



Original Article

Risk factors and clinical outcomes of breakthrough yeast bloodstream infections in patients with hematological malignancies in the era of newer antifungal agents

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Abstract

Although yeast bloodstream infections (BSIs) are increasingly being reported in patients with hematological malignancies undergoing antifungal therapy, clinical information regarding breakthrough infections is scarce. The aim of this study was to determine the risk factors for and clinical outcomes of breakthrough yeast BSIs in patients with hematological malignancies in the era of newer antifungal agents. Between 2011 and 2014, all consecutive patients with hematological malignancies who developed yeast BSIs were included in a case-control study wherein breakthrough infections (cases) and *de novo* infections (controls) were compared. Of 49 patients with yeast BSIs, 21 (43%) met the criteria for breakthrough infections. The proportions of *Candida krusei* and *Candida tropicalis* in the cases and controls were significantly different (32% [7/22] vs. 3% [1/29], $P = .015$; 5% [1/22] vs. 38% [11/29], $P = .007$, respectively). Acute leukemia, presence of a central venous catheter and neutropenia in the 3 days prior to BSI were significant risk factors for breakthrough infections. Six-week mortality rates was 33% [7/21] in the cases and 43% [12/28] in the controls ($P = .564$). Refractory neutropenia and the Pitt bacteremia score were independent predictors of 6-week mortality. In conclusion, breakthrough infections accounted for a significant proportion of yeast BSIs in patients with

hematological malignancies. However, these infections did not increase the risk of death by themselves. Our results suggest that current clinical management of breakthrough yeast BSIs, which includes switching to a different antifungal class and prompt catheter removal is reasonable.

Key words: breakthrough infection, yeast, bloodstream infection, hematological malignancy.

Introduction

Despite recent advances in diagnosis, prophylaxis and treatment, invasive fungal infections (IFIs) remain a leading cause of morbidity and mortality in immunocompromised or critically ill patients.^{1–3} *Candida albicans* is a major cause of invasive yeast infections, but recently, yeast infections caused by non-*albicans* *Candida* species and other rare yeasts have increased.^{4–7} These less common yeasts usually colonize human skin and mucosal surfaces and are opportunistic pathogens associated with life-threatening infections in immunocompromised hosts. Notably, a significant number of invasive infections caused by these emerging pathogens occurs as breakthrough infections.^{6,7}

Breakthrough invasive candidiasis is an unresolved problem in immunocompromised patients, particularly those with hematological malignancies.^{3,8} To date, few retrospective studies have investigated the risk factors for and outcomes of breakthrough candidemia compared to *de novo* candidaemia.^{9–12} Moreover, most of these studies were confined to candidemia patients and were published more than a decade ago, before the newer broad-spectrum antifungal agents came into use. The change in the epidemiology of IFIs, advances in antifungal agents, and updated strategies for the prevention and treatment of IFIs warrant a reevaluation of breakthrough invasive yeast infections. Therefore, we conducted a study to determine the risk factors for and clinical outcomes of breakthrough yeast bloodstream infections (BSIs) in patients with hematological malignancies in the era of newer antifungal agents.

Methods

Study design, hospital Setting, and patients

We conducted a case-control study from a prospective observational cohort of adult patients with hematological malignancies who developed yeast BSIs between January 2011 and December 2014. All patients aged 18 years or more who were admitted to the Catholic Blood and Marrow Transplantation (BMT) Center, a 1,355-bed tertiary-care teaching hospital located in the Republic of Korea were included in this cohort. All consecutive patients with yeast BSIs were enrolled in the case-control study. Those with breakthrough infections were designated as case patients, while those with

de novo infections were included in the control group. In patients with yeast BSIs, blood cultures were usually repeated every 3 days until no infection was detected. During the study period, oral fluconazole tablets (50–400 mg daily), itraconazole oral solution (2.5 mg/kg twice daily), micafungin (50 mg daily) and posaconazole oral suspension (200 mg 3 times daily) were used as primary antifungal prophylaxis. For empirical or targeted therapy against breakthrough IFIs, we preferred to change the antifungal class including amphotericin B deoxycholate (1 mg/kg daily), caspofungin (loading dose of 70 mg, then 50 mg daily), liposomal amphotericin B (3–5 mg/kg daily), and voriconazole (loading dose of 6 mg/kg twice daily, then 3 mg/kg twice daily). Removal of central venous catheters (CVCs) was preferred in all non-neutropenic patients, while in neutropenic patients, infectious disease specialists decided whether to remove the CVC if it appeared to be the source of infection. The study was approved by the Institutional Review Board of Seoul St. Mary's Hospital, and informed consents were waived (KC16RISI0623).

Data collection

The annual usage of antifungal agents for patients admitted to the Catholic BMT Center during the study period was determined by calculating the number of defined daily doses (DDD) per 1,000 patient-days, as recommended by the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology (www.whocc.no/atc_ddd_index/).

Clinical and microbiological data were collected by infectious diseases specialists at the participating BMT Center. The following variables were recorded: patient demographics; type of underlying hematological malignancies; history of previous chemotherapy and hematopoietic stem cell transplantation; comorbidities; risk factors for yeast BSIs in the 4 weeks prior to the first positive blood culture including intensive care unit residence, use of corticosteroid (mean minimum dose of 10 mg daily of prednisone equivalent for >14 days), surgery, hyperalimentation, presence of CVC and neutropenia; prior and concurrent use of antibiotics and antifungals; Pitt bacteremia score at the onset of yeast BSI; clinical characteristics of yeast BSI episodes; antifungal therapy and clinical outcomes.

Definitions

A yeast BSI was defined as at least one blood culture that yields yeast from a patient with compatible clinical signs or symptoms. *Candida* spp. other than *C. albicans*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, and *Candida tropicalis* were termed ‘uncommon *Candida* spp.’.¹³ The day of sampling for the first positive blood culture was considered to be the time of onset of a yeast BSI. Breakthrough infection was defined as an infection occurring in a patient receiving systemic antifungal agents for at least 5 days for any reason before the onset of a yeast BSI.¹⁰ Neutropenia was defined as an absolute neutrophil count less than 500 cells/mm³ or expected count of less than 500 cells/mm³ within the following 2–3 days.¹⁴ The definition of septic shock was adapted from the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee.¹⁵ The Pitt bacteremia score was calculated to assess the severity of illness at the onset of yeast BSIs.¹⁶ The source of the yeast BSI was classified based on clinical evidence of infection regardless of whether causative organisms were recovered from the affected site. Definition of CVC-related BSIs were defined as one of the following criteria: (i) culture of the same organism from both the catheter tip and at least one percutaneous blood culture; or (ii) culture of the same organism from at least two blood samples (one from a catheter hub and the other from a peripheral vein) and growth detected from the catheter hub sample at least 2 h before growth detected from the peripheral vein sample.¹⁷ Polymicrobial BSIs were defined as isolation of ≥ 2 different yeast spp. or a yeast with concomitant bacterial organisms from blood cultures obtained within a 48 h period.¹⁸ Time to initiation of appropriate antifungal therapy was defined as the number of days from the onset of a yeast BSI to administration of appropriate antifungal therapy. Appropriate antifungal therapy was defined as a loading or therapeutic dose of a qualifying antifungal agent including azoles, echinocandins and polyenes, based on the results of susceptibility testing, if available. Appropriate doses of antifungal agents for *Candida* spp. were determined by the updated Infectious Diseases Society of America guidelines.¹⁹ The appropriateness of antifungal therapy for yeasts other than *Candida* spp. was based on the European Society for Clinical Microbiology and Infectious Diseases and European Confederation of Medical Mycology joint clinical guidelines.²⁰

To evaluate the response to antifungal therapy at 2 weeks, we used a modified version of the Mycoses Study Group and European Organization for Research and Treatment of Cancer guidelines: persistent isolation of yeast spp. from blood specimens and death were termed as ‘treatment failure’.²¹ Mortality attributable to yeast BSIs was defined

as any of the following: (i) blood cultures positive for yeast spp. at the time of death; (ii) failure to resolve signs and symptoms related to yeast BSIs at the time of death; or (iii) death at least 14 days after the onset of yeast BSIs without another explanation.¹⁸ The follow-up duration was 100 days after the onset of the yeast BSI, loss to follow-up or death from any cause.

Microbiology and susceptibility tests

Blood cultures were processed using the Bactec Fx automated blood culture system (BD Diagnostics, Sparks, MD, USA). Yeast spp. identification and antifungal susceptibility testing were performed using a commercially available automated system (Vitek[®]2; bioMérieux, Hazelwood, MO, USA). Interpretation of susceptibility was based on the recent minimal inhibitory concentration breakpoints adopted by the Clinical and Laboratory Standards Institute M27-S4.²²

Statistical analyses

Statistical analysis was performed using SPSS version 15.0 (SPSS Korea, Seoul, Korea). Continuous variables were represented using the median and interquartile range (IQR). The χ^2 test or Fisher’s exact test was used to compare categorical variables. Student’s *t*-test or the Mann–Whitney *U*-test was used to compare continuous variables. Multivariate analysis was performed by logistic regression analysis for the risk factors associated with breakthrough infections. Cox regression analysis was performed to identify the predictors of 6-week mortality. Variables with *P*-values of $< .20$ by univariate analysis were entered in the multivariable model. Kaplan–Meier survival estimates were used to generate survival curves and differences between survival curves were assessed by means of the log-rank test. Two-sided *P*-values $< .05$ were considered statistically significant.

Results

Incidence of yeast BSIs and patient characteristics

Among 4,249 adult patients who underwent 10,148 admissions, significant yeast BSIs occurred in 49 patients. The overall incidence yeast BSIs was 22 cases per 1,000 patient-days (4.8 cases per 1,000 hospital admissions). Twenty-one patients (43%) had infections that met the definition for breakthrough infections.

Regardless of the indication of antifungal therapy, fluconazole and itraconazole were most widely used during the study period (Fig. 1). The annual usage of polyenes

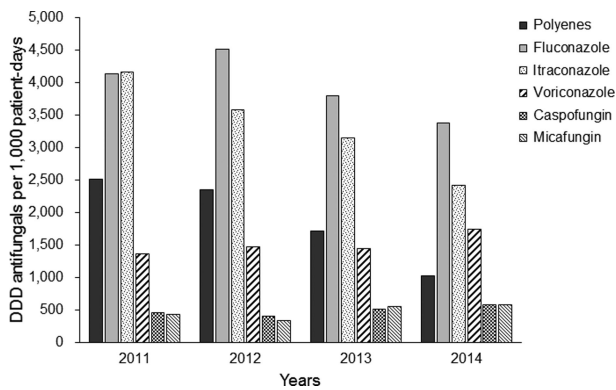


Figure 1. Annual use of antifungal drugs at the Catholic Blood and Marrow Transplantation Center from January 2011 to December 2014. DDD, defined daily doses. **Note.** Posaconazole was only available through the Korean Orphan Drug Center by early 2014 in Korea, and no statistics could be calculated.

decreased from 2,510 DDD per patient-day in 2011 to 1,018 DDD per patient-days in 2014, whereas the usage of voriconazole, caspofungin, and micafungin tended to increase slowly.

Table 1 shows the study patients' demographic and clinical characteristics. The two patient groups (cases and controls) did not differ significantly in age, sex, comorbidities, risk factors for yeast BSIs, severity of illness, and source of infections. The total duration of neutropenia was significantly longer in the case group (median, 15 days; IQR, 8–39 days) than the control group (median, 0 days; IQR, 0–3 days; $P = .038$). Neutropenia in the 3 days prior to a BSI and prior azole exposure in the 4 weeks prior to a BSI were significantly frequent in the case group than the control group. Among the 21 patients with breakthrough yeast BSIs, 15 (71%) were receiving azoles (11 patients on fluconazole, 3 patients on itraconazole, and 1 patient on posaconazole). Three patients (14%) developed breakthrough yeast BSIs while receiving echinocandins (2 patients on caspofungin and 1 patient on micafungin), while another 3 (14%) developed them during polyene therapy (Table 2).

Distribution of yeast spp. and risk factors for breakthrough yeast BSIs

A total of 51 yeast spp. were isolated from 49 patients (Fig. 2). Two patients had polymicrobial BSIs (*C. albicans*/*Candida dubliniensis* and *C. tropicalis*/*Candida lusitanae*). *C. tropicalis* (12/51, 24%) was the most common yeast spp., followed by *C. albicans* (10/51, 10%), *C. glabrata* (8/51, 16%), and *C. krusei* (8/51, 16%). Uncommon *Candida* spp. accounted for 14% (7/51) of BSIs. Four non-*Candida* yeast spp. (8%), including *Pseudozyma aphidis*, *Saccharomyces cerevisiae*, and

Trichosporon asahii, were isolated. There were significant differences in the distribution of yeast spp. between the two patient groups (Fig. 3). *C. krusei* was more prevalent in the case group than the control group (32% vs. 3%, $P = .015$), while the opposite was true for *C. tropicalis* (5% vs. 38%, $P = .007$). Among the 22 yeast isolates obtained from the case group, 10 isolates (45%) were resistant to the antifungal agent that the patient was receiving when the breakthrough infection occurred, while 7 (32%) were susceptible. Susceptibility profiles of the other five isolates (23%) were not available.

In comparison to the control group, breakthrough yeast BSIs occurred more frequently in patients with acute leukemia (62% vs. 25%; $P = .018$) or neutropenia in the 3 days prior to a yeast BSI (86% vs. 43%; $P < .001$). Table 3 shows the results of univariate and multivariate analyses of risk factors for breakthrough yeast BSIs. On multivariate analysis, acute leukemia, presence of a CVC and neutropenia in the 3 days prior to a yeast BSI were significantly associated with breakthrough yeast BSIs.

Antifungal treatment, removal of CVCs, and clinical outcomes of yeast BSIs

First-line antifungal agents for the treatment of yeast BSIs were significantly different between the cases and controls ($P < .001$). Polyenes were the most commonly used first-line antifungal agent in both groups (13/21, 62% and 15/28, 54%, respectively). However, the second most frequently used antifungal agent was echinocandins in the case group (7/21, 33%) and azoles in the control group (9/28, 32%). The median time to initiation of appropriate antifungal therapy was 2 days in both the cases (IQR, 1–4 days) and the controls (IQR, 1–3 days) after the onset of yeast BSIs ($P = .60$). The total duration of antifungal therapy for yeast BSIs did not differ between the cases (median, 19 days; IQR, 13–30 days) and controls (median, 18 days; IQR, 6–27 days) ($P = .94$).

Among the 44 patients who developed yeast BSIs in the presence of CVCs, the CVC was removed in 12 (57%) of 21 cases and 19 (83%) of 23 controls ($P = .10$). The CVC was retained in two non-neutropenic patients with other sources of infection and in three neutropenic patients with CVCs-related BSIs who were hemodynamically unstable. The median time for removal of CVCs in the cases and controls was 8 days (IQR, 3.5–19 days) and 3 days (IQR, 2–7 days) after the onset of the yeast BSI, respectively ($P = .70$). The removal of CVCs within 48 h after the onset of yeast BSIs was observed in 14% (3/21) of cases and 43% (12/28) of controls ($P = .06$).

Table 1. Demographic and clinical characteristics of the patients with breakthrough yeast bloodstream infections (cases) compared to those with *de novo* yeast bloodstream infections (controls).

Characteristics	All patients (<i>n</i> = 49)	Cases (<i>n</i> = 21)	Controls (<i>n</i> = 28)	<i>P</i>
Age, median years (IQR)	58 (49–65)	54 (50–63)	62 (49–65)	.84
Male sex	26 (53)	13 (62)	13 (46)	.39
Underlying hematological malignancy				.06
Acute leukemia	20 (41)	13 (62)	7 (25)	
Myelodysplastic syndrome	8 (16)	4 (19)	4 (14)	
Lymphoma	8 (16)	2 (10)	6 (21)	
Multiple myeloma	7 (14)	1 (5)	6 (21)	
Other ^a	6 (12)	1 (5)	5 (18)	
Treatment of hematological malignancy				.46
Chemotherapy	29 (59)	14 (67)	15 (54)	
Hematopoietic stem cell transplantation	6 (12)	3 (14)	3 (11)	
Supportive therapy	14 (29)	4 (19)	10 (36)	
Comorbidities				
Diabetes mellitus	13 (27)	7 (33)	6 (21)	.51
Chronic kidney disease	2 (4)	0 (0)	2 (7)	.50
Chronic liver disease	3 (6)	1 (5)	2 (7)	1.00
Prior hospital stay, median days (IQR)	15 (8–34)	22 (15–35)	11 (4–28)	.68
Risk factors for yeast BSIs ^b				
ICU residence	10 (20)	3 (14)	7 (25)	.48
Corticosteroid ^c	20 (41)	10 (48)	10 (36)	.56
Surgery	7 (14)	4 (19)	3 (11)	.44
Hyperalimentation	38 (78)	17 (81)	21 (75)	.74
Central venous catheter	44 (90)	21 (100)	23 (82)	.06
Prior use of antibiotics	46 (94)	19 (91)	27 (96)	.57
Neutropenia in the 3 days prior to a yeast BSI	30 (61)	18 (86)	12 (43)	<.01
Prior azole exposure within 4 weeks prior to a yeast BSI	20 (41)	19 (91)	1 (4)	<.01
Pitt bacteremia score, median (IQR)	1 (0–3)	1 (0–2)	1 (0–3)	.93
Source of yeast BSIs				.19
Central venous catheter	21 (43)	9 (43)	12 (43)	
Gastrointestinal tract	12 (24)	7 (33)	5 (18)	
Unknown	10 (20)	5 (24)	5 (18)	
Other ^d	6 (12)	0 (0)	6 (22)	
Polymicrobial BSIs ^e	23 (47)	12 (57)	11 (39)	.26
First-line antifungal agent				<.01
Azole	10 (20)	1 (5)	9 (32)	
Echinocandin	11 (22)	7 (33)	4 (14)	
Polyene	28 (57)	13 (62)	15 (54)	
Time to initiation of appropriate antifungal therapy for yeast BSIs, median days (IQR)	2 (1–3)	2 (1–4)	2 (1–3)	.60
Total duration of antifungal therapy for yeast BSIs, median days (IQR)	18 (11–27)	19 (13–30)	18 (6–27)	.94

Note. Data are no. (%) of patients, unless otherwise indicated.

BSI, bloodstream infection; ICU, intensive care unit; IQR, interquartile range.

^aSevere aplastic anemia (*n* = 3), hemophagocytic lymphohistiocytosis (*n* = 2), and chronic myeloid leukemia (*n* = 1).

^bRisk factors within 30 days prior to a yeast bloodstream infection.

^cMean minimum dose of 10 mg/day of prednisone equivalent for >14 days.

^dGenitourinary tract (*n* = 5) and deep soft tissue (*n* = 1).

^eIsolation of ≥2 different species of yeast or a yeast with concomitant bacterial species from blood cultures obtained within a 48-h period.

Table 2. Summary of breakthrough yeast bloodstream infections in patients with hematological malignancies.

Patients No.	Sex/age	Underlying hematological malignancy	Existing antifungal agent	Source	Yeast species	Susceptibility to existing antifungal agent	First-line antifungal agent	Outcome at 6 weeks
1	M/48	Acute leukemia	Micafungin	CVC	<i>Candida krusei</i>	Unknown	Amphotericin B	Died
2	F/60	Lymphoma	Fluconazole	Unknown	<i>Candida krusei</i>	Resistant	Amphotericin B	Survived
3	M/54	Acute leukemia	Amphotericin B	GI tract	<i>Candida krusei</i>	Unknown	Caspofungin	Survived
4	M/43	Myelodysplastic syndrome	Amphotericin B	CVC	<i>Saccharomyces cerevisiae</i>	Susceptible	Caspofungin	Survived
5	M/63	Multiple myeloma	Itraconazole	CVC	<i>Candida albicans</i>	Susceptible	Amphotericin B	Died
6	M/68	Acute leukemia	Fluconazole	GI tract	<i>Candida dubliniensis</i>	Resistant	Amphotericin B	Survived
7	M/46	Acute leukemia	Fluconazole	Unknown	<i>Candida tropicalis</i>	Susceptible	Amphotericin B	Died
8	M/68	Myelodysplastic syndrome	Amphotericin B	CVC	<i>Candida pelliculosa</i>	Unknown	Amphotericin B	Survived
9	F/51	Myelodysplastic syndrome	Fluconazole	GI tract	<i>Candida guilliermondii</i>	Susceptible	Amphotericin B	Died
10	F/54	Lymphoma	Fluconazole	GI tract	<i>Candida glabrata</i>	Resistant	Caspofungin	Survived
11	M/42	Acute leukemia	Fluconazole	GI tract	<i>Candida krusei</i>	Resistant	Amphotericin B	Survived
12	F/62	Acute leukemia	Fluconazole	CVC	<i>Candida albicans</i>	Unknown	Amphotericin B	Survived
13	F/53	Acute leukemia	Fluconazole	CVC	<i>Candida krusei</i>	Resistant	Amphotericin B	Survived
14	M/56	Acute leukemia	Posaconazole	GI tract	<i>Candida glabrata</i>	Susceptible	Caspofungin	Survived
15	F/54	Myelodysplastic syndrome	Itraconazole	CVC	<i>Trichosporon asahii</i>	Resistant	Voriconazole	Survived
16	M/29	Severe aplastic anemia	Fluconazole	GI tract	<i>Candida albicans</i>	Susceptible	Caspofungin	Survived
17	M/51	Acute leukemia	Caspofungin	Unknown	<i>Pseudozyma aphidis</i>	Resistant	Caspofungin	Survived
18	F/73	Acute leukemia	Itraconazole	CVC	<i>Candida krusei</i>	Resistant	Amphotericin B	Died
19	F/51	Acute leukemia	Fluconazole	CVC	<i>Candida inconspicua</i>	Resistant	Caspofungin	Survived
20	M/69	Acute leukemia	Fluconazole	Unknown	<i>Candida glabrata</i>	Resistant	Amphotericin B	Died
21	M/56	Acute leukemia	Caspofungin	Unknown	<i>Candida glabrata</i>	Susceptible	Amphotericin B	Died

CVC, central venous catheter; GI, gastrointestinal.

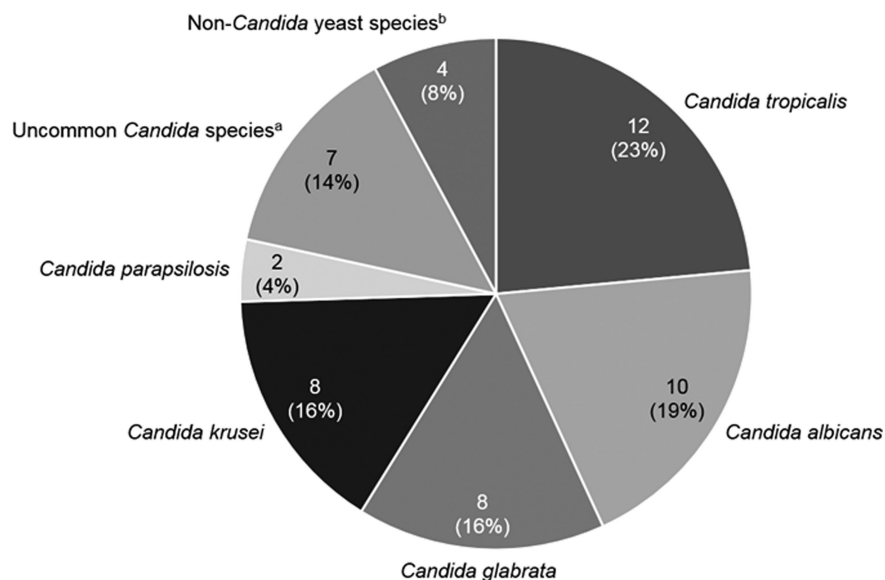


Figure 2. Distribution of yeast species causing bloodstream infections (BSIs) in patients with hematological malignancies. **Note.** Data are no. (%) of isolates. ^a*Candida dubliniensis* ($n = 1$), *Candida guilliermondii* ($n = 1$), *Candida inconspicua* ($n = 1$), and *Candida pelliculosa* ($n = 1$) in breakthrough BSIs; *Candida famata* ($n = 1$), and *Candida lusitanae* ($n = 2$) in *de novo* BSIs. ^b*Saccharomyces cerevisiae* ($n = 1$), *Trichosporon asahii* ($n = 1$), and *Pseudozyma aphidis* ($n = 1$) in breakthrough BSIs; *Saccharomyces cerevisiae* ($n = 1$) in *de novo* BSI.

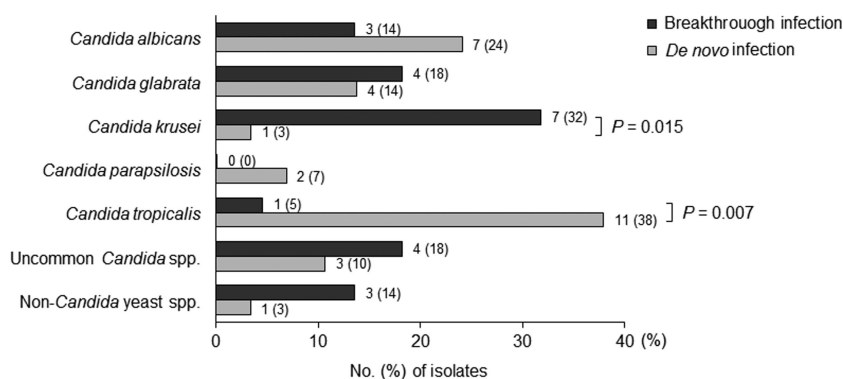


Figure 3. Comparison of the distribution of yeast species isolated from breakthrough and *de novo* yeast bloodstream infections.

Table 3. Logistic regression analysis for risk factors associated with breakthrough yeasts bloodstream infections.

Characteristics	OR (95% CI)	P	Adjusted OR (95% CI)	P
Male sex	1.88 (0.59–5.93)	0.29	–	NA
Acute leukemia	6.57 (1.74–24.77)	0.005	6.63 (1.36–32.35)	0.019
Supportive therapy for hematological malignancies	2.36 (0.62–8.98)	0.21	–	NA
Prior hospital stay ≥ 4 weeks	1.85 (0.54–6.30)	0.33	–	NA
Presence of a central venous catheter	4.35 (0.47–40.40)	0.19	24.70 (1.61–379.68)	0.021
Neutropenia in the 3 days prior to a yeast BSI	8.00 (1.91–33.54)	0.004	10.67 (1.88–60.64)	0.008

BSI, bloodstream infection; CI, confidence interval; NA, not available; OR, odds ratio.

The clinical outcomes of the cases and controls are presented in Table 4. Seven of 21 (33%) cases and 12 of 28 (43%) controls were defined as treatment failure at 2 weeks ($P = .56$). Among the four cases and three controls who showed microbiologic failure at 2 weeks, six patients had

removed the CVCs. At 2 weeks, the frequency of death was 14% (3/21) of the cases and 32% (9/28) of controls ($P = .19$). The crude mortality at 6 weeks was 33% (7/21) for the cases and 43% (12/28) for the controls ($P = .56$). The mortality attributable to yeast BSIs at 6 weeks and overall

Table 4. Comparison of clinical outcomes between patients with breakthrough yeast bloodstream infections (cases) and those with *de novo* yeast bloodstream infections (controls).

Variables	Cases (n = 21)	Controls (n = 28)	P
Ocular involvement ^a	4/10 (40)	6/11 (55)	.67
Septic shock	4 (19)	8 (29)	.52
Continuous renal replacement therapy	1 (5)	6 (21)	.21
Mechanical ventilation	3 (14)	3 (11)	1.00
Treatment failure at 2 weeks	7 (33)	12 (43)	.56
Microbiologic failure ^b	4/18 (22)	3/19 (16)	.69
Death	3 (14)	9 (32)	.19
Mortality at 6 weeks			
Crude	7 (33)	12 (43)	.56
Attributable	6 (29)	9 (32)	1.00
Overall mortality			
Crude	13 (62)	18 (64)	1.00
Attributable	6 (29)	9 (32)	1.00

Note. Data are no. (%) of patients, unless otherwise indicated.

^aData are event/evaluable no. (%) of patients.

^bPersistent isolation of yeast species from blood specimens at 2 weeks. Data are event/survivors no. (%) of patients.

Table 5. Predictors of 6-week mortality in all patients with yeast bloodstream infections.

Characteristics	HR (95% CI)	P	Adjusted HR (95% CI)	P
Male sex	2.05 (0.78–5.39)	.1583
Diabetes mellitus	1.93 (0.76–4.93)	.1735
Refractory neutropenia	11.24 (4.15–30.42)	<.001	61.49 (10.25–368.85)	<.001
Source of infection, genitourinary tract	2.32 (0.67–7.99)	.1859
<i>Candida glabrata</i>	2.09 (0.75–5.86)	.1692
Pitt bacteremia score	1.63 (1.32–2.02)	<.001	1.89 (1.14–3.11)	.013
Inappropriate antifungal regimen	2.50 (1.01–6.15)	.0541
Delay in initiation of antifungal therapy >48 h	2.66 (1.07–6.62)	.0437
Retention of a central venous catheter	2.15 (0.80–5.78)	.1399
Breakthrough infection	2.62 (0.86–7.99)	.0928

CI, confidence interval; HR, hazard ratio.

mortality was similar for the two groups (29% vs. 32%; $P = 1.00$; 62% vs. 64%; $P = 1.00$).

Table 5 demonstrates the predictors of 6-week mortality. On univariate analysis, breakthrough infection (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.27–1.72; $P = .41$) and the retention of CVCs 48 h after the onset of yeast BSIs (HR, 1.19; 95% CI, 0.45–3.13; $P = .73$) was not associated with higher mortality at 6 weeks. After multivariate analysis, refractory neutropenia (adjusted HR, 38.71; 95% CI, 9.09–164.89) and the Pitt bacteremia score (adjusted HR, 2.15; 95% CI, 1.43–3.23) remained independent predictors of mortality at 6 weeks. The Kaplan-Meier survival curve shows no difference between survival in the two patient groups (Fig. 4). The median (IQR) time to death was 23 days (2–86 days) for the case group and 7 days (4–67 days) for the control group ($P = .313$).

Discussion

In the present study, breakthrough infections accounted for a significant proportion (43%) of yeast BSIs in patients with hematological malignancies. Compared to *de novo* infections, breakthrough infections were more often caused by *C. krusei*. Acute leukemia, presence of a CVC and neutropenia were significantly associated with breakthrough infections. Refractory neutropenia and severity of illness at the onset of yeast BSIs were independent prognostic factors.

Since the first case of breakthrough candidemia was reported in 1993, a number of studies on breakthrough candidemia have been published.^{10–12,23–25} Most of these studies were performed in patients with cancer. A recent study showed that breakthrough candidemia occurred more frequently in hematological (37%) rather than oncological (10%) patients.⁸ In another study, breakthrough

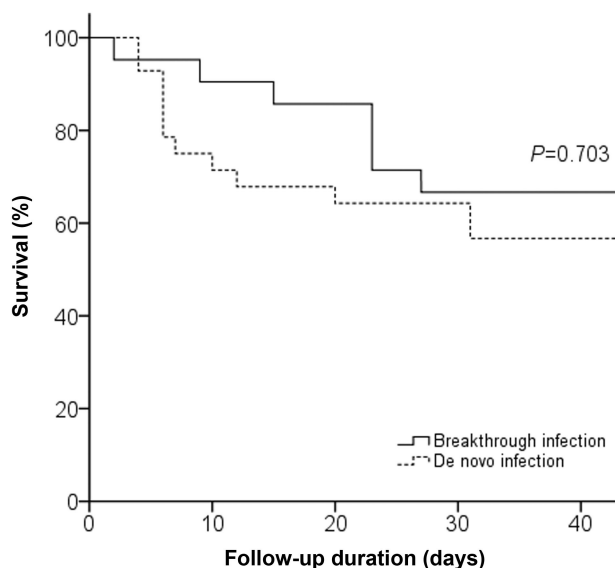


Figure 4. Kaplan–Meier estimates of survival in patients with breakthrough and *de novo* yeast bloodstream infections.

infection accounted for 53% of all cases of candidemia in patients with hematological malignancies.³ Antifungal prophylaxis and empirical or preemptive antifungal therapy are recommended for patients with anticipated prolonged and profound neutropenia, such as hematopoietic stem cell transplant recipients or patients undergoing intensive chemotherapy for acute leukemia. Therefore, such patients have a high risk of contracting candidemia and are also more frequently exposed to antifungal agents. This could be a possible explanation for the high incidence of breakthrough infections in patients with hematological malignancies.

Although candidemia predominantly originates from sources other than a CVC such as the gastrointestinal tract in neutropenic patients,²⁶ CVCs and other intravascular devices are suggested to be important risk factors in the development breakthrough candidaemia.²⁷ For example, they could provide an entrance site or reservoir for *Candida* spp. in a biofilm. However, previous studies failed to identify the presence of a CVC as a risk factor for breakthrough candidaemia.^{10,12,28} The authors presumed that it was impossible to evaluate the role of a CVC in breakthrough candidemia because most patients had a CVC. In our study, a CVC was the source of infection in less than 50% of patients. Even though most patients with yeast BSIs had a CVC, it was a significant factor associated with breakthrough infections. This might be due to some differences in the study design and epidemiology including the subject of study (the general population, patients with cancer or hematological malignancies) and the proportion of breakthrough infections (10 to 45%).

Trends in the distribution of various yeast spp. causing breakthrough infections were consistent with those of previous studies.^{8,10–12,29,30} Most patients who developed a breakthrough infection were receiving azoles and were infected with azole-resistant *Candida* spp., especially *C. krusei* and non-*Candida* yeast spp. However, we also found breakthrough infections due to strains susceptible to an antifungal agent currently being administered such as *C. albicans*, which might have resulted from the relatively protective environment of CVCs or suboptimal concentrations of antifungal drugs due to drug interactions or poor intestinal absorption. Therefore, the removal of CVCs should be considered for breakthrough yeast BSIs caused by strains susceptible to a previously administered antifungal agent regardless of the absolute neutrophil count or the source of infection. Like previous studies,^{8,10,11,25} this study showed no differences in the severity of infection at the onset of BSIs, crude mortality and mortality attributable to yeast BSIs between breakthrough and *de novo* infections. Therefore, current clinical practice in our institution which includes a switch to a different antifungal class and prompt removal of CVCs is appropriate for treatment of breakthrough yeast BSIs.

In contrast to previous studies, our study involves newer antifungal agents and a relatively homogeneous population. However, this study has some limitations. First, since the study was conducted at a single tertiary-care teaching hospital, the results may not be generalizable to other institutions. Second, antifungal susceptibility could not be determined for all isolates. Third, the number of patients was relatively small.

In conclusion, patients with hematological malignancies had a higher incidence of yeast BSIs than the general population. Breakthrough infections accounted for 43% of all episodes. Some differences existed between the clinical, epidemiological, and *in vitro* susceptibility data of breakthrough and *de novo* infections. Current strategies for breakthrough yeast BSIs including a switch to a different antifungal class and prompt removal of CVCs would be reasonable. However, clinical study data on this issue are very limited and large-scale, multicenter studies should be designed. Moreover, evidence-based monitoring for a high-risk group and development of new diagnostic tool for earlier detection of yeast BSIs are warranted to improve the clinical outcomes.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

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