adjustments made for weight and renal function. Lower doses of fluconazole were considered inadequate. Breakthrough candidemia was defined as the initial positive blood culture for *Candida* spp. being drawn while the patient was receiving an adequate dose of an antifungal agent for 1 day or greater.

2.3. Statistical analysis

Categorical variables were compared using χ^2 or Fisher's exact test as appropriate, continuous variables were compared using the *t* test, and ordinal data were compared using the Wilcoxon rank sum test. Multivariable logistic regression analysis was used to identify factors independently associated with 4-week mortality. Factors identified in a univariate model as significant with a $P \leq 0.1$ and those for which an association with mortality was plausible based upon previously published literature were entered into the model. Statistics were calculated with the help of SPSS software version 16.0 (SPSS, Chicago, IL).

3. Results

Data were collected from 23 centers (21 in the United States, 2 in Canada) from March 2004 through September 2007, at which time 1271 patients with candidemia had been entered in the database. After exclusions, remaining patients with *C. glabrata* BSI were then matched to *C. albicans* patients by sex, age within 5 years, and underlying illness resulting in 161 pairs, as illustrated in Table 1. There were no statistically significant differences in underlying illness categories such as immune deficiency, solid organ or hematopoietic stem cell transplant type, malignancy type, serum creatinine, presence of neutropenia, organ support such as hemodialysis, TPN, mechanical ventilation, acute cardiac support, ventricular shunt, or central venous catheter use. There was a trend toward more frequent corticosteroid use in the patients infected with *C. glabrata*, but this did not reach statistical significance.

Antifungal use in the 30 days before initial positive culture draw is shown in Table 2. Patients infected with *C. glabrata* were more likely to have received antifungal therapy before candidemia (89 [55%] versus 60 [37%], $P = 0.001$) and, specifically, fluconazole (72 [45%] versus 45 [28%], $P = 0.002$) or voriconazole (11 [7%] versus 1 [0.6%], $P = 0.005$). Minor nonsignificant differences in prior antifungal therapy with the polyenes, echinocandins, and other azoles were noted. Five patients (2 *C. albicans*, 3 *C. glabrata*) were treated for a mean of 2.4 days with an adequate dose of an antifungal at the time that blood cultures were drawn. These cases were characterized as breakthrough candidemia and were not included in the analysis of initial therapy. In contrast, 7 patients who developed candidemia while receiving low-dose fluconazole (5 *C. glabrata* and 2 *C. albicans*) were included in the analysis.

Initial therapy by antifungal is noted in Table 3. The choice of first antifungal in patients infected with *C. glabrata* was less likely to include an adequate dose of fluconazole (19 [12%] versus 84 [52%], $P < 0.001$) compared with those infected with *C. albicans*. Initial therapy was more likely to be an echinocandin (71 [44%] versus 42 [26%], $P = 0.001$) or inadequately dosed fluconazole (52 [32%] versus