Blood Stream Infections by *Candida glabrata* and *Candida krusei*: A Single-Center Experience

Hee Kyoung Choi, Su Jin Jeong, Han Sung Lee, Bum Sik Chin, Suk Hoon Choi, Sang Hoon Han, Myung Soo Kim, Chang Oh Kim, Jun Yong Choi, Young Goo Song, and June Myung Kim

Department of Internal Medicine, AIDS Research Institute, Yonsei University College of Medicine, Seoul, Korea

Background/Aims: The increasing incidence of *Candida glabrata* and *Candida krusei* infections is a significant problem because they are generally more resistant to fluconazole. We compared the risk factors associated with *C. glabrata* and *C. krusei* fungemia with *Candida albicans* fungemia and examined the clinical manifestations and prognostic factors associated with candidemia.
Methods: We retrospectively reviewed demographic data, risk factors, clinical manifestations, and outcomes associated with *C. glabrata* and *C. krusei* fungemia at a tertiary-care teaching hospital during a 10-years period from 1997 to 2006.
Results: During the study period, there were 497 fungemia episodes. *C. glabrata* fungemia accounted for 23 episodes and *C. krusei* fungemia accounted for 8. Complete medical records were available for 27 of these episodes and form the basis of this study. Compared to 54 episodes of *C. albicans* fungemia, renal insufficiency and prior fluconazole prophylaxis were associated with development of *C. glabrata* or *C. krusei* fungemia. The overall mortality was 67%. The fungemia-related mortality of *C. glabrata* and *C. krusei* was higher than that of *C. albicans* (52 vs. 26%, *p*=0.021). Empirical antifungal therapy did not decrease the crude mortality. Multiple logistic regression analysis showed that high APACHE II scores, catheter maintenance, and shock were independently associated with an increased risk of death.
Conclusions: Renal insufficiency and prior fluconazole prophylaxis were associated with the development of *C. glabrata* or *C. krusei* fungemia. Fungemia-related mortality of *C. glabrata* or *C. krusei* was higher than that of *C. albicans*. Outcomes appeared to be related to catheter removal, APACHE II scores, and shock. **(Korean J Intern Med 2009;24:263-269)**

Keywords: Candidemia; Risk factors; Mortality

INTRODUCTION

Recently, we have seen an increase in the frequency of non-*albicans* species of *Candida*, such as *C. glabrata*, *C. krusei*, *C. tropicalis*, and *C. parapsilosis*, as the cause of fungemia [1,2]. *C. krusei* is intrinsically resistant to fluconazole because of a decreased susceptibility of 14α-demethylase [3], and *C. glabrata* is relatively resistant to fluconazole due to an energy-dependent efflux mecha-

nism [4]. The increasing proportion of fungemia due to *C. glabrata* and *C. krusei* has important implications for therapy.

We evaluated the risk factors associated with *C. glabrata* and *C. krusei* fungemia in comparison with *Candida albicans* fungemia. We also examined the clinical manifestations and prognostic factors associated with candidemia.

Correspondence to Jun Yong Choi, M.D.
Department of Internal Medicine, Yonsei University College of Medicine,134 Shinchon-dong, Seodaemun-gu, Seoul 120-792, Korea
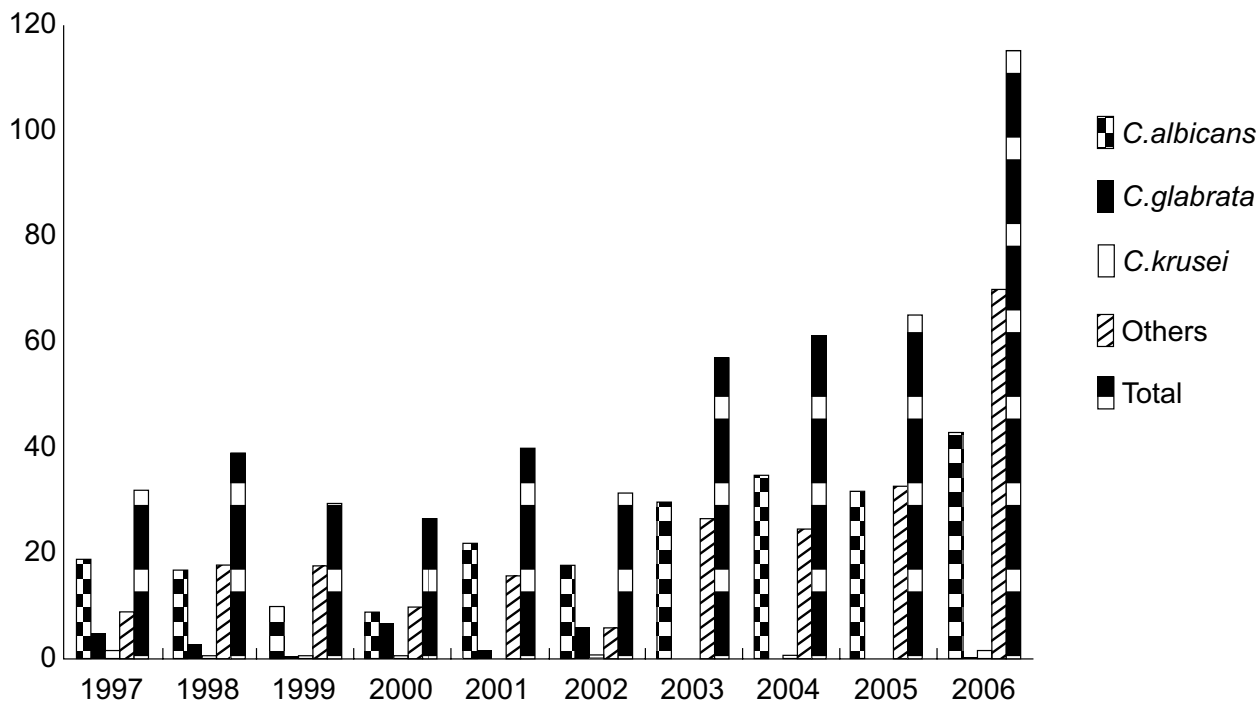Tel: 82-2-2228-1975, Fax: 82-2-393-6884, E-mail: seran@yuhs.ac

Figure 1. Annual fungemia episodes and causative organisms over a 10 year period at Severance Hospital.

METHODS

Study design

All episodes of fungemia that occurred between January 1997 and December 2006 at Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, a 1500-bed tertiary-care teaching hospital, were identified. We retrospectively reviewed demographic data, risk factors, clinical manifestations, and outcomes associated with *C. glabrata* and *C. krusei* fungemia. In addition, we selected 54 patients who had *C. albicans* fungemia as the control group. Cases and controls were matched 1 to 2 by age, sex, and the time of fungemia.

Definitions

An episode of fungemia was defined as the isolation of any pathogenic species of *Candida* from at least one blood culture specimen from a patient with signs and symptoms of infection. A second episode of fungemia occurring in the same patient within 4 weeks of the first episode was counted as the same episode. Recovery from candidemia was defined as the resolution of all clinical manifestations and no further positive blood cultures within 1 weeks after therapy. Failure to respond was defined as the persistence of clinical signs and symptoms or persistent candidemia caused by the same *Candida* species after the onset of

therapy.

Death was attributed to *Candida* infection if the patient did not respond to therapy and there was no other obvious cause of death, such as a major hemorrhage or other infection. We defined early mortality as death within 3 to 7 days after diagnosis and late mortality as death between days 8 and 30. Patients who received no antifungal therapy were excluded from the analysis.

Statistical analysis

The χ^2 test and Fisher's exact test were used to determine categorical predictors of infection and outcome. Continuous variables were compared using the *t*-test. Multiple logistic regression analysis was performed to identify independent predictors of death; variables included the APACHE II scores, catheter maintenance, shock, non-*albicans* species, and early treatment. P values of less than 0.05 were considered statistically significant. All statistical analysis was performed with (SPSS Inc., Chicago, IL, USA).

RESULTS

Incidence, demographic and clinical characteristics

During the study period, there were 497 fungemia

Table 1. Demographics, clinical manifestations, and risk factors of *C. glabrata* and *C. krusei* fungemia

	C. glabrata or *C. krusei* (n=27)	*C. albicans* (n=54)	*p* value
Age, years	48±25	49±23	NS
Male/female	12/15	12/15	NS
Underlying disease			
Cardiovascular disease	9 (33)	19 (35)	NS
Diabetes mellitus	10 (37)	16 (30)	NS
Cirrhosis	2 (7)	4 (7)	NS
Renal insufficiency	5 (19)	2 (4)	0.038
Dialysis	2 (7)	2 (4)	NS
Autoimmune disease	0 (0)	3 (6)	NS
Solid-organ cancer	9 (33)	19 (35)	NS
Hematologic malignancy	5 (19)	5 (10)	NS
Prematurity	1 (4)	2 (4)	NS
Bone marrow transplant	1 (4)	2 (4)	NS
Solid-organ transplant	0 (0)	1 (2)	NS
HIV/AIDS	0 (0)	0 (0)	NS
Radiotherapy	2 (7)	5 (9)	NS
Immunosuppressive drugs	14(52)	23 (43)	NS
Burns/trauma	2 (7)	5 (9)	NS
Central venous catheter use	24 (89)	49 (91)	NS
Parenteral nutrition	24 (89)	44 (82)	NS
Mechanical ventilation	11 (41)	26 (48)	NS
Prior major surgery, within 30 days	4 (15)	15 (28)	NS
Neutropenia	5 (19)	7 (13)	NS
Use of prophylactic fluconazole	12 (44)	6 (11)	0.001
Hospital days	67±50	77±72	NS
Hospital days before fungemia	38±33	42±47	NS
Stay in ICU, days	25±50	19±41	NS
Stay in ICU before fungemia, days	15±31	11±25	NS
APACHE II score	17±7	18±7	NS
Clinical manifestations			
Endophthalmitis	0 (0)	0 (0)	NS
Osteomyelitis	1 (4)	1 (2)	NS
CNS infection	0 (0)	1 (2)	NS
Endocarditis	0 (0)	1 (2)	NS
Abscess	0 (0)	2 (4)	NS
Peritonitis	4 (15)	6 (11)	NS
Acute renal failure	11 (41)	21 (39)	NS
Shock	18 (67)	27 (50)	NS

Values are number (percentage) or mean±SD.
NS, not significant; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; ICU, intensive care unit ; CNS, central nervous system.

episodes. *C. glabrata* fungemia accounted for 23 episodes (4.6%) and *C. krusei* fungemia accounted for eight (1.6%). The proportion of fungemias due to *C. glabrata* or *C. krusei* ranged from 0-29% per year (Fig. 1).

Complete medical records were available for 27 of the 31 episodes with non-*albicans* infections and 54 of the 234 episodes with *C. albicans* infections; therefore, 27 and 54 cases of each bloodstream infection were compared.

Candida glabrata fungemia occurred in 12 men (44% of subjects) and 15 women (56% of subjects). Their mean age was 48±25 years. The majority of patients had multiple

Table 2. Treatment outcomes of 27 episodes of *C. glabrata* and *C. krusei*

	AmB (n=13)	Flu (n=3)	No treatment (n=9)	Op + AmB (n=1)	Flu + Am B (n=1)
Recovery from candidemia	10 (77)	0 (0)	2 (22)	1 (100)	0 (0)
Mortality*	7 (54)	3 (100)	7 (78)	0 (0)	1 (100)
Fungemia-related mortality	3 (23)	3 (100)	7 (78)	0 (0)	1 (100)

Values are number (percentage).
AmB, amphotericin B; Flu, fluconazole; Op, operation.
* Overall mortality at day 30.

underlying illnesses and other risk factors that have been associated with fungemia. The most common underlying illnesses were diabetes mellitus (37%), cardiovascular diseases (33%), and solid-organ cancer (33%). No patient developed endophthalmitis, central nervous system infection, endocarditis, or abscesses during the follow-up period. One patient had osteomyelitis and four had peritonitis as a primary infection. Eleven patients developed acute renal failure (ARF) and 18 presented with septic shock (Table 1).

Risk factors for *C. glabrata* or *C. krusei*

Compared to 54 episodes of *C. albicans* fungemia, renal insufficiency and prior fluconazole prophylaxis were associated with the development of *C. glabrata* or *C. krusei* fungemia (Table 1).

Treatment and outcomes of fungemia

Of the 27 episodes, 18 (67%) were treated with an antifungal agent. Nine episodes (33%) were not treated because of death before diagnosis (5 patients), discharge to another hospital (1 patient), or no reason was documented (3 patients). Of the nine episodes for which an antifungal agent was not used, two patients showed recovery from the *Candida* infection. They were not treated with any antifungal agent, but the central venous catheter was removed. Of the 18 episodes for which an antifungal agent was used, three were treated with fluconazole alone, 13 episodes were treated with ampho-

tericin B formulation alone, and one case with osteomyelitis was treated with amphotericin B formulation and surgery. One patient was treated with fluconazole initially, and this was switched to amphotericin B after the species was documented to be *C. glabrata*. For 10 of the 13 episodes (77%) treated with amphotericin B, additional blood cultures grew no yeast by the end of therapy. The mortality rate for episodes treated with amphotericin B was 54% (7 of 13 episodes), and fungemia-related mortality constituted 23% (3 of 13 episodes). All patients who did not achieve microbiological success died of fungemia (Table 2).

Overall, the early and late mortality of *C. glabrata* and *C. krusei* fungemia were not significantly different from that due to *C. albicans*. However, the fungemia-related mortality for *C. glabrata* and *C. krusei* was higher (52%, 14/27) than that due to *C. albicans* (26%, 14/54, p=0.021, Table 3).

In the univariate analysis, patients whose central venous catheters were not removed (p<0.01) or who had high APACHE II scores (p=0.01) had a higher crude mortality. Receiving appropriate antifungal therapy within 24 hours was not associated with a risk of mortality (p=0.21). Septic shock was associated with an increased risk of mortality (p<0.01, Table 4).

Multiple logistic regression analysis showed that increasing APACHE II scores (one-point increments) (odds ratio [OR] 1.262, 95% CI 1.116-1.427, p<0.01), catheter maintenance (OR 8.982, 95% CI 1.715-47.032,

Table 3. Differences in outcome between *C. glabrata*, *C. krusei*, and *C. albicans*

	C. glabrata or *C. krusei* (n=27)	*C. albicans* (n=54)	p value
Recovery from candidemia	13 (48)	37 (69)	0.075
Mortality	18 (67)	26 (48)	NS
Early mortality	4 (15)	11 (20)	
Late mortality	14 (52)	15 (28)	
Mortality related to fungemia	14 (52)	14 (26)	0.021

Values are number (percentage).
NS, not significant.

Table 4. Univariate analysis of the factors associated with death in patients with candidemia

	Survivors (n=37)	Non-survivors (n=44)	*p* value
Continuous variables			
Age, years	52±23	44±24	NS
APACHE II score	21±6.7	14±5.4	0.01
Categorical variables			
Catheter maintenance	5 (13.5)	19 (43.2)	<0.01
Fluconazole prophylaxis	7 (18.9)	11 (25.0)	NS
Early treatment (<24 hours)	13/35 (37.1)	9/37 (24.3)	NS
Hypertension	10 (27.0)	18 (40.9)	NS
Diabetes mellitus	10 (27.0)	16 (36.4)	NS
Chronic renal failure	4 (10.8)	6 (13.6)	NS
Autoimmune disease	1 (2.7)	2 (4.5)	NS
Hematologic malignancy	3 (8.1)	7 (15.9)	NS
Immunosuppressant	14 (37.8)	19 (43.2)	NS
Solid cancer	13 (35.1)	15 (34.1)	NS
Total parenteral nutrition	31 (83.8)	38 (86.4)	NS
Non-*albicans*	9 (24.3)	18 (40.9)	NS
Acute renal failure	11 (29.7)	21 (47.7)	NS
Shock	10 (27.0)	34 (77.3)	<0.01

Values are number (percentage) or mean±SD.
NS, not significant.

p<0.01), and shock (OR 14.465, 95% CI 3.573-58.557, *p*<0.01) were independently associated with death (Table 5).

DISCUSSION

Candida species are now the fourth most common cause of nosocomial bloodstream infections and are associated with a crude mortality rate of 39%, which is the highest mortality rate associated with any form of nosocomial bloodstream infection [1]. During the past decade, an increase in the incidence of bloodstream infections due to *Candida* species other than *C. albicans* has been reported [2,5-7]. However, no increase in *C. glabrata* or *C. krusei* fungemia was evident in our study.

Candida krusei and *C. glabrata* infections can cause

serious complications as they have higher crude mortality than other *Candida* species, such as *C. albicans* or *C. parapsilosis* [1]. In our study, non-*albicans* fungemia did not cause complications such as endophthalmitis or endocarditis. However, the true incidence of these complications is likely to have been higher, because echocardiography was performed in fewer than half of the episodes and ophthalmological examinations were conducted in five cases only. In our analysis, the crude mortality for non-*C. albicans* (*C. glabrata* or *C. krusei*) fungemia was not different from that due to *C. albicans* fungemia. This is consistent with the findings of Klevay et al. [8], Blot et al. [9], and Bassetti et al. [10], who found that mortality did not differ by species. However, fungemia-related mortality was significantly higher among patients with *C. glabrata* or *C. krusei* fungemia.

Previous investigations have suggested that prior

Table 5. Multivariate analysis of the factors associated with death in patients with candidemia

	OR	95% CI	*p* value
APACHE II score (one-point increments)	1.26	1.11-1.42	<0.01
Catheter maintenance	9.14	1.69-49.53	0.01
Shock	14.68	3.54-60.86	<0.01
Non-*albicans*	1.26	0.32-5.00	0.746
Early treatment (<24 hours)	0.37	0.09-1.48	0.159

OR, odds ratio; CI, confidence interval.

exposure to antifungal agents [2,11,12], exposure to anti-microbial agents, especially vancomycin or piperacillin-tazobactam [13], age [14,15], and underlying hematologic malignancy [11,16] were predisposing factors for non-*albicans* fungemia.

Although there is a historical association between fluconazole use and the increased incidence of relatively resistant non-*albicans Candida* species, the degree to which fluconazole plays a role in the risk to individual patients remains unclear [17]. Fluconazole prophylaxis was a predisposing factor in our analysis. However, not all studies have linked fluconazole use to increased colonization and infection by *C. glabrata* or *C. krusei*. Lin et al. [13] reported that exposure to fluconazole was not found to be a significant risk factor for developing non-*C. albicans* candidemia. Similarly, Safdar et al. [18] reported that the predominance of *C. glabrata* and *C. krusei* breakthrough infections was similar to that seen with high-dose fluconazole (400 mg) prophylaxis, and no adverse effect of low-dose fluconazole in terms of an increased incidence of non-susceptible *Candida* species was seen.

In several studies, predictors of death from candidemia were APACHE II scores at the time of fungemia [18-22], length of hospitalization [23], delayed or inappropriate treatment [21,24,25], neutropenia [19,20,26,27], and central venous catheter maintenance [20,27]. We observed that increasing APACHE II scores (OR 1.262, 95% CI 1.116-1.427, p<0.01), catheter maintenance (OR 8.982, 95% CI 1.715-47.032, p<0.01), and shock (OR 14.465, 95% CI 3.573-58.557, p<0.01) were independently associated with the risk of death. This was similar to previous studies, while empirical antifungal therapy, which was started within 24 hours from the time when the blood samples were obtained, but before identification of the organism, did not improve outcome. Bias was likely in the selection of antifungal agents used in various patients. Immunocompromised patients were perhaps more likely to have been given amphotericin B, and very sick patients received no therapy because of early death due to fungemia.

There are several limitations to this study. First, data were collected from a single center, resulting in a limited sample size that could be influenced by local outbreaks, specific infection-control practices, or regional suscepti-bility patterns. Second, the retrospective nature of this analysis may be susceptible to reviewer bias. Third, the small sample size when various subsets were assessed with regard to mortality precludes meaningful statistical

analysis of many of these factors.

In conclusion, renal insufficiency and prior fluconazole prophylaxis were associated with the development of *C. glabrata* or *C. krusei* fungemia. Fungemia-related mor-tality due to *C. glabrata* or *C. krusei* was higher than due to *C. albicans*.

The outcomes appeared to be related to catheter re-moval, APACHE II scores, and shock. Future prospective studies including data from multiple centers that analyze antimicrobial use and subsequent colonization and infection by *C. glabrata* and *C. krusei* will lead to a better understanding of the epidemiology of these increasingly important pathogens.

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