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

Ting-Yu Tseng, Tsung-Chia Chen, Cheng-Mao Ho, Po-Chang Lin, Chia-Huei Chou, Chia-Ta Tsai, Jen-Hsien Wang, Chih-Yu Chi, Mao-Wang Ho

Division of Infectious Diseases, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan
Section of Infectious Diseases, Department of Internal Medicine, Taichung Hospital, Taichung, Taiwan
Department of Laboratory Medicine, Taichung, Taiwan
Internal Medicine, China Medical University Hospital, Taichung, Taiwan
Department of Nursing, Hungkuang University, Taichung, Taiwan
School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan

Available online 2017; received in revised form 31 August 2016; accepted 31 August 2016

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 Sensi-titre 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 30 (83.3%) patients had central venous catheter in place. Thirty-day overall mortality was 16.7%. In multivariate logistical regression analysis, catheter
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,\(^1\) and rarely recognized as an invasive pathogen.\(^1\) 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.\(^5,6\)

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\(^6\) 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.\(^13\) 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 (Bio-
Mérieux, 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, fluocytosine 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, fluocytosine,
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-A39 and species-
specific CBPs from CLSI M27-S411 were used to categorize
isolates as susceptible (S), intermediate (I) or resistant (R).
For C. guilliermondii, the ECVs of anidulafungin, caspo-
fungin 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 resis-
tant. The ECVs and CBPs of nine antifungal agents for C.
guilliermondii used in this study are summarized inTable 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. Uni-
ivariate comparisons were made between the non-survival
and survival groups to identify factors of the association
between fungemia and mortality. The independent vari-
ables of death were identified by stepwise logistic regres-
sion 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 Staphy-
lococcus species (n = 3, 8.3%) was the most common isolate
in patients with concomitant bacteremia. Enterococcus spe-
cies, Streptococcusagalactiae, Bacillus cereus, Elizabeth-
kingia 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 break-
through 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 mor-
tality 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 inhibi-
tory 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).

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

\(^a\) 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 \(\geq\)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.
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 fluconazole, 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, 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. Similar to prior studies, malignancy, especially gastrointestinal solid tumors, remained the most common underlying disease (50%) in patients with CG-BSI. However, other risk factors for invasive candidiasis, 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 was unknown.

CG-BSI was highly associated with CVC use in our study and others. Catheter removal plays an important role in the management of candidemic patients with CVC, 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. 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., however, Nucci et al. 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 \textit{C. guilliermondii}, 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.\textsuperscript{1,2,24} In the previous case series of CG-BSI, the 30-day overall mortality ranged from 0% to 38%.\textsuperscript{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.\textsuperscript{5,22} For example, in CG-BSI study by Girmenia et al. only patients with hematologic malignancies were enrolled.\textsuperscript{5} In another study by Chen et al., the patients’ characteristics also differed from our studied patients.\textsuperscript{22} A case series with 5 cases of \textit{C. guilliermondii} fungemia by Pasqualotto et al. showed no mortality.\textsuperscript{29} In comparison of candidemic crude mortality caused by different \textit{Candida} species, the mortality associated with \textit{C. guilliermondii} was relatively low.\textsuperscript{21} This is probably due to low virulence of \textit{C. guilliermondii} noted in murine study.\textsuperscript{30}

In testing the antifungal susceptibility of \textit{Candida} spp., the results of the SYO method are comparable with those of the CLSI BMD reference method.\textsuperscript{13,31,32} In the present study, the SYO method was used to test \textit{in vitro} antifungal susceptibility of 22 \textit{C. guilliermondii} isolates. In view of echinocandin susceptibility, Santos et al.\textsuperscript{33} and Huang et al.\textsuperscript{34} reported that none of the \textit{C. guilliermondii} isolates showed resistance to echinocandin. Contrarily, Pfaffer et al. found that \textit{C. guilliermondii} exhibited decreased susceptibility to echinocandins than the more common isolates of \textit{Candida}.\textsuperscript{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 \textit{C. guilliermondii} needs to be confirmed in the future.

According to previous studies, \textit{C. guilliermondii} is one of the fungal pathogens most likely to display \textit{in vitro} resistance to amphotericin B and fluconazole.\textsuperscript{6,35–38} In contrast to other more commonly isolated \textit{Candida} species, \textit{C. guilliermondii} appears to be less susceptible to fluconazole, but susceptible to novel triazoles.\textsuperscript{6,8,21,24,25} Chen et al. reported a good \textit{in vitro} activity of triazoles against up to 96%–100% \textit{C. guilliermondii} isolates by ECV.\textsuperscript{22} In an early study conducted by Pfaffer et al., no evidence of increasing resistance to triazoles among \textit{C. guilliermondii} isolates was reported.\textsuperscript{25} In our study, decreased \textit{in vitro} susceptibility to triazoles was observed among \textit{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 \textit{in vitro} susceptibility to triazole remains to be explored. Resistance to amphotericin B was rarely reported in the literature.\textsuperscript{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.\textsuperscript{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 \textit{in vitro} susceptibility.

In conclusion, CG-BSI is a rare cause of candidemia in clinical practice and associated with lower mortality than other \textit{Candida} species. Removal of a CVC remained a major determinant of mortality. Non-susceptibility of \textit{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.

**Acknowledgments**

The study was supported by grants from the China Medical University Hospital (CMUH-DMR-100-030).

**References**

9. Clinical and Laboratory Standards Institute (CLSI). Reference method for broth dilution antifungal susceptibility testing of


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.