Journal of Microbiology, Immunology and Infection (2019) 52, 612–619

Available online at www.sciencedirect.com

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Original Article

Clinical manifestations of candidemia caused by uncommon *Candida* species and antifungal susceptibility of the isolates in a regional hospital in Taiwan, 2007–2014

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Received 16 June 2017; received in revised form 9 August 2017; accepted 9 August 2017
Available online 26 August 2017

KEYWORDS
Candidemia;
Uncommon candida species;

Abstract *Objective:* This retrospective study investigated clinical manifestations of candidemia caused by uncommon *Candida* species and antifungal susceptibility of the isolates in a regional hospital in Taiwan.

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http://dx.doi.org/10.1016/j.jmii.2017.08.007

Healthcare-associated infection;
Antifungal susceptibility testing;
Azoles;
Echinocandin

Methods: The uncommon *Candida* species was initially defined as *Candida* species other than *C. albicans, C. tropicalis, C. glabrata* complex, *C. parapsilosis* complex and *C. krusei*. All uncommon *Candida* isolates were identified and confirmed by molecular methods. In vitro susceptibility testing of the uncommon *Candida* species to nine antifungal agents was conducted using the broth microdilution method with the Sensititre YeastOne (SYO) system (Trek Diagnostic Systems, Ltd., East Grimstead, UK).
Results: Twenty-one patients, comprising 11 males and 10 females with a median age of 69 years, were recruited. Cancer (n = 11) was the most common underlying disease, 19 (90.5%) cases had prior antibiotic exposure, and only two patients had prior antifungal use. The overall in-hospital mortality rate was 38.1% (n = 8). *C. guilliermondii* (n = 11) was the most common pathogen, followed by *C. curvata* (n = 3). *C. guilliermondii* isolates exhibited relatively high rates of azole minimum inhibitory concentrations (MICs) above epidemiological cut-off values (ECVs), whereas *C. pelliculosa* and *C. lusitaniae* isolates all remained susceptible to azoles. All three *C. curvata* isolates had high caspofungin (>8 mg/L) and fluconazole MICs (8 mg/L) and could be defined as multidrug-resistant.
Conclusions: Uncommon *Candida* species frequently exhibit high rates of non-susceptibility to antifungals. Identification of all *Candida* isolates at the species level from blood samples is of value for treatment.

Introduction

Invasive candidiasis has become a great threat to public health, and it affects more than 250,000 people every year and is associated with more than 50,000 mortalities.[1] In several population-based studies, the incidence of candidemia was found to be increasing globally due to the growing population of immunocompromised hosts and the increasing use of invasive devices.[2–5] In Taiwan, several studies have shown similar findings regarding increasing invasive candidiasis among different populations, especially in the setting of nosocomial infections.[6–9]

In addition to an increasing number of cases, the species distribution of candidemia has changed recently. Although *C. albicans* remains the dominant pathogen underlying invasive candidiasis and accounts for approximately 50% of all cases, the incidence rates of candidemia caused by *non-albicans Candida* species, including *C. tropicalis, C. glabrata* complex, *C. parapsilosis* complex and *C. krusei* are increasing.[1,4,7] In general, more than 90% of invasive candidiasis are caused by these five *Candida* spp., including *C. albicans, C. tropicalis, C. glabrata* complex, *C. parapsilosis* complex and *C. krusei*.[10–12] However, some uncommon *Candida* spp., such as *C. guilliermondii, C. pelliculosa, C. lipolytica, C. dubliniensis*, have also been reported to be one of the etiologies of candidemia.[13–15] Moreover, the understanding of the clinical significance and microbiologic characteristics among these uncommon *Candida* spp. is limited due to their rare occurrence.[13] Therefore, an investigation of uncommon *Candida* spp. is urgently needed. In this study, we retrospectively reviewed the clinical characteristics of candidemia caused by uncommon *Candida* spp. We also assayed the in vitro susceptibility of these uncommon *Candida* spp. isolates to antifungal agents.

Patients and methods

Study design and setting

This study was retrospectively conducted at the Chi Mei medical center, Liouying campus, a 900-bed hospital in southern Taiwan. All patients with candidemia were identified from a computerized database from the microbiology department between 2007 and 2014. After the exclusion of five common *Candida* spp., including *C. albicans, C. tropicalis, C. glabrata* complex, *C. parapsilosis* complex, and *C. krusei*, 33 *Candida* isolates were found, of which only 25 isolates were available from subculture. The cases with molecular method-confirmed uncommon *Candida* spp. bloodstream infections (BSIs) were then subjected to further analysis. The medical records of all patients with BSIs due to uncommon *Candida* spp. were retrospectively reviewed and the following information was collected: age, gender, underlying conditions (history of immunosuppressant drug or steroid use, diabetes mellitus, liver cirrhosis, end-stage renal disease, and cancer), risk factors (presence of central venous catheter (CVC), Foley catheter, or Port-A-Cath; recent abdominal surgery; chemotherapy, total parenteral nutrition, gastrointestinal bleeding, use of acid-reducing agents, and prior use of broad spectrum antibiotics), laboratory data, microbiological findings, and patient outcome.

Phenotypic identification of the isolates

Fungal blood cultures obtained from January 2007 to December 2014 at the hospital were analyzed. BACTEC Myco/F Lytic bottles (Becton Dickinson Microbiology Systems, Sparks, MD) containing 5–10 mL of blood were incubated in a BACTEC 9240 culture system (Becton

Dickinson Microbiology Systems) at 35 °C. Each patient was included only once at the time the first bloodstream infection was detected. All isolates were inoculated onto CMA agar (Oxoid) with 1% Tween 80, and then, all plates were incubated at 26 °C for 72 h. Isolates were identified by investigation under a microscope (40× objective) according to their chlamydospore, blastospore and/or hyphal formation. Additionally, the assimilation profile of all yeast isolates was performed using commercially available API strips (ID32C; bioMérieux, Marcy l'Etoile, France), which were read and interpreted at 48 h.

Gene sequencing of the isolates

All uncommon *Candida* isolates were identified by polymerase chain reaction (PCR) and by direct sequencing of the 28 S rRNA and internal transcribed spacer (ITS) regions. The D1—D2 region of the large-subunit RNA gene and the ITS regions of each isolate were amplified by PCR, sequenced, and then compared with sequences in public databases using the BLAST algorithm. The fungus-specific primers ITS1 (5′-TCCGTAGGTGAACCTGCGG-3′) and ITS4 (5′-TCCTCCG CTTATTGATATGC-3′) were used to amplify the ITS regions, respectively.[16] For the D1-D2 region amplification, primers NL1 (5′-GCATATCAATAAGCGGAGGAAAAG-3′) and NL4 (5′-GGTCCGTGTTTCAAGACGG-3′) were used.[17] PCR products were sequenced on a model 377 sequencing system (Applied Biosystems, Taipei, Taiwan).

Antifungal susceptibility testing of the isolates

The susceptibility of the 21 preserved non-duplicate *Candida* species blood isolates (one isolate from each patient) to nine antifungal agents was determined by using the Clinical Laboratory Standards Institute (CLSI) broth microdilution method with the Sensititre YeastOne (SYO) system (part YO-10; Trek Diagnostic Systems, Ltd., East Grimstead, U.K.) according to the manufacturer's instructions. Plates containing serial 2-fold dilutions of the antifungal agents across 12 dilutions were inoculated using a prepared suspension of the organism. On the day of the test, a working yeast suspension of approximately 1.5×10^3 CFU/mL was prepared in SYO inoculum broth (Trek Diagnostic Systems). The dried SYO panels were rehydrated by dispensing 100 μL of working yeast suspension into each well using a multichannel pipetting device. The SYO panels were covered with adhesive seals and incubated at 35 °C for 24 h in a non-CO_2 incubator. The colorimetric MIC endpoints were read using a reading mirror that displayed the underside of the wells. A color change from blue (negative, no growth) to red (positive, growth) was taken as evidence of yeast growth. Colorimetric MIC results for all test agents were defined as the lowest concentration of antifungal agent that prevented the development of red colonies (first blue well). *C. parapsilosis* ATCC 22019 was used as quality control isolates. For uncommon *Candida* spp., other than for *C. guilliermondii*, clinical breakpoints were undefined. Therefore, isolates that showed MICs higher than the epidemiologic cutoff value (ECV) were considered potentially resistant.[18] There were no ECVs for *C. curvata, C. lipolytica, C. pulcherrima* and *C. palmioleophila*. Therefore, those isolates were excluded from susceptibility comparisons.

Definition

Candidemia was defined as at least one set of positive blood culture of *Candida* species in patients with compatible clinical signs/symptoms of infections. The diagnosis of infection focus of candidemia was made based on clinical, bacteriological, and radiological investigations. Catheter-related bloodstream infection (CRBSI) was defined as a positive semi-quantitative tip culture (≥15 colony-forming units), candidemia, and/or high clinical suspicion. Urinary tract infection (UTI) was defined as positive urine culture with growth of $\geq 10^5$ CFU/mL and pyuria. If no primary focus could be identified, the candidemia was classified as primary. In-hospital mortality was defined as death due to any cause during hospitalization. Uncommon *Candida* species was defined as *Candida* species other than *C. albicans, C. tropicalis, C. glabrata* complex, *C. parapsilosis* complex and *C. krusei*, as identified by molecular methods.

Results

Distribution of Candida spp. causing BSI

Fig. 1 shows the distribution of *Candida* spp. BSI with time. Among 626 episodes of candidemia, *C. albicans* (n = 331, 53.3%) was the most common species, followed by *C. tropicalis* (n = 100, 16.1%) and *C. glabrata* complex (n = 88, 14.2%). No *C. krusei* isolate was identified during this period. Initially, 24 uncommon *Candida* spp., including *C. guilliermondii* (n = 10), *C. pelliculosa* (n = 3), *C. curvata* (n = 3), *C. sake* (n = 3), *C. lusitaniae* (n = 2), *C. lipolytica* (n = 1), *C. famata* (n = 1), and *C. pulcherrima* (n = 1), were identified by conventional methods.

Molecular identification of uncommon *Candida* spp.

After employing a molecular method of identification, we found six discordances between conventional and molecular methods in terms of *Candida* species. Among these discordant results, three *C. sake* isolates became one *C. guilliermondii* and two *Lodderomyces elongisporus* isolates, one *C. guilliermondii* isolate became a *C. glabrata* isolate, one *C. pelliculosa* isolate became *C. guilliermondii* isolate, and one *C. famata* isolate became a *C. palmioleophila* isolate. Finally, only 21 cases with molecular method-confirmed uncommon *Candida* spp. were identified. Among these, *C. guilliermondii* (n = 11) was the most common pathogen, followed by *C. curvata* (n = 3), *C. pelliculosa* (n = 2), and *C. lusitaniae* (n = 2), following by one isolate of each of the following: *C. palmioleophila, C. lipolytica,* and *C. pulcherrima*.

Susceptibilities of the isolates

The in vitro susceptibility results for nine antifungal agents were available for all 21 isolates (Table 1). *C. guilliermondii* isolates exhibited relatively high rates of azole MICs

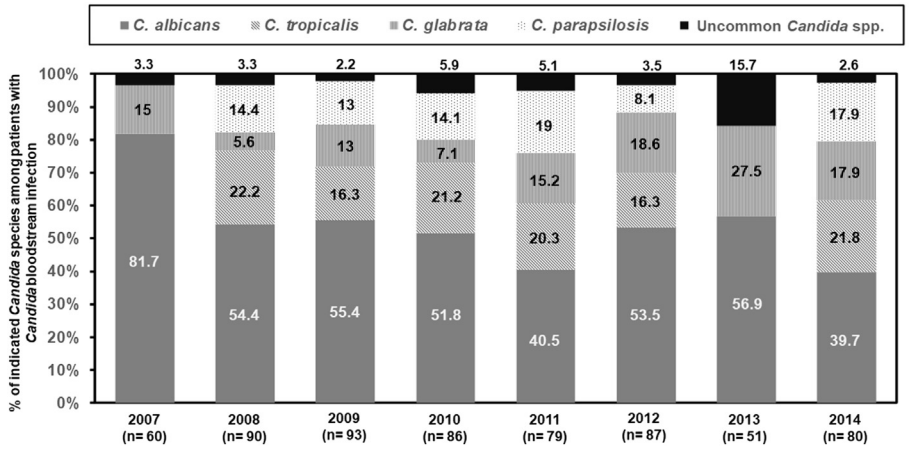

Figure 1. Annual number of candidemia cases at Chi Mei Medical Center, Liouying campus in Taiwan from 2007 to 2014, and species distribution of *Candida* blood isolates (number denotes %). No *Candida krusei* isolate was identified during this period.

above ECVs (fluconazole 45%, voriconazole 36%, and posaconazole 18%), whereas *C. pelliculosa* and *C. lusitaniae* isolates all remain susceptible to azoles (Table 1). Caspofungin MIC clinical breakpoints have been proposed only for *C. guilliermondii*.[18] Consequently, 7 *C. guilliermondii* isolates (64%) were susceptible to caspofungin (MIC ≤2 mg/L), and 4 isolates were resistant (MIC ≥8 mg/L). One *C. lipolytica* isolate had a relatively high fluconazole MIC (4 mg/L) but low caspofungin MICs (0.06 mg/L), and one *C. palmioleophila* isolate had similar results (MICs for fluconazole and caspofungin were 4 and 0.12 mg/L, respectively). All three *C. curvata* isolates had high caspofungin (>8 mg/L)

Table 1 In vitro susceptibility of 21 uncommon *Candida* spp. to nine antifungal agents using the broth microdilution method.

No	Minimum inhibitory concentration (mg/L)								
	Caspofungin	Anidulafungin	Micafungin	Fluconazole	Voriconazole	Itraconazole	Posaconazole	5-Flucytosine	Amphotericin B
C. guilliermondii									
1	1	2	0.5	4	0.12	0.5	0.25	≤0.06	1
2	>8	2	2	4	0.12	0.5	0.5	0.12	0.5
3	0.25	1	0.5	16	0.25	0.5	0.25	≤0.06	0.5
4	2	2	1	4	0.12	0.5	0.5	≤0.06	1
5	1	2	0.5	2	0.03	0.25	0.12	≤0.06	≤0.12
6	0.12	1	0.5	8	0.12	0.25	0.06	≤0.06	≤0.12
7	1	2	1	2	0.06	0.25	0.25	≤0.06	0.25
8	>8	4	4	16	0.5	0.5	0.5	0.25	2
9	>8	>8	>8	16	0.5	1	0.5	0.25	1
10	8	4	>8	>256	>8	1	>8	>64	>8
11	2	2	1	32	1	1	1	≤0.06	1
C. curvata									
12	>8	>8	>8	8	0.25	0.5	0.5	64	1
13	>8	>8	>8	8	0.25	0.5	0.5	32	1
14	>8	>8	>8	8	0.25	0.5	0.5	32	1
C. pelliculosa									
15	0.03	<0.015	0.03	4	0.12	0.12	0.25	<0.06	0.5
16	0.03	<0.015	0.03	4	0.12	0.12	0.5	<0.06	0.5
C. lusitaniae									
17	0.25	0.25	0.12	0.25	<0.008	0.06	0.03	<0.06	0.5
18	0.5	0.25	0.06	0.5	0.015	0.12	0.03	<0.06	1
C. palmioleophila									
19	0.12	0.06	0.03	4	0.12	0.25	0.25	≤0.06	≤0.12
C. lipolytica									
20	1	0.5	2	8	0.12	0.25	0.5	NA	0.5
C. pulcherrima									
21	0.5	1	0.5	0.5	0.015	0.12	0.015	0.12	0.25

NA, not applicable.

and fluconazole MICs (8 mg/L). Although ECVs for that species have not been defined, on the basis of ECV and clinical breakpoints for other *Candida* spp., those isolates could be considered nonsusceptible to azoles and echinocandins, defining them as multidrug-resistant.

Clinical characteristics

A total of 21 episodes of uncommon *Candida* spp. BSI were identified, and their clinical characteristics are summarized in Table 2. The patients ranged in age from 1 to 79 years (median, 69 years), and 52.4% (n = 11) of them were classified as elderly patients with an age ≥ 65 years. In total, 52.4% (n = 11) of patients were male. All candidemia episodes were classified as healthcare-associated infections. Eighteen (86.7%) episodes of candidemia were obtained in the general ward, and another three (14.3%) cases contracted infections during their stay in the intensive care unit (ICU). Overall, cancer (n = 11) and hypertension (n = 9) were the most common underlying diseases, followed by diabetes mellitus (n = 6).

Nineteen (90.5%) cases had prior broad-spectrum antibiotics exposure, and only two patients had prior antifungal agent use. The Charlson comorbidity index ranged from 0 to 6 (median 3). Most patients had various risk factors for candidemia, such as the presence of central venous catheter (n = 15), including the Port-A-Cath or Foley catheter (n = 8), recent chemotherapy (n = 9), use of total parenteral nutrition (n = 6), gastrointestinal tract bleeding (n = 6) or recent abdominal surgery (n = 3), but only one patient (4.8%) had neutropenia during their episode of candidemia. In addition to three cases with primary candidemia, the most common source of secondary candidemia was central line-associated (n = 9), followed by intra-abdominal infection (n = 6) and urinary tract infection (n = 3). There were 6 and 9 patients who had acute respiratory failure and required ICU admission, respectively. Five patients received antifungal therapy with azole-based regimens, five received echinocandin-based regimens, two received amphotericin B treatment, and nine patients didn't receive any antifungal treatment. Eight patients expired during hospitalization, and the in-hospital mortality rate was 38.1%.

Discussion

This study, which investigated the clinical manifestations of uncommon *Candida* species fungemia, had several significant findings. First, after excluding the major five common candida species, including *C. albicans, C. tropicalis, C. glabrata, C. parapsilosis* and *C. krusei, C. guilliermondii* was the most common pathogen causing candidemia, followed by *C. curvata*. Rarely, *C. pelliculosa*, *C. lusitaniae, C. palmioleophila, C. lipolytica,* and *C. pulcherrima* were also identified in this series. The distribution of these uncommon *Candida* species in this study is different from the findings of previous studies.[19–21] In the global investigation based on the SENTRY Antimicrobial Surveillance Program,[21] among a total of 1354 *Candida* bloodstream infections, 50 (3.7%) were identified as miscellaneous species, including *C. dubliniensis* (16 isolates), *C. guilliermondii* (eight isolates), *C. kefyr* (six isolates), *C. famata* (three isolates), *C. lipolytica* (three isolates), *C. rugosa* (two isolates), *C. sake* (two isolates), *C. pelliculosa* (two isolates), and one isolate each of *C. lambica, C. utilis, C. haemulonii, C. norvegensis*, and *C. inconspicua*. In a multicenter study of a total of 134 nosocomial *Candida* infections in children in Turkey, in addition to five major common candida species, *C. lusitaniae* (3.7%) was the most common pathogen, followed by *C. kefyr* (2.2%), *C. guilliermondii* (1.5%), and *C. dubliniensis* (0.7%).[19] Based on a Brazilian National Surveillance Program for 137 episodes of nosocomial candidemia,[20] the uncommon *Candida* species included *C. pelliculosa* (1.5%), *C. lusitaniae* (0.7%), *C. famata* (0.7%), and *C. guilliermondii* (0.7%). All of the above findings indicate that the distribution of uncommon *Candida* species shows significant variation according to different study places, designs, and populations.[22] Therefore, it is important to conduct population-based or institutional surveillance to establish local epidemiology.

Second, three rare *Candida* species, including *C. curvata, C. pulcherrima* and *C. palmioleophila* were identified and confirmed by molecular methods in this series. This study is the first report of human infections caused by *C. curvata*. We demonstrated that this rare pathogen can cause primary candidemia or fungemia secondary to catheter-associated urinary tract infection. In addition, although several reports have demonstrated another pathogen,[23,24] *C. pulcherrima*, is associated with human infections, for the first time, we report a case of central line-associated bloodstream infection caused by *C. pulcherrima* in Taiwan. Regarding *C. palmioleophila*, our finding is consistent with a previous report that *C. palmioleophila* could be misidentified as *C. famata* or *C. guilliermondii*.[25] However, the clinical significance of this pathogen remains unclear due to limited reports.[25–27] Our findings suggest that *C. curvata, C. pulcherrima* and *C. palmioleophila* should be considered as possible *Candida* species causing fungemia. Moreover, further large-scale studies using molecular methods for the identification of *Candida* species are warranted to help understand the clinical characteristics of these uncommon *Candida* species.

Third, all cases were identified as healthcare-associated infections, and most had various risk factors for candidemia. These findings are consistent with a previous study of 90 episodes of candidemia due to *C. albicans* in Taiwan that more than 40% of patients had various underlying diseases including malignancy, DM, and impaired renal function.[28] Nearly all patients had received antibiotics prior to acquisition of candidemia. It is also true for patients with *C. albicans* candidemia that 78.9% patients had prior exposure of broad spectrum antibiotics.[28] Most important of all, the clinical outcome of the patients in this study was poor, and the overall in-hospital mortality rate was 38.1%. Although previous reports showed the mortality rate of *C. albicans* candidemia upto more than 50%,[28–30] which was higher than the previous study of uncommon *Candida* spp., the differences may be due to different study designs, patient populations and treatment policy. Further large-scale study is warranted to compare the clinical significance between *C. albicans* and uncommon *Candida* spp. candidemia. Overall, this study help us further realize the clinical characteristics of uncommon *Candida* spp. BSI.

Table 2 Clinical characteristics of 21 patients with bloodstream infection caused by uncommon *Candida* spp.

Candida species/case no. (year of report)	Age	Gender	Underlying disease	Risk factor	Previous *Candida* colonization	CCI	Source of infection	Antifungal regimen	Mortality
C. guilliermondii									
1 (2007)	51	M	DM, HTN, Left buccal synovial sarcoma	Receiving chemotherapy, Port-A, prior use of BSA	None	3	CVC-related	Nil	No
2 (2007)	60	M	Right buccal cancer	Receiving chemotherapy, Port-A, neutropenia, prior use of BSA	None	2	CVC-related	Nil	No
3 (2008)	49	M	Old TB, esophageal cancer	Receiving chemotherapy, Port-A	None	6	CVC-related	Caspofungin	No
4 (2008)	76	F	Chronic hepatitis C	Foley catheter	None	1	CAUTI	Fluconazole	No
5 (2009)	68	M	Small-cell lung cancer	Receiving chemotherapy, Port-A, prior use of BSA	None	4	CVC-related	Nil	No
6 (2009)	75	F	HTN, pancreatic cancer	Receiving chemotherapy, Port-A, prior use of BSA, UGIB, use of PPI	None	5	IAI-related	Fluconazole	Yes
7 (2010)	44	F	Breast cancer	Receiving chemotherapy, Port-A, prior use of BSA	Sputum	2	CVC-related	Caspofungin	Yes
8 (2011)	60	M	HTN	Foley catheter, CVC, prior use of BSA	None	0	Primary candidemia	Amphotericin-B	No
9 (2013)	79	M	Short bowel syndrome	TPN, CVC, prior use of BSA, UGIB, use of PPI	None	1	CVC-related	Nil	No
10 (2013)	53	F	DM, HCC	Receiving chemotherapy, Port-A, prior use of BSA	None	3	IAI-related	Fluconazole	No
11 (2014)	1	F	Nil	Recent abdominal surgery, prior use of BSA	Wound	0	IAI-related	Voriconazole	No
C. curvata									
12 (2011)	69	M	DM, HTN,CHF	Foley catheter, prior use of BSA	None	6	Primary candidemia	Fluconazole	Yes
13 (2012)	74	F	DM, HTN,CHF	Foley catheter, prior use of BSA	Urine	4	CAUTI	Nil	No
14 (2013)	69	M	HTN, HCC	UGIB, use of PPI, prior use of BSA	None	3	Primary Candidemia	Nil	No
C. pelliculosa									
15 (2008)	72	F	Nil	TPN, CVC, Recent abdominal surgery, prior use of BSA	None	0	IAI-related	Nil	Yes
16 (2010)	72	M	DM, HTN	TPN, CVC, Recent abdominal surgery, prior use of BSA, UGIB, use of PPI	Urine	4	IAI-related	Amphotericin-B	No
C. lusitaniae									
17 (2013)	58	M	HTN, CVA	Foley catheter, prior use of BSA	Sputum	4	IAI-related	Nil	Yes
18 (2013)	73	F	Nil	TPN, CVC, Foley catheter, prior use of BSA, UGIB, use of PPI	None	4	CVC-related	Micafungin	Yes

(*continued on next page*)

Table 2 (*continued*)

Candida species/case no. (year of report)	Age	Gender	Underlying disease	Risk factor	Previous *Candida* colonization	CCI	Source of infection	Antifungal regimen	Mortality
C. palmioleophila 19 (2010)	50	F	DM, CKD, cervical cancer	Foley catheter, CVC, Receiving chemotherapy, TPN, prior use of BSA, Steroid using, UGIB, use of PPI	Urine	9	CAUTI	Micafungin	Yes
C. lipolytica 20 (2011)	64	M	Common bile duct adenocarcinoma	Receiving chemotherapy, Port-A, prior use of BSA	None	4	CVC-related	Nil	Yes
C. pulcherrima 21 (2014)	89	F	HTN, colorectal cancer	CVC, Foley catheter, TPN, prior use of BSA	Urine	2	CVC-related	Anidulafungin	No

CCI, Charlson Comorbidity Index; DM, diabetes mellitus; HTN, hypertension; BSA, broad-spectrum antibiotics; CVC, central venous catheter; TB, tuberculosis; CAUTI, catheter-associated urinary tract infection; TPN, total parenteral nutrition; UGIB, upper gastrointestinal bleeding; PPI, proton pump inhibitor; HCC, hepatocellular carcinoma; IAI, intraabdominal infection; CHF, congestive heart failure; CVA, cerebrovascular accident; CKD, chronic kidney disease.

Finally, we performed the MIC tests of nine antifungal agents for each clinical isolate and had several notable findings. *C. guilliermondii* isolates exhibited high rates of azole resistance, especially for fluconazole (45%), in agreement with the data of previous reports.[13,31,32] Similarly, echinocandin resistance among *C. guilliermondii* bloodstream isolates in our study was also high (a caspofungin MIC >8 mg/L was observed for 36% of isolates). In contrast, Jung et al. reported that a caspofungin MIC >1 mg/L was observed for only 13% of *C. guilliermondii* isolates.[13] *C. pelliculosa* isolates exhibited decreased susceptibility to fluconazole (MIC >2 mg/L was observed for 100% of isolates), compared to previous reports.[33,34]

This study has several limitations. First, the case number was limited in the present work. However, as the fungemia caused by these *Candida* species is extremely rare and difficult to identify, our findings still provide useful information regarding the clinical manifestations of these uncommon *Candida* species-associated infections. Second, this study was conducted in a single hospital, so our findings may not be generalizable to other hospitals. Each hospital should conduct institutional surveillance to establish its own epidemiology.

In conclusion, candidemia due to uncommon *Candida* species is emerging in healthcare-associated infections, especially among patients with multiple comorbidities. Uncommon *Candida* species frequently exhibit high rates of nonsusceptibility to azoles and echinocandins, and the identification of all *Candida* isolates at the species level from blood are of value for further treatment.

Conflicts of interest

All authors declare no conflict of interest.

Acknowledgments

We thank Ya-Feng Wu (Bacteriology Laboratory, Department of Clinical Pathology, Chi Mei Medical Center, Liouying) for her help in collecting the data.

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