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Early initiation of appropriate treatment is associated with increased survival in cancer patients with *Candida glabrata* fungaemia: a potential benefit from infectious disease consultation

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Abstract

In patients with malignancies, *Candida glabrata* is one of the most frequent non-*albicans Candida* clinical isolates. As antifungal resistance in *C. glabrata* is common, we investigated the relationship between early appropriate antifungal treatment, infectious disease (ID) consultation and mortality in a contemporary cohort of cancer patients with *C. glabrata* fungaemia. We included patients with at least one *C. glabrata*-positive blood culture and symptoms or signs of infection seen at the MD Anderson Cancer Center between March 2005 and September 2013. *In vitro* susceptibility to antifungals was defined according to the 2010 CLSI clinical breakpoints. One-hundred and forty-six episodes of candidaemia were studied. Thirty isolates (20.5%) had fluconazole MIC $\geq$ 64 mg/L and 15 (10.3%) were caspofungin-resistant. Early (within 48 h after blood culture collection) initiation of appropriate antifungal treatment (hazard ratio 0.374, p 0.003) and early ID consultation (hazard ratio 0.421, p 0.004) were associated with decreased mortality, after adjustment for significant confounders. Thirty-two of 58 patients (55.2%) followed by ID were on appropriate antifungals within 48 h, compared with 16/88 patients (18.2%) who were not followed by ID an ID specialist (p <0.001). The median time-to-reporting of blood culture positivity for yeast was 71 h. Delayed time-to-reporting was associated with increased 28-day all-cause mortality (log-rank p 0.023). The benefits from early initiation of appropriate antifungal treatment and ID consultation were more prominent in patients with non-catheter-related candidaemia. In conclusion, in cancer patients with *C. glabrata* fungaemia, early ID consultation may lead to timely initiation of appropriate treatment and improved clinical outcomes.

Keywords: Antifungal resistance, cancer, *Candida glabrata*, candidaemia, infectious disease consultation
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Introduction

In patients with cancer, the widespread use of antifungals in the setting of prophylaxis and pre-emptive or empiric treatment protocols has led to a notable shift from *albicans* to non-*albicans Candida* species [1–4]. *Candida glabrata* is among the most frequent species isolated from patients with malignancies, and the main species exhibiting multiazole, echinocandin and multidrug resistance (MDR; resistance to at least two classes of antifungals) [5,6].

Previous studies of candidaemia showed that early administration of fluconazole improved survival rates [7,8]. Adherence to national guidelines and infectious disease (ID) consultation led to a significant decrease in mortality rates [9,10]. Nevertheless, the relationship between early appropriate antifungal treatment and clinical success is not clear in the current era of high prevalence of resistance, especially in immunocompromised

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hosts: some recent studies showed improved outcomes with early initiation of appropriate treatment [11–14], whereas others did not [15–18].

As cancer patients with *C. glabrata* bloodstream infections often have multiple risk factors for treatment failure and adverse outcomes [2,4,5,19], it is important to identify interventions associated with increased survival, independent of host factors and source control. Therefore, we sought to investigate the correlation of clinical outcomes with early initiation of appropriate treatment and ID consultation, in a contemporary cohort of cancer patients with *C. glabrata* fungaemia.

Patients and methods

Data collection

We included patients with at least one blood culture(s) positive for *C. glabrata*, in addition to symptoms, signs (fever, hypothermia, tachycardia, hypotension or altered mental status) and/or laboratory findings (leucocytosis or leucopenia, thrombocytopenia or acidosis) consistent with infection, seen at MD Anderson Cancer Center between March 2005 and September 2013. We retrospectively reviewed electronic medical records for clinical and laboratory data on the day of blood culture collection, treatment, ID consultation, 28-day mortality and in-hospital all-cause mortality. Speciation of *C. glabrata* and antifungal susceptibility testing were performed as previously described (see Supporting information) [2–4,20,21]. The study was approved by the Institutional Review Board.

Definitions

Catheter-related candidaemia was defined as a patient with a colony count in a blood culture obtained via a central venous catheter (CVC) at least fivefold greater than the colony count in a peripheral blood culture, or a case with positive catheter tip culture [2,22].

Appropriate treatment was defined as amphotericin B for susceptible isolates, an echinocandin for isolates with caspofungin MIC <0.5 mg/L, or 800 mg of fluconazole daily for isolates with fluconazole MIC <64 mg/L (dose-dependent) [1,11,23]. Given the suboptimal responses of serious *C. glabrata* infections to azoles and the lack of clinical breakpoints for voriconazole, voriconazole was considered appropriate treatment only for fluconazole dose-dependent isolates with MIC <1 mg/L (one dilution above the epidemiological breakpoint) [21,23]. ID consultation within 48 h after blood culture collection referred to both the initial consultation and patients who were already followed by ID an ID specialist.

Statistical analysis

Normality of distribution was tested with the Kolmogorov–Smirnoff test. Continuous variables were compared with Student's *t*-test or the Mann–Whitney *U*-criterion for variables that were not normally distributed. Categorical variables were compared using the chi-square or Fisher exact test (expected frequency <5). We identified early interventions as those that occurred within 48 h after blood culture collection, and repeated all survival analyses after excluding patients who died within that time period.

Time-to-event survival analyses have been widely implemented in studies of candidaemia [11,24] as they allow more power to unmask potential physiological benefits [25], given the complex patient populations and frequent small sample sizes. However, in the critically ill, it has been argued that logistic regression using a dichotomous outcome is more appropriate, because for patients who die in the hospital, a prolonged stay does not reflect actual benefit [25]. Therefore, we addressed two outcome measures: a) 28-day survival analysed by the log-rank test and Cox regression, and b) all-cause in-hospital mortality rates, compared by binary logistic regression. The proportional hazards assumption was tested graphically and by building time-dependent variables. Numerical parameters were tested in different models both as scale and dichotomous variables (greater than versus less than the mean and/or widely used cut-off values of clinical significance). Clinically relevant parameters (univariate $p < 0.2$) were included at model entry. Appropriate treatment and ID consultation were forced separately in all multivariate analyses. Variables were retained in the final model if the p value was <0.05.

All analyses were performed with SPSS statistical software, version 21, IBM Corporation (Armonk, NY, USA). Two-tailed p values <0.05 were considered statistically significant. Values of $p > 0.05$ but <0.1 were noted as indicating trends.

Results

Patient population and *in vitro* susceptibilities

We identified 146 episodes of *C. glabrata* fungaemia. The demographic, clinical and laboratory characteristics of all patients are listed in Table 1. Thirty isolates (21%) had fluconazole MIC ≥64 mg/L. Twenty-four isolates (16%) were intermediate and 15 (10.3%) were resistant to caspofungin. Ten of 15 caspofungin-resistant isolates (67%) met the definition for MDR [6]: nine had fluconazole MIC ≥64 mg/L and one was resistant to amphotericin B. Antifungal MIC distributions are summarized in the Supporting information, Fig. S1.

Factors associated with all-cause mortality

The 28-day all-cause mortality rate was 40% (58/146), and the in-hospital mortality rate was 46.6% (68/146). Factors

TABLE 1. Basic demographic, clinical and laboratory characteristics of the 146 patients studied on the day of the positive for *Candida glabrata* blood culture collection[a]

Characteristic	*n* (%)
Host	
Age (years, mean (SD), range)	55.02 (14.99), 12–85
Male sex	75 (51)
Solid tumour[b]	99 (68)
Haematological malignancy	47 (32)
AML	17 (12)
ALL	5 (3)
Lymphoma	15 (10)
Multiple myeloma	4 (3)
Myelodysplastic syndrome	2 (1)
Other	4 (3)
HSCT	16 (11)
Diabetes mellitus	23 (16)
Chronic kidney disease	24 (16)
Chronic liver disease	18 (12)
Recent abdominal surgery (within 1 month)	26 (18)
TPN	36 (25)
Clinical disease	
Fever (>38 °C)	63 (43)
Mixed bloodstream infection	28 (19)
ICU stay	59 (40)
Mechanical ventilation	27 (19)
Septic shock (administration of vasopressor)	34 (23)
APACHE II score, mean (SD)	14.58 (6.97)
APACHE II score ≥20	38 (26)
Presence of a central line	131 (90)
Catheter-related candidaemia	60 (41)
Recent (within 1 month) drug exposures	
Chemotherapy	69 (47)
Corticosteroids	85 (58)
Antibacterials	144 (99)
Azoles	44 (30)
Echinocandins	32 (22)
Laboratory findings	
Neutropenia (AMC < 500/μL)	28 (19)
AMC 100–500/μL	9 (6)
AMC < 100/μL	19 (13)
Lymphopenia (ALC < 500/μL)	86 (59)
Monocytopenia (AMC < 100/μL)	39 (27)
AKI or ARF[c]	48 (33)
Acute liver injury[d]	23 (16)

Abbreviations: AKI, acute kidney injury; ALC, absolute lymphocyte count; ALL, acute lymphoblastic leukaemia; AMC, absolute monocyte count; AML, acute myeloid leukaemia; APACHE, acute physiology and chronic health evaluation score; ARF, acute renal failure; HSCT, haematopoietic stem cell transplantation; ICU, intensive care unit; TPN, total parenteral nutrition.
[a]Data are presented as absolute numbers (%) unless otherwise indicated for normally distributed variables or median numbers (25th-75th percentile) for variables that were not normally distributed.
[b]Forty-seven (32%) gastrointestinal tumours, 12 (8%) gynaecological tumours, 9 (6%) genitourinary tumours, 6 (4%) breast tumours, 6 (4%) lung tumours, 4 (3%) thyroid tumours, 4 (3%) sarcomas, 3 (2%) head and neck tumours, 2 (1%) central nervous system tumours, and 6 (4%) other tumours.
[c]Decrease in estimated glomerular filtration rate by 50% or 100% from baseline, respectively, or initiation of renal replacement treatment.
[d]Threefold increase in alanine aminotransferase level from baseline.

significantly associated with 28-day crude mortality are listed in Table 2. There was no association with age, sex or type of malignancy. Acute Physiology and Chronic Health Evaluation (APACHE) II score, recent corticosteroid administration, mixed bacterial bloodstream infections, non-catheter-related candidaemia, lack of early appropriate antifungal treatment and absence of early ID consultation were independently associated with increased 28-day mortality. Exclusion of patients who died within 48 h after blood culture collection or entering the APACHE II score as a categorical variable (≥15 vs.<15 or <20), did not affect the significance of independent associations between 28-day mortality and other parameters.

The mean time-to-reporting of culture positivity for yeast (available for 129 patients) was 75 h (SD 33.76, median 71 h, 25th–75th percentile: 21–96 h). Delayed time-to-reporting (> 72 h) was associated with increased 28-day all-cause mortality (log-rank p 0.023).

Early appropriate antifungal treatment

Patients who received early appropriate antifungal treatment were more likely to be in the intensive care unit (52.1% versus 34.7%, p 0.044) and in septic shock (33.3% versus 18.4%, p 0.044), compared with those who did not. Early appropriate antifungal treatment was independently associated with decreased 28-day mortality (Table 2) and in-hospital mortality (adjusted odds ratio 0.31, p 0.011; see Supporting information, Table S1). The antifungal agents administered during the first 48 h and at any time before hospital discharge or death are summarized in Table 3. Among the 48 patients who received early appropriate antifungal treatment, appropriate therapy constituted starting an antifungal agent in 30 patients (62.5%) and modifying existing antifungals in eight patients (16.7%). Ten patients (20.8%) were already receiving appropriate antifungal treatment at the time of positive blood culture.

ID consultation

Patients who underwent early ID consultation were more likely to have received haematopoietic stem cell transplantation (19% versus 5.7%, p 0.012), be in septic shock (32.8% versus 17%, p 0.028), and have fluconazole-resistant isolates (29.3 versus 14.8%, p 0.033), compared with those who did not. In multivariate analysis, we observed a strong contribution of early ID consultation to 28-day survival, after controlling for other confounders (adjusted hazard ratio, 0.421; p 0.004, Table 2). We also noted a trend for independent association between early ID consultation and in-hospital mortality (adjusted odds ratio 0.462, p 0.063; see Supporting information, Table S1).

Thirty-two of 58 patients (55%) who had early ID consultation (57%; 32 of the 56 who survived more than 48 h) received appropriate antifungals within 48 h after blood culture collection, as opposed to 16 of 88 patients (18%) who did not undergo early ID consultation (17.5%; 14 of the 80 patients who survived more than 48 h; p <0.001). Therefore, the effects of early appropriate antifungal treatment and ID consultation were less significant when both parameters were included in multivariate analysis than with inclusion of either of them alone (Table 2; see Supporting information, Table S2).

Among the 26 patients with early ID consultation who were not started on early appropriate antifungal treatment, two patients received an echinocandin plus an azole for MDR isolates. Four additional patients were treated with echinocandins for caspofungin-resistant isolates; seven patients received

TABLE 2. Factors associated with 28-day all-cause mortality in cancer patients with *Candida glabrata* fungaemia

	Univariate analysis			Multivariate analysis		
Factor	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
ICU stay	2.169	1.291–3.643	0.003			
HSCT	1.77	0.869–3.607	0.116			
Neutropenia	1.525	0.835–2.784	0.170			
Monocytopenia	1.485	1.141–1.934	0.003			
APACHE II score	1.107	1.066–1.150	<0.001	1.084	1.041–1.129	<0.001
Mechanical ventilation	2.712	1.549–4.750	<0.001	2.156	1.124–4.138	0.021
Septic shock	2.735	1.604–4.663	<0.001			
AKI or ARF	1.884	1.120–3.171	0.017			
Fever	0.517	0.299–0.896	0.019			
Corticosteroids[a]	2.961	1.596–5.494	0.001	2.919	1.550–5.499	0.001
Catheter-related candidaemia	0.451	0.253–0.802	0.007	0.496	0.268–0.919	0.026
Mixed bloodstream infection	1.906	1.058–3.436	0.032	2.961	1.580–5.550	0.001
Fluconazole resistance (≥64 mg/L)	1.727	0.971–3.074	0.063			
Caspofungin resistance (≥0.5 mg/L)	2.117	1.036–4.324	0.04			
Echinocandin pre-exposure[a]	2.075	1.197–3.598	0.009			
CVC removal within 48 h after blood culture collection[b]	0.356	0.157–0.998	0.049			
ID consultation within 48 h after blood culture collection[c]	0.678	0.392–1.174	0.166	0.537	0.290–0.996	0.048[c]
Appropriate treatment within 48 h after blood culture collection[d]	0.463	0.245–0.874	0.018	0.469	0.237–0.930	0.030[d]

Abbreviations: AKI, acute kidney injury; ARF, acute renal failure; CVC, central venous catheter; HR, hazard ratio; HSCT, haematopoietic stem cell transplantation; ICU, intensive care unit; ID, infectious disease.
[a]Within 1 month before blood culture collection.
[b]Among patients with a central venous catheter in place.
[c]HR 0.421, 95% CI 0.233–0.760 (p 0.004) after removal of appropriate treatment within 48 h after blood culture collection from the model and HR 0.418, 95% CI 0.220–0.796 (p 0.008) after exclusion of patients who died within 48 h after blood culture collection.
[d]HR 0.374, 95% CI 0.197–0.709 (p 0.003) after removal of ID consultation from the model and HR 0.357, 95% CI 0.178–0.718 (p 0.004) after exclusion of patients who died within 48 h after blood culture collection.

fluconazole <800 mg daily (two of those isolates had fluconazole MIC ≥64 mg/L). Thirteen patients (50%) did not receive any early antifungal treatment. Ten of those patients were started on appropriate treatment after blood cultures were reported as positive. The remaining three patients died before their blood cultures were reported as positive. Therefore, delayed diagnosis (13/26, 50%) and resistance (8/26, 30.7%) were the main reasons for lack of early appropriate antifungal treatment in patients who underwent early ID consultation.

Catheter-related versus non-catheter-related *C. glabrata* fungaemia

Sixty patients had catheter-related candidaemia based on paired quantitative blood cultures. Two of those also had a positive catheter tip culture. The positive associations of early initiation of appropriate treatment and early ID consultation with 28-day survival and discharge from the hospital were observed predominantly in patients with non-catheter-related candidaemia (Fig. 1; see Supporting information, Tables S2 and S3).

In all patients with a CVC, and in those with catheter-related candidaemia, catheter removal within 48 h after blood culture collection was associated with decreased all-cause mortality in univariate, but not multivariate, analysis. We did not find an association between mortality and early CVC removal in patients with CVC and non-catheter-related candidaemia (Table 2, Fig. 1).

TABLE 3. Antifungal treatment in 146 cancer patients with *Candida glabrata* fungaemia, *n* (%)

	Initial treatment[a]	Any treatment[b]
No treatment	56 (38.4)	24 (16.4)
Azole monotherapy	34 (23.3)	23 (15.8)
Echinocandin monotherapy	38 (26)	62 (42.5)
AMB monotherapy	4 (2.7)	4 (2.7)
Multiple antifungals		
Azole + echinocandin	9 (6.2)	16 (11)
Azole + AMB	—	2 (1.4)
Echinocandin + AMB	4 (2.7)	7 (4.8)
Azole + echinocandin + AMB	1 (0.7)	8 (5.5)

Abbreviation: AMB, Amphotericin-B.
[a]Antifungal treatment administered within 48 h after blood culture collection.
[b]Any antifungal treatment administered from the date of candidaemia until death or discharge from the hospital.

Discussion

In the present series of cancer patients with *C. glabrata* fungaemia, early initiation of appropriate treatment and ID consultation were associated with decreased all-cause mortality, after adjustment for other confounders. This effect was more prominent in immunocompromised and critically ill patients with non-catheter-related candidaemia, such as those with prolonged neutropenia or complicated intra-abdominal pathology.

Appropriate antifungal treatment given within 48 h after blood culture collection was independently associated with decreased 28-day and in-hospital mortality, which is in agreement with some [2,11–14], but not all [15–18], previous reports. In all of those previous studies, a significant proportion of fungaemia episodes were caused by *Candida albicans*. Timely

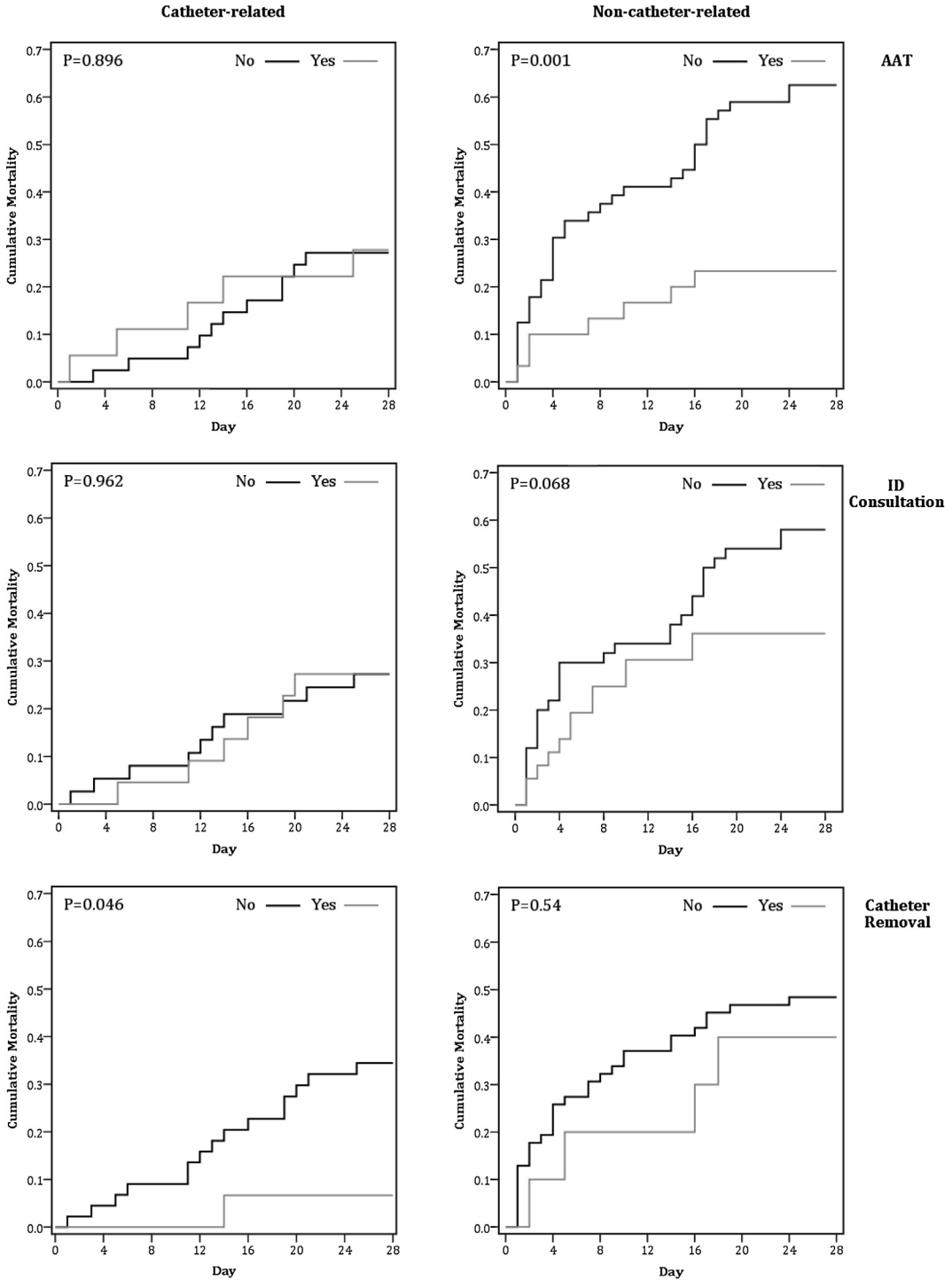

FIG. 1. Comparison of Kaplan–Meier curves by the log-rank test in cancer patients with catheter-related candidaemia (left) or candidaemia from other sources (right), showing the association of early (within 48 h after blood culture collection) interventions (AAT, ID and CVC removal) with 28-day all-cause mortality. Abbreviations: AAT, appropriate antifungal treatment; ID, infectious disease consultation; CVC, central venous catheter.

initiation of appropriate treatment is particularly important for infections with *C. glabrata*, a species that is virulent and often resistant to antifungals [5], but is associated with slower *in vitro* growth, which can delay the initiation of treatment [11,13]

The correlation between time-to-positivity and outcome is of particular interest. In a previous study of candidaemia, delayed culture positivity was associated with decreased all-cause mortality, in contrast to our results [11]. However, the

majority of episodes were caused by *C. albicans* and *Candida tropicalis*, both of which exhibit faster *in vitro* growth [11,13], compared with *C. glabrata*. In our study, the median time-to-reporting of *C. glabrata*-positive blood cultures was almost 3 days, and longer times-to-reporting correlated with increased mortality. Our results underscore the importance of a high clinical suspicion and timely administration of effective treatment in *C. glabrata* fungaemia, before blood cultures are reported as positive. Indeed, the high mortality associated with candidaemia in the present and previous [7,8,14] reports can be attributed to the long time that is needed for culture-based diagnosis [26]. Specifically, in a recent study of candidaemic patients in septic shock [14], the median time-to-positivity across different *Candida* species was more than 2 days (55 h), but administration of appropriate antifungals within 24 h after blood culture collection was independently associated with increased survival rates, in agreement with our findings. Furthermore, in our study, delayed culture-based diagnosis was the main reason for not initiating appropriate antifungals within 48 h after blood sample collection, among patients who were followed by ID specialists. It should be noted that new technologies, such as β-D-glucan and PCR-based assays, can assist in the early diagnosis of candidaemia and guide the initiation of empirical treatment, leading to better clinical outcomes [26].

In our study, threefold more patients who had an ID consultation than those who did not received adequate treatment for candidaemia within 48 h after blood culture collection. Early ID consultation was associated with decreased all-cause mortality after controlling for host characteristics and disease severity, especially in patients with non-catheter-related candidaemia. Our findings are in agreement with those in two previous reports [9,10]. Nevertheless, factoring local epidemiology regarding species distribution and resistance into therapeutic decision-making is paramount in the care of patients with candidaemia and, to our knowledge, no previous studies focused on the role of early ID consultation input for candidaemia in the current era of high non-*albicans Candida* spp. prevalence and antifungal resistance. In one of the studies described above, the researchers did not report susceptibility or timing of ID consultation [9]. In the other, most of the isolates were susceptible to fluconazole [10]. In cancer patients with candidaemia, ID consultation can contribute to optimization of care through not only prompt initiation of appropriate antifungals and source control, but also management of other concomitant infections, medication toxicity and antifungal stewardship [27]. The latter is of particular importance in the cancer patient population, because our rates of *in vitro* caspofungin and MDR were among the highest reported to date.

Similar to previous studies [12,22], early CVC removal was associated with increased survival only in the subgroup of patients with catheter-related fungaemia, whereas timely initiation of appropriate treatment was associated with decreased mortality in those with non-catheter-related infections. The benefit of early catheter removal decreased after adjustment for other confounders, which was similar to a previous study [28], but contrasted with the results of other investigators [12,24,29]. It should be noted that the absence of an independent association in our study may have resulted from the small number of patients who underwent early CVC removal. Although removal of a catheter is considered the standard of care in the treatment of candidaemia [1], larger prospective studies are still needed to better identify the independent association between early CVC removal and outcomes in catheter-associated *C. glabrata* fungaemia.

Our retrospective, single-centre study had several limitations. First, our observations might not be applicable to different patient groups at risk for candidaemia, or different *Candida* species. Second, using caspofungin MIC without data regarding FKS mutations might have led to overestimation of echinocandin resistance [5]. Third, a significant proportion of patients (38%, Table 3) did not receive any antifungal treatment within 48 h, and in the majority of those who did (63%), antifungal therapy was initiated, not changed. Therefore, our study was not powered to detect differences regarding early administration of specific antifungals, modification of treatment, or combination regimens. Finally, our outcome measure was all-cause mortality, and we did not report any data on *Candida*-attributable mortality or mycological response. However, the autopsy rate at our institution is low [30], and sterilization of blood cultures does not always reflect the success and effective timing of interventions, especially after initiation of the sepsis cascade in immunocompromised patients. By assessing all-cause mortality, an objective outcome measure widely used in retrospective studies of candidaemia [11,14,15–20,24], we believe that we captured an important benefit from timely appropriate treatment and ID consultation.

In conclusion, in cancer patients with *C. glabrata* fungaemia, having high rates of antifungal resistance, early initiation of appropriate treatment and ID consultation were associated with increased survival. Candidaemia is another indication where early involvement of an ID specialist may lead to timely initiation of adequate treatment and improved outcomes, along with judicious use and appropriate de-escalation of antifungals.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cmi.2014.07.006.

Transparency Declaration

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Author contributions

D.F. and D.P.K. were responsible for study design and data analysis; D.F. and A.K. were responsible for clinical data collection and, with J.J.T., for laboratory data collection. All authors contributed to manuscript preparation.

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