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Original Article

Clinical features, antifungal susceptibility, and outcome of *Candida guilliermondii* fungemia: An experience in a tertiary hospital in mid-Taiwan

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Abstract *Backgrounds: Candida guilliermondii* is rarely isolated from clinical specimen. *C. guilliermondii* fungemia is seldom reported in the literature. The aims of this study were to report the clinical features, antifungal susceptibility, and outcomes of patients with *C. guilliermondii* fungemia.
Methods: From 2003 to 2015, we retrospectively analyzed the clinical and laboratory data of patients with *C. guilliermondii* fungemia in a tertiary hospital in mid-Taiwan. We performed a multivariable logistic regression analysis to identify the risk factors of mortality. The Sensititre YeastOne microtiter panel assessed the susceptibility of antifungal agents.
Results: In this study, we identified 36 patients with *C. guilliermondii* fungemia. The median age of patients was 50.5 years (range, 17 days to 96 year) and 20 cases (56%) were male. The incidence of *C. guilliermondii* fungemia was 0.05 per 1000 admissions. Malignancy was the most common co-morbidity, and 25 (69%) patients had central venous catheter in place. Thirty-day overall mortality was 16.7%. In multivariate logistical regression analysis, catheter

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retention was an independent risk factor of mortality. According to epidemiological cutoff values, most clinical isolates (21/22, 95.5%) belonged to the wild-type MIC distributions for amphotericin B and flucytosine; however, the isolates were less susceptible to fluconazole (68%) and echinocandins (77—91%).

Conclusion: Despite the lower mortality rate associated with *C. guilliermondii* fungemia, the removal of a central venous catheter remained an independent factor influencing the outcome of patients. The clinical significance of less susceptibility of *C. guilliermondii* to triazoles and echinocandins remains to be elucidated.

Introduction

Despite the advances in modern medicine, fungal infections still cause significant morbidity and mortality in human.[1] Regarding nosocomial fungal bloodstream infection (BSI), *Candida* species remains the most common causative pathogen.[1,2] So far, more than 17 different *Candida* species have been identified as BSIs pathogens, and *Candida albicans* is the one most extensively studied. On the other hand, the epidemiological and clinical features of non-*albicans Candida* species, except for *Candida parapsilosis*, *Candida tropicalis*, *Candida krusei*, and *Candida glabrata*, are less well-known.[3] *Candida guilliermondii* is part of the normal flora of human skin and mucosa,[4] and rarely recognized as an invasive pathogen.[3] For their rarity in clinical specimen, infections caused by *C. guilliermondii* are less well studied. In the past two decades, however, infections caused by *C. guilliermondii* have been increasing significantly, particularly in immunocompromised and pediatric patients.[5—8]

Currently, the *in vitro* antifungal susceptibility testing of *Candida* species is based on the clinical breakpoints proposed by the Clinical & Laboratory Standards Institute (CLSI), M27-A3[9] or the European Committee on Antimicrobial Susceptibility Testing (EUCAST).[10] In a supplement version of M27-A3, the CLSI M27-S4,[11] species-specific clinical breakpoints (CBPs) are suggested for some *Candida* species, including *C. guilliermondii*. In the absence of species-specific CBPs, epidemiological cutoff values (ECVs) are used as an alternative to identify potentially resistant or less susceptible isolates.[12—14]

The aims of our study were to elucidate the clinical manifestations, risk factors, and outcome of patients with *C. guilliermondii* fungemia. We also evaluated the *in vitro* antifungal susceptibility pattern of *C. guilliermondii* in this cohort study.

Materials and methods

Patients and setting

From January 2003 to September 2015, all patients with *C. guilliermondii* BSI (CG-BSI) reported by the microbiological department of China Medical University Hospital, a 2000-bed teaching hospital in mid-Taiwan, were identified. The demographics, co-morbidities, therapeutic agents, and outcomes of patients were thoroughly reviewed and analyzed. All clinical and laboratory data were retrieved from the first CG-BSI episode. This study was approved by the Institutional Review Board of China Medical University Hospital (CMUH104-REC2-036).

Definitions

We defined candidemia when *Candida* species were isolated from at least one blood culture in patients with symptoms or signs of systemic infection. The duration of candidemia was defined as the time interval between the first and last positive blood cultures that yielded same pathogen. The candidemia episode was regarded as nosocomial if candidemia occurred $\geq$48 h after admission,[1] or if the patient had been hospitalized within two weeks before this admission or was referred from a long-term care unit. Appropriate treatment was regarded as an antifungal agent at an adequate dosage prescribed with matched *in vitro* susceptibility of the pathogen for at least 7 days.[15] Candidemia occurred in patients receiving antifungal agents, whether prophylactic or therapeutic, is considered a breakthrough candidemia. Concomitant bacteremia was defined when bacteremia developed within a 24 h period before or after the onset of CG-BSI.[16] Mixed candidemia was defined as isolation of two or more different species of candida from blood culture with clinical significance. Broad-spectrum antibiotics were antimicrobial agents with an activity against both gram-positive and gram-negative microorganisms.[17] Central venous catheters (CVC) included port-A catheters, double lumen and Hickman catheters. The severities of underlying diseases and illness were assessed by the Charlson comorbidity index[18] and APACHE (acute physiology and chronic health evaluation) II scores,[19] respectively. The primary outcome was 30-day overall mortality.

Laboratory methods and antifungal susceptibility test

We processed blood samples collected from each patient in BD BACTEC™ 9000 Series or BD BACTEC FX Instrumented Blood Culture Systems (Becton, Dickinson, Sparks, MD, USA). Isolates were identified as *C. guilliermondii* with the

use of ID 32 C of API Yeast Identification system (BioMérieux, Inc. Marcy-l'Étoile, France). The ATB FUNGUS 3® panel (bioMérieux, La Balme-les Grottes, France) was used to test *C. guilliermondii* susceptibility to fluconazole, itraconazole, voriconazole, flucytosine and amphotericin B at the initial detection of fungemia. Preserved isolates of *C. guilliermondii* were cultured on Sabouraud dextrose agars and incubated at 35 °C for 24 h. Nine antifungal drugs (amphotericin B, fluconazole, itraconazole, flucytosine, voriconazole, anidulafungin, caspofungin, micafungin, and posaconazole) were tested by using a Sensititre YeastOne® (SYO) microtiter panel (Thermo Fisher Scientific Sensititre, East Grinstead, UK). CBPs from CLSI M27-A3[9] and species-specific CBPs from CLSI M27-S4[11] were used to categorize isolates as susceptible (S), intermediate (I) or resistant (R). For *C. guilliermondii*, the ECVs of anidulafungin, caspofungin and micafungin were established using the SYO method,[12] and the ECVs of other antifungal agents were established using CLSI broth microdilution (BMD) method.[14] Isolates with MICs higher than the ECVs were regarded as non-wild type (non-WT) and considered potentially resistant. The ECVs and CBPs of nine antifungal agents for *C. guilliermondii* used in this study are summarized in Table 3. Echinocandins was interpreted by CBPs according to CLSI M27-S4 and other antifungal agents by ECVs.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median (range) according to their homogeneity. Differences in characteristics between subjects were compared with *t* tests. For dichotomous variables, we used chi-square tests (or Fisher exact test if <5 expected observation in any cell), if appropriate. In all comparisons, $p < 0.05$ (two-tail test) was considered significant. Univariate comparisons were made between the non-survival and survival groups to identify factors of the association between fungemia and mortality. The independent variables of death were identified by stepwise logistic regression of multivariate analysis for the significant risk factors. Data analyses were carried out using the program SPSS (version 20.0; SPSS Inc., Chicago, IL, USA).

Results

Clinical and laboratory characteristics of patient with *C. guilliermondii* fungemia

From January 2003 to September 2015, 4213 episodes of candidemia were identified, and 1.9% (79/4213) of them were *C. guilliermondii*. During this period, the incidence of CG-BSI was 0.05 per 1000 admissions. Thirty-six patients with CG-BSI were identified and enrolled into the present study. The clinical characteristics, risk factors, therapeutic regimens and outcomes of patients are summarized in Table 1. Detailed information about the 36 patients is listed in Supplement Table 1. Their median age was 50.5 year-old (range, 17 days to 96 years), and 75% of them were >18 years. Malignancy was the most common underlying disease (50%), followed by liver diseases (41.7%), renal insufficiency (27.8%) and diabetes mellitus (22.2%).

Twenty-five patients (69%) had a CVC at the time of CG-BSI. Removal of the catheter was performed in 23 cases (92%), and most of them (18/25, 72%) had the catheter removed over 48 h after the application of antifungal agents. The remaining two patients without CVC removal died. Confirmed CVC infection caused by *C. guilliermondii* was documented in nine of the 25 patients (36%). Among the studied patients, eight cases (22.2%) had concomitant bacteremia and two cases (5.6%) had mixed candidemia. Coagulase-negative *Staphylococcus* species (n = 3, 8.3%) was the most common isolate in patients with concomitant bacteremia. *Enterococcus* species, *Streptococcus agalactiae*, *Bacillus cereus*, *Elizabethkingia meningoseptica* and *Burkholderia cepacia* were the other bacterial isolates. Half of the patients (50%) had concomitant bacterial infection, which was not significantly associated with 30-day mortality ($p = 0.329$) in univariate analysis. The detail of the sources of concomitant bacteremia is shown in Supplement Table 1.

Three-quarters and 14% of our patients received broad-spectrum antibiotic therapy and antifungal agents before the occurrence of candidemia, respectively. Eight patients (22%) developed shock at the onset of candidemia; 25% (2/8) died in 30 days after the onset of candidemia. For the reasons of abdominal surgery, total parenteral nutrition (TPN) use, or prolonged febrile neutropenia, five patients with breakthrough fungemia received either prophylactic or empirical fluconazole use before the occurrence of candidemia. It was interesting to note that 80% (4/5) of *C. guilliermondii* isolates from these five patients were WT to fluconazole.

Treatment and outcome

Eighty percent (29/36) of the patients received antifungal agents, and fluconazole was the most commonly used agent (75%), followed by echinocandins (25%). Ten patients received antifungal treatment within 48 h of positive *C. guilliermondii* blood culture. Nineteen patients received antifungal treatment >48 h from positive blood culture. Interestingly, among seven patients without antifungal therapy, six of them had favorable outcomes. Nosocomial CG-BSI occurred in 31 patients (86%). There were no deaths among the non-nosocomial cases. The 30-day overall mortality was 16.7% (6/36). Among the six deceased patients, five died in septic shock and one in respiratory failure. Five deceased patients received antifungal agents, but two of them did not reach mycological eradication before their death. The mean APACHE II score of the six deceased patients was higher than that of alive ones (17.7 vs 9.8, $p = 0.688$).

In patients with CG-BSI, several risk factors of mortality were identified by univariate analysis, including a higher Charlson comorbidity score (7.0 vs. 2.6, $p = 0.032$), hyperbilirubinemia (50% vs. 10%, $p = 0.045$), and CVC retention (100% vs. 50%, $p = 0.024$). Only CVC retention ($p = 0.031$) retained statistically significant in multivariate logistic regression analysis (Table 2).

In vitro susceptibility of antifungal agents

Table 3 lists the antifungal susceptibility (minimal inhibitory concentration, MIC) of the 22 available isolates of *C. guilliermondii* to nine antifungal agents tested by SYO.

Table 1 Risk factors of mortality in 36 patients with *C. guilliermondii* fungemia (n = 36).

	Median (range), or n (%)	Mortality status (in 30 days)		
		Survived (n = 30)	Died (n = 6)	P value
Patients characteristics				
Age	50.5 (17 day–96 year)	49	66	0.511
Males	20 (55.6)	18 (60)	2 (33.3)	0.226
Underlying comorbidity				
Diabetes mellitus	8 (22.2)	6 (20.0)	2 (33.3)	0.403
Liver diseases[a]	15 (41.7)	11 (36.7)	4 (66.7)	0.182
GFR<60 ml/min/1.73 m^2	10 (27.8)	8 (26.7)	2 (33.3)	0.544
COPD	5 (13.9)	5 (16.7)	0 (0)	0.378
Malignancy	18 (50.0)	15 (50.0)	3 (50.0)	0.671
CVC	25 (69.4)	21 (70.0)	4 (66.7)	0.609
Abdominal surgery (<30 days)	8 (22.2)	7 (23.3)	1 (16.7)	0.597
Chemotherapy (<30 days)	8 (22.2)	7 (23.3)	1 (16.7)	0.597
Use of corticosteroids (<6 months)	13 (36.1)	12 (40)	1 (16.7)	0.276
Parenteral nutrition (<30 days)	13 (36.1)	10 (33.3)	3 (50.0)	0.369
Broad-spectrum antibiotic use (<30 days)	27 (75.0)	21 (70.0)	6 (100.0)	0.152
Breakthrough candidemia	5 (13.9)	4 (13.3)	1 (16.7)	0.622
Concomitant bacterial infection	18 (50.0)	14 (46.7)	4 (66.7)	0.329
Delay-onset of candidemia[e]	25 (69.4)	19 (63.3)	6 (100.0)	0.091
Charlson Comorbidity score	3 (0–10)	2.6	7.0	0.032
APACHE II score	10.5 (1–23)	9.8	17.7	0.688
Laboratory data				
Hypotension[b]	8 (22.2)	6 (20.0)	2 (33.3)	0.403
Fever >38°C	23 (63.9)	19 (63.3)	4 (66.7)	0.631
WBC, μL	8290 (20–27400)	9100	8250	0.316
CRP, mg/dl	6.61 (0.18–32.85)	6.61	8.37	0.620
Serum creatinine, mg/dl	0.80 (0.22–6.50)	0.78	0.94	0.011
GPT>50 IU/L	9 (28.3)	8 (26.7)	1 (16.7)	0.525
Hyperbilirubinemia (>1.3 mg/dL)	6 (16.7)	3 (10.0)	3 (50.0)	0.045
Neutropenia (<30 days)[c]	2 (5.6)	2 (6.7)	0 (0)	0.690
Catheter-related infections				
Remove CVC	23/25 (92.0)	21/21 (100)	2/4 (50.0)	0.109
Duration between onset of candidemia and catheter removal	6 (1–48 days)	4	2.4	0.602
Delayed catheter removal[d]	16/25 (64.0)	15/21 (71.4)	1/4 (25.0)	0.116
Treatment and outcome				
Treatment duration, days (mean/range)	18/1-162	19/6-162	5/1-13	0.223
Appropriate antifungal treatment[f] (%)	13/22[f] (59.1)	12/18 (66.7)	1/4 (25.0)	0.167
Antifungal treatment[g] with				
Echinocandins	9/29 (31.0)	9/24 (37.5)	0	0.131
Fluconazole	27/29 (93.1)	22/24 (91.7)	5/5 (100.0)	0.680
Voriconazole	1/29 (3.4)	1/24 (4.2)	0	0.828
Flucytocine	1/29 (3.4)	1/24 (4.2)	0	0.828
Amphotericin B	4/29 (13.8)	3/24 (12.5)	1/5 (20.0)	0.553
Appropriate antibiotic treatment[h] for concomitant bacterial sepsis	12/18[h] (72.2)	9/14 (64.3)	4/4 (100.0)	0.234

[a] Liver diseases include liver cirrhosis, hepatitis, hyperbilirubinemia.
[b] A decrease in systolic blood pressure to a level of less than 90 mmHg or the use of inotropic agents.
[c] Absolute neutrophil count <500 cells/mm^3.
[d] Delayed catheter removal is defined as remove catheter more than 48 h after treatment initiation.
[e] Delay-onset of candidemia was defined as candidemia occurred ≥14 days after admission.[39]
[f] Appropriate antifungal therapy was defined as adequate dose for at least 7 days and the isolates were susceptible in SYO test. Only 22 isolates from 22 patients were available for *in vitro* test with SYO method.
[g] Twenty-nine patients received antifungal treatment, but only 22 of them had *in vitro* test for appropriateness.
[h] Appropriate antibiotic treatment was defined as antibiotic treatment for concomitant bacterial infection followed the clinical guideline or susceptibility test. Eighteen patients had concomitant bacterial infection. The patients without concomitant bacterial infection were not included in this data.
Abbreviations: COPD = chronic obstructive pulmonary disease, CRP = C reactive protein, CVC = central venous catheter; GFR = glomerular filtration rate; ICU = intensive care unit; WBC = white blood cell.

Table 2 Multivariate logistic regression analysis of risk factors associated with mortality in *C. guilliermondii* fungemia.

	Univariable			Multivariable		
	Odds ratio	95% CI	p value	Odds ratio	95% CI	p value
Charlson Comorbidity score	1.282	0.956–1.718	0.032	1.179	0.845–1.646	0.332
Hyperbilirubinemia	9.000	1.223–66.231	0.045	6.681	0.649–68.785	0.110
Non-removal of catheter[a]	15.000	1.095–205.494	0.024	25.244	1.343–474.626	0.031

[a] Non-removal of catheter is defined as the central venous catheter not been removed till death.
Abbreviations: CI = confidence interval, CVC = central venous catheter.

Table 3 *In vitro* susceptibility of 22 *C. guilliermondii* isolates to 9 antifungal agents as determined by YeastOne method.

Antifungal agent	MIC (μg/ml)			Susceptibility, No.(%) of isolates					
				ECV*		CBPs**			
	50%	90%	Range	WT	Non-WT	S	I	R	NS
Amphotericin B	0.5	0.5	0.25 to 8	21 (95.5)	1 (4.5)	–	–	–	–
Flucytosine	≤0.06	0.25	≤0.06 to 2	21 (95.5)	1 (4.5)	–	–	–	–
Fluconazole	8	64	0.5 to 256	15 (68.2)	7 (31.8)	–	–	–	–
Itraconazole	0.5	4	0.06 to 16	17 (77.3)	5 (22.7)	–	–	–	–
Posaconazole	0.5	1	0.03 to 8	16 (72.7)	6 (27.2)	–	–		–
Voriconazole	0.12	0.1	0.015 to 8	14 (63.6)	8 (36.4)	–	–	–	–
Anidulafungin	2	4	0.5 to 8	20 (90.9)	2 (9.1)	16 (72.7)	4 (18.2)	2 (9.1)	6 (27.2)
Caspofungin	0.5	>8	0.25 to 8	17 (77.3)	5 (22.7)	17 (77.3)	0 (0)	5 (22.7)	5 (22.7)
Micafungin	1	2	0.25 to 8	20 (90.9)	2 (9.1)	20 (90.9)	1 (4.5)	1 (4.5)	2 (9.1)

Abbreviations: CBP, clinical breakpoints; I, intermediate; Non-WT, non-wild type; R, resistant; S, susceptible; S-DD, dose-dependent susceptible; WT, wild type.
* Epidemiologic cutoff value (ECV) of amphotericin B, flucytosine, fluconazole, itraconazole, posaconazole, voriconazole, anidulafungin, caspofungin and micafungin: 2 μg/ml, 1 μg/ml, 8 μg/ml, 1 μg/ml, 0.5 μg/ml, 0.25 μg/ml, 4 μg/ml, 2 μg/ml, 2 μg/ml.[9,11]
** Species-specific clinical breakpoints (CBP) of echinocandins approved by CLSI M27-S4: S ≤ 2 μg/ml, I 4 μg/ml, R ≥ 8 μg/ml.[12,14]

According to CBPs, 72.7%, 77.3% and 90.9% of *C. guilliermondii* isolates were susceptible to anidulafungin, caspofungin and micafungin, respectively. According to the standards of ECVs, most isolates (≥90%) were WT to flucytosine, amphotericin B, anidulafungin and micafungin. Less than 80% of *C. guilliermondii* were non-WT strains in azoles (WT for fluconazole, 65%; voriconazole, 65%; itraconazole, 77.3% and posaconazole, 72.7% respectively).

Among the 22 patients with an MIC test result by SYO method, 17 cases received antifungal therapy and 15 patients received appropriate antifungal treatment. From the time that the first blood culture that was positive was drawn, nine patients received antifungal treatment after 48 h. Two patients with fluconazole non-WT strains infection received fluconazole without treatment failure. Six patients received echinocandin treatment and all of them survived. Only one isolate was non-WT to amphotericin B and this isolate was also non-WT to other antifungal agents, and this patient had a favorable outcome after removal of CVC and treatment with fluconazole alone. Four patients received amphotericin B treatment and one patient ended in death but all isolates were WT to amphotericin B.

Discussion

Similar to one prior report,[20] our data confirmed that *C. guilliermondii* was a rare cause of candidemia (1.9%), and the incidence of CG-BSI was 0.05 per 1000 admissions. The age and sex distribution of our patients were consistent with the patients of other previous studies.[5,21,22] Similar to prior studies,[5,21–23] malignancy, especially gastrointestinal solid tumors, remained the most common underlying disease (50%) in patients with CG-BSI. However, other risk factors for invasive candidiasis,[24] such as neutropenia, were seldom observed in our patients. Only 2 patients (5.6%) had neutropenia. 8 (22.2%) patients presented with shock and 8 (22.2%) had received chemotherapy before. The reason for lower rate of shock presentation in our CG-BSI patients than other studies[5,22] was unknown.

CG-BSI was highly associated with CVC use in our study and others.[5,23,25] Catheter removal plays an important role in the management of candidemic patients with CVC,[5] which was also demonstrated in our study. In one meta-analysis, CVC removal was associated with a better clinical outcome in patients with invasive candidiasis, especially in those patients with high APACHE II score ranged between 12 and 35.[26] In our study, those 2 patients with CVC catheters retention had high APACHE II score (14 and 17) and resulted in death. The importance of CVC removal within 72 h of candidemia detection was emphasized by Raad et al.[27]; however, Nucci et al.[28] found that early CVC removal (within 24 h or 48 h after treatment initiation) in non-neutropenic adults with candidemia did not influence patient mortality. Similar to the findings reported by Nucci et al., delayed CVC removal did not significantly influence

the mortality of patients with CG-BSI. One possible reason was that due to the low virulence of *C. guilliermondii*,[30] the death of patients was primarily related to their underlying diseases. Although CVC removal is an independent mortality determinant, the impact of delayed catheter removal needs further study.

The reported 30-day overall mortality rate of patients with candidemia is high (35%–60%), but few reports focus on CG-BSI.[1,2,24] In the previous case series of CG-BSI, the 30-day overall mortality ranged from 0% to 38%.[5,22,29] However, relatively lower mortality rate (16.7%) was observed in our study. The possible explanation was that our patients' characteristics of underlying conditions were different from others.[5,22] For example, in CG-BSI study by Girmenia et al. only patients with hematologic malignancies were enrolled.[5] In another study by Chen et al., the patients' characteristics also differed from our studied patients.[22] A case series with 5 cases of *C. guilliermondii* fungemia by Pasqualotto et al. showed no mortality.[29] In comparison of candidemic crude mortality caused by different *Candida* species, the mortality associated with *C. guilliermondii* was relatively low.[21] This is probably due to low virulence of *C. guilliermondii* noted in murine study.[30]

In testing the antifungal susceptibility of *Candida* spp., the results of the SYO method are comparable with those of the CLSI BMD reference method.[13,31,32] In the present study, the SYO method was used to test *in vitro* antifungal susceptibility of 22 *C. guilliermondii* isolates. In view of echinocandin susceptibility, Santos et al.[33] and Huang et al.[34] reported that none of the *C. guilliermondii* isolates showed resistance to echinocandin. Contrarily, Pfaller et al. found that *C. guilliermondii* exhibited decreased susceptibility to echinocandins than the more common isolates of *Candida*.[6,21,24,25] Decreased percentage of susceptibility to echinocandins (anidulafungin 72.7%, caspofungin 77.3%, micafungin 90.9%) was also detected in the present study. However, the clinical significance of decreased echinocandin susceptibility of *C. guilliermondii* needs to be confirmed in the future.

According to previous studies, *C. guilliermondii* is one of the fungal pathogens most likely to display *in vitro* resistance to amphotericin B and fluconazole.[6,35–38] In contrast to other more commonly isolated *Candida* species, *C. guilliermondii* appears to be less susceptible to fluconazole, but susceptible to novel triazoles.[6,8,21,24,25] Chen et al. reported a good *in vitro* activity of triazoles against up to 96%–100% *C. guilliermondii* isolates by ECV.[22] In an early study conducted by Pfaller et al., no evidence of increasing resistance to triazoles among *C. guilliermondii* isolates was reported.[25] In our study, decreased *in vitro* susceptibility to triazoles was observed among *C. guilliermondii* isolates; only 63.6%–77.3% of isolates were WT for fluconazole, voriconazole, itraconazole and posaconazole. Despite less susceptible to triazole, no treatment failure was observed in patients treated with triazole for CG-BSI during the study period, and the clinical significance of decreased *in vitro* susceptibility to triazole remains to be explored. Resistance to amphotericin B was rarely reported in the literature.[5,22,24] In the present study, 95.5% of isolates were WT to amphotericin B.

Three major limitations were found in our study. First, this study was conducted in a single site and enrolled small number of patients. Our results may not be applicable or generalized to other hospitals. Second, for its retrospective in nature, some important data might be missed and not included in our study. Such shortcoming may influence the results of analysis. Third, although high agreement between the SYO method and the CLSI method in testing minimum inhibitory concentration (MIC) has been reported, discrepancy between these two methods does exist and may influence the interpretation of susceptibility results.[13,31,32] Fourth, among 36 patients, only 22 isolates were available for susceptibility test by SYO method. This made us more difficult to define the correlation between clinical response and *in vitro* susceptibility.

In conclusion, CG-BSI is a rare cause of candidemia in clinical practice and associated with lower mortality than other *Candida* species. Removal of a CVC remained a major determinant of mortality. Non-susceptibility of *C. guilliermondii* to triazoles and echinocandins was demonstrated in this study, but the clinical significance of this observation warrants further study.

Conflicts of interest

All authors declare there is no conflict of interest.

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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.jmii.2016.08.015.