Journal of Microbiology, Immunology and Infection (2017) 50, 97—103

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ORIGINAL ARTICLE

Epidemiology, antifungal susceptibilities, and risk factors for invasive candidiasis from 2011 to 2013 in a teaching hospital in southwest China

Shuli Pu, Siqiang Niu, Chuanming Zhang, Xiuyu Xu, Mei Qin, Shifeng Huang, Liping Zhang*

Department of Laboratory Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China

Received 18 June 2014; received in revised form 11 December 2014; accepted 12 January 2015
Available online 30 January 2015

KEYWORDS
Antifungal susceptibility;
Epidemiology;
Invasive candidiasis;
Risk factor

Abstract *Background:* Invasive candidiasis (IC) is the most common cause of invasive fungal infections. Identification of risk factors for such infection may help in the empirical therapeutic decision-making process. We conducted this study to characterize the clinical epidemiology of such infection and to differentiate risk factors between *Candida albicans* and *Candida non-albicans* species.
Methods: We retrospectively evaluated patients with IC from 2011 to 2013. Clinical data, antibiotic therapy, underlying condition, and invasive procedures were analyzed and compared between *C. albicans* and *C. non-albicans* species.
Results: C. albicans was the most frequently isolated *Candida* species (48.6% of all IC patients), although *C. non-albicans* spp. were more commonly isolated overall. *C. albicans*, *Candida tropicalis*, and *Candida parapsilosis* have a high susceptibility rate to all antifungal agents (>90%), whereas *Candida glabrata* showed decreased susceptibility to fluconazole and itraconazole. Amphotericin B demonstrated excellent antifungal activity against all *Candida* species. Univariate analyses showed that IC patients with *C. albicans* had a higher ratio of older age ($p = 0.008$), solid tumor ($p = 0.029$), and hypoproteinemia ($p = 0.019$), whereas those with *C. non-albicans* spp. had a higher ratio of hospital length of stay ($p = 0.005$), usage of corticosteroids ($p = 0.011$), duration on corticosteroids ($p = 0.005$), chemotherapy ($p = 0.022$), hematologic malignancy ($p = 0.039$), neutropenia ($p = 0.030$), and usage of glycopeptides ($p = 0.002$). Multivariate analyses showed that a significant predictor of IC due to *C. albicans* was hypoproteinemia [odds ratio (95% confidence interval) = 2.133 (1.164—3.908), $p = 0.014$].

* Corresponding author. Department of Laboratory Medicine, The First Affiliated Hospital of Chongqing Medical University, No. 1 Friendship Road, Yuzhong district,Chongqing, China.
E-mail address: 1309898173@qq.com (L. Zhang).

http://dx.doi.org/10.1016/j.jmii.2015.01.005

Conclusion: C. albicans was the most frequently isolated *Candida* species. The risk factors between *C. albicans* and *C. non-albicans* species are different.

Introduction

Fungi have emerged as a major cause of human disease since the early 1980s, especially among patients with immunocompromised and serious underlying disease.[1–4] Invasive fungal infections seriously threaten the health of hospitalized patients, causing substantial morbidity, mortality, and increases in hospital costs.[5,6] Invasive candidiasis (IC) is the most common cause of invasive fungal infections, accounting for 70–90% of all invasive mycoses.[7,8] Candidemia is the fourth leading cause of bloodstream infection in the USA.[9] Thus, IC has a significant influence on patient outcomes and the health care economy.[10] It is clear that IC has emerged as an important public health problem.[5,11]

Although *Candida albicans* was the predominant species in a majority of countries, the proportion of *Candida non-albicans* species has increased rapidly in IC patients recently.[12] This change has been attributed to the increasing use of azole antifungals and invasive procedures.[12] There are remarkable geographical differences in the epidemiology of *Candida* infection.[13] *C. albicans* accounts for 50–70% of *Candida* infection in the USA, whereas *C. non-albicans* species are more common in Asia, South America, and southern Europe.[14,15] Thus, knowledge of recent, local epidemiological patterns, and susceptibility to antifungals is of great importance.[5]

The purpose of this study is to describe the current epidemiology, antifungal susceptibility to *Candida*, and the differences in risk factors between *C. albicans* and *C. non-albicans* species for IC in southwest China. We believe that the data obtained from this study will help develop clinical practice recommendations to improve the management and outcomes of such cases.

Methods

Study design and patients

We performed a retrospective study in the First Affiliated Hospital of Chongqing Medical University, a teaching facility in southwest China. All *Candida* species isolated from blood, other sterile body fluids (including ascitic fluid, drainage fluid, cerebrospinal fluid, and bile), catheters, and pus from patients with *Candida* infection in different wards from January 2011 to December 2013 were included in this study. However, *Candida* strains from sputum and urine were excluded. For patients with more than one IC episode, only the first episode was included. All patients gave informed consent.

Clinical data [including age, sex, hospital length of stay, patient source, 30-day mortality, all-cause in-hospital mortality, intensive care unit (ICU) stay, and length of ICU stay] of patients with invasive *Candida* infection were recorded on standardized forms. Antibiotic therapy, underlying condition [including diabetes mellitus, organ dysfunction, solid tumor, hematologic malignancy, hypoproteinemia (serum total protein $<$ 60 g/L or albumin $<$25 g/L), severe anemia (hemoglobin $<$60 g/L), and neutropenia (absolute neutrophil count $<$ 500 cells/μL)], and invasive procedures within prior 4 weeks (including blood product transfusion, hemodialysis, mechanical ventilation, tracheal intubation, indwelling gastric tube, urinary catheter, drainage tube, enema, total parental nutrition, arterial catheter, central venous catheter, and surgery) were also recorded.

Antifungal susceptibility testing

The susceptibility of 257 *Candida* strains to five antifungal agents (amphotericin B, flucytosine, fluconazole, itraconazole, and voriconazole) was tested *in vitro* using ATB FUNGUS 3 system (bioMérieux, La Balme-les Grottes, France). For quality control, *C. albicans* isolates (ATCC 64548) were used. The results were interpreted using the Clinical and Laboratory Standards Institute M27-A3 microbroth dilution method.

Statistical analysis

Data were analyzed using SPSS software version 21.0 (SPSS Inc., Chicago, IL, USA). The comparison of risk factors between *C. albicans* and *C. non-albicans* species for IC was performed using univariate analysis followed by multivariate regression. Univariate analysis was performed using the Chi-square test or Fisher's exact test for categorical variables and the Mann–Whitney *U* test for numerical variables. Each risk factor with a $p < 0.05$ on univariate analysis was examined further using multivariate logistic regression. A p value < 0.05 was considered significant.

Results

Patient characteristics and distribution of *Candida*

A total of 297 nonrepeatable episodes of invasive fungi infections were detected from January 2011 to December 2013, of which 257 (86.5%) IC patients were enrolled in this study according to the diagnostic criteria of IC.[16] Patients included 170 (66.1%) males and 87 (33.9%) females. The mean age was 59.15 ± 17.81 years, and 145 patients were

older than 60 years. *C. albicans* and *C. non-albicans* spp. were responsible for 48.6% (125 of 257) and 51.4% (132 of 257) of IC cases, respectively. The *C. non-albicans* spp. isolated included 45 (17.5%) *Candida tropicalis*, 42 (16.3%) *Candida parapsilosis*, 33 (12.8%) *Candida glabrata*, four (1.6%) *Candida krusei*, three (1.2%) *Candida sake*, two (0.8%) *Candida dubliniensis*, two (0.8%) *Candida guilliermondii*, and one (0.4%) *Candida intermedia*.

The distribution of these 257 IC specimens was as follows: 93 (36.2%) blood, 29 (11.3%) ascitic fluid, 29 (11.3%) catheters, 18 (7.0%) drainage fluid, 13 (5.1%) pus, nine (3.5%) cerebrospinal fluid, eight (3.1%) bile, six (2.3%) vitreous body, six (2.3%) puncture fluid, six (2.3%) exudate, five (1.9%) pleural fluid, and 35 (13.6%) specimens in other normally sterile sites. The most frequent wards were the ICUs (31.1%, 80 of 257), the gastrointestinal surgery (15.6%, 40 of 257), the hepatobiliary surgery (10.1%, 26 of 257), the urinary surgery (5.8%, 15 of 257), and the neurosurgery (5.1%, 13 of 257) wards.

Susceptibility of *Candida* isolates to antifungal drugs

The *in vitro* susceptibility results of the 257 *Candida* isolates to five antifungal agents are presented in Table 1. *C. albicans*, *C. tropicalis*, and *C. parapsilosis* had a high susceptibility to all the antifungal agents, whereas *C. glabrata* showed a low susceptibility (only 54.5%) to fluconazole and itraconazole. Amphotericin B demonstrated excellent antifungal activity against all *Candida* species.

Mortality rate of patients with IC

Among patients with IC, the 30-day mortality rate was 9.7% (25 of 257). The 30-day mortality rates of *C. albicans* and *C. non-albicans* were 8.0% (10 of 125) and 11.4% (15 of 132), respectively (Table 2). The respective 30-day mortality rates among *C. non-albicans* were as follows (Table 2): *C. tropicalis*, 15.6% (7/45); *C. parapsilosis*, 14.3% (6/42); *C. glabrata*, 3.0% (3/33); and others, 8.3% (1/12). Patients with *C. tropicalis* IC had the highest rate of 30-day mortality, whereas those with *C. glabrata* IC had the lowest mortality rate. The all-cause in-hospital mortality was 14.4% (37/257). The all-cause in-hospital mortality rates of IC patients with each *Candida* species were demonstrated in Table 2.

Risk factors for *C. albicans* ICs compared with *C. non-albicans* ICs

Univariate analyses showed a significant difference between patients with *C. albicans* and patients infected with *C. non-albicans* spp. with regard to age, hospital length of

Table 1 *In vitro* susceptibility data of *Candida* spp

Species (No.)	Antifungal agent	MIC (μg/mL)			%		
		Range	50%	90%	S	SDD	R
Candida albicans (125)	Amphotericin B	≤0.5 to 1	≤0.5	≤0.5	100		0
	Flucytosine	≤0.062 to >16	0.125	0.25	97.6		2.4
	Fluconazole	≤0.125 to 8	0.25	0.5	97.6		2.4
	Itraconazole	≤0.062 to 4	≤0.062	0.125	93.6		6.4
	Voriconazole	≤0.062 to >8	≤0.062	≤0.062	94.4		5.6
Candida tropicalis (45)	Amphotericin B	≤0.5 to 1	≤0.5	1	100		0
	Flucytosine	≤0.062 to 4	0.125	0.125	100		0
	Fluconazole	0.25 to >128	1	2	97.8		2.2
	Itraconazole	≤0.062 to 4	0.125	0.25	100		0
	Voriconazole	≤0.062 to 0.125	≤0.062	0.125	100		0
Candida parapsilosis (42)	Amphotericin B	≤0.5 to 2	≤0.5	1	100		0
	Flucytosine	≤0.062 to 4	0.125	0.25	100		0
	Fluconazole	0.25 to 4	0.5	2	97.6		2.4
	Itraconazole	≤0.062 to 1	0.125	0.25	97.6		2.4
	Voriconazole	≤0.062 to 0.125	≤0.062	≤0.062	100		0
Candida glabrata (33)	Amphotericin B	≤0.5 to 1	≤0.5	1	100		0
	Flucytosine	≤0.062 to >16	0.125	0.5	97.0		3.0
	Fluconazole	0.25 to >128	8	32	54.5	31.8	13.7
	Itraconazole	0.125 to >8	2	4	54.5		45.5
	Voriconazole	≤0.062 to >8	0.25	0.5	90.9		9.1
Others[a] (12)	Amphotericin B	≤0.5 to 1	≤0.5	1	100		0
	Flucytosine	≤0.062 to 8	0.25	1	75.0		25.0
	Fluconazole	0.5 to 64	8	32	50.0		50.0
	Itraconazole	≤0.062 to >8	0.5	2	50.0		50.0
	Voriconazole	≤0.062 to 0.5	0.25	0.5	100		0

[a] Others include *Candida krusei* ($n = 4$), *Candida sake* ($n = 3$), *Candida dubliniensis* ($n = 2$), *Candida guilliermondii* ($n = 2$), and *Candida intermedia* ($n = 1$).
MIC = minimum inhibitory concentration; R = resistant; S = susceptible; SDD = dose-dependent susceptible.

Table 2 Mortality rate of different species

Species (No.)	30-d mortality (n = 25)		All-cause in-hospital mortality (n = 37)	
	n (%)	% mortality in species	n (%)	% mortality in species
Candida albicans (125)	10 (40.0)	8.0	17 (45.9)	13.6
Candida non-albicans (132)	15 (60.0)	11.4	20 (54.1)	15.2
Candida tropicalis (45)	7 (28.0)	15.6	9 (24.3)	20.0
Candida parapsilosis (42)	6 (24.0)	14.3	7 (18.9)	16.7
Candida glabrata (33)	1 (4.0)	3.0	3 (8.1)	9.1
Others[a] (12)	1 (4.0)	8.3	1 (2.7)	8.3

[a] Others include *Candida krusei* (n = 4), *Candida sake* (n = 3), *Candida dubliniensis* (n = 2), *Candida guilliermondii* (n = 2), and *Candida intermedia* (n = 1).

stay, usage of corticosteroids, duration on corticosteroids, chemotherapy, solid tumor, hematologic malignancy, hypoproteinemia, neutropenia, and usage of glycopeptides. A comparison between *C. albicans* and *C. non-albicans* spp. demonstrated that IC patients with *C. albicans* had a higher ratio of older age (p = 0.008), solid tumor (p = 0.029), and hypoproteinemia (p = 0.019), whereas those with *C. non-albicans* spp. had a higher ratio of hospital length of stay (p = 0.005), usage of corticosteroids (p = 0.011), duration on corticosteroids (p = 0.005), chemotherapy (p = 0.022), hematologic malignancy (p = 0.039), neutropenia (p = 0.030), and usage of glycopeptides (p = 0.002; Table 3). Multivariate analyses showed that a significant predictor for IC due to *C. albicans* was hypoproteinemia [odds ratio (95% confidence interval) = 2.133 (1.164−3.908), p = 0.014; Table 4].

Discussion

The epidemiology and antifungal susceptibility of invasive *Candida* infections in different wards are scarcely defined in China. Our study described the distribution, *in vitro* antifungal susceptibility, and the difference of risk factors between *C. albicans* and *C. non-albicans* spp. infection from January 2011 to December 2013 in southwest China.

In our study, invasive *Candida* infection is the most common invasive fungal infection, accounting for 86.5% (257 of 297) of all invasive mycoses, in accordance with reports by Lamagni et al.[7,8] Although *C. albicans* was the most common *Candida* species, *C. non-albicans* spp. are increasing in frequency in China[17] and worldwide.[18] This may be due to surgery, aging of population, and the increasing use of low-cost azoles.[13] In this study, *C. albicans* was the most frequently isolated *Candida* species (48.6% of all IC patients), although *C. non-albicans* spp. were more commonly isolated overall. *C. tropicalis*, *C. parapsilosis*, and *C. glabrata* were the most common strains among *C. non-albicans* spp., which concurs with the report of Vincent et al.[19]

In our study, patients infected with *C. albicans*, *C. tropicalis*, and *C. parapsilosis* had a high susceptibility rate to the five antifungal agents (>90%). There were consistent findings in some previous reports, which suggested that azole resistance was uncommon in *C. albicans*, *C. parapsilosis*, and *C. tropicalis* (<10%).[18,20] Resistance to fluconazole and itraconazole was more common in other *C. non-albicans* spp. (such as *C. glabrata*, *C. krusei*, and *C. guilliermondii*), implying that these antifungal agents should not be used in IC patients with these *C. non-albicans* species infection. Because the susceptibilities to antifungal agents were different between *C. albicans* and *C. non-albicans*, the information about the difference in the clinical risk factors between them may be useful to physicians to guide the initial empirical treatment. Patients with *C. tropicalis* IC had the highest rate of 30-day mortality, whereas those with *C. glabrata* IC had the lowest mortality rate. However, there is no evidence to show that higher resistance rates among *C. non-albicans* species will be related to the patient's mortality.

Univariate analyses showed a significantly higher rate of *C. non-albicans* spp. in IC patients with a long stay in hospital, chemotherapy, hematologic malignancy, neutropenia, long-term use of corticosteroids, and usage of glycopeptides, whereas *C. albicans* infection was more likely associated with older age, solid tumor, and hypoproteinemia. Other published studies reported that *C. non-albicans* spp. had been associated with hematologic malignancy, neutropenia, allogenic stem cell transplantation, prior fluconazole prophylaxis, and chemotherapy.[12,21−23] Multivariate analyses showed that hypoproteinemia was a significant predictor for patients with IC due to *C. albicans*. A long-term study carried out in China showed that hypoproteinemia, endotracheal intubation, and the presence of *C. albicans* were found to predict rapid mortality independently.[24] Compared with other *Candida* species, *C. albicans* has been found to be more likely to inhabit the human gastrointestinal tract.[25] In addition, hypoproteinemia is always associated with surgical site infection in patients undergoing general surgery procedures.[26] Therefore, it can be hypothesized that hypoproteinemia caused by gastrointestinal tract surgery and the related infection may finally result in *C. albicans* infection.

The limitations of this study must be stressed. The major one is a definitive conclusion could not be made because of insufficient number of cases. Besides, the risk factors investigated in this study may not be comprehensive and did not include some risk factors assessed in other studies. Furthermore, minimum inhibitory concentration of echinocandins, which are important antifungal agents against

Table 3 Characteristics of *Candida albicans* and *Candida non-albicans* in normally sterile site infection cases

Variables	*C. albicans* (n = 125)	*C. non-albicans* (n = 132)	p
	n (%)	n (%)	
Male sex	84 (67.2)	86 (65.2)	0.729
Elderly (≥60 y)	81 (64.8)	64 (48.5)	0.008*
Hospital stay, d	10 (2—20)	15 (5—32)	0.005*
ICU stay	74 (59.2)	70 (53.0)	0.319
Length of ICU stay, d	1 (0—5)	1 (0—12)	0.480
Corticosteroids	29 (23.2)	50 (37.9)	0.011*
Duration on corticosteroids, d	0 (0—0)	0 (0—1)	0.005*
Immunosuppressive agents	3 (2.4)	2 (1.5)	0.677
Chemotherapy	3 (2.4)	12 (9.1)	0.022*
30-d mortality	10 (8.0)	15 (11.4)	0.363
All-cause in-hospital mortality	17 (13.6)	20 (15.2)	0.723
Patient source			
Gastrointestinal surgery	22 (17.6)	18 (13.6)	0.381
Hepatobiliary surgery	13 (10.4)	13 (9.8)	0.883
Urinary surgery	8 (6.4)	7 (5.3)	0.708
Neurosurgery	3 (2.4)	10 (7.6)	0.058
Invasive procedures within prior 4 wk			
Blood product transfusion	63 (50.4)	65 (49.2)	0.853
Hemodialysis	4 (3.2)	7 (5.3)	0.405
Mechanical ventilation	57 (45.6)	46 (34.8)	0.079
Tracheal intubation	49 (39.2)	37 (28.0)	0.058
Indwelling gastric tube	77 (61.6)	70 (53.0)	0.165
Urinary catheter	97 (77.6)	92 (69.7)	0.151
Drainage tube	84 (67.2)	75 (56.8)	0.087
Enema	55 (44.0)	44 (33.3)	0.079
Total parental nutrition	10 (8.0)	17 (12.9)	0.202
Arterial catheter	41 (32.8)	59 (44.7)	0.051
Central venous catheter	63 (50.4)	77 (58.3)	0.202
Surgery	84 (67.2)	77 (58.3)	0.142
Underlying condition			
Diabetes mellitus	22 (17.6)	29 (22.0)	0.380
Organ dysfunction	22 (17.6)	17 (12.9)	0.292
Solid tumor	28 (22.4)	16 (12.1)	0.029*
Hematologic malignancy	2 (1.6)	9 (6.8)	0.039*
Hypoproteinemia	98 (78.4)	86 (65.2)	0.019*
Severe anemia	11 (8.8)	12 (9.1)	0.935
Neutropenia	0 (0.0)	6 (4.5)	0.030*
Antibiotic therapy			
β-Lactams	40 (32.0)	55 (41.7)	0.109
Cephalosporins	92 (73.6)	82 (62.1)	0.049*
Carbapenems	50 (40.0)	63 (47.7)	0.212
Aminoglycosides	30 (24.0)	43 (32.6)	0.128
Quinolones	24 (19.2)	32 (24.2)	0.328
Glycopeptides	22 (17.6)	46 (34.8)	0.002*
Nitroimidazoles	61 (48.8)	58 (43.9)	0.435

Data are expressed no. (%) of patients or median and interquartile range unless otherwise indicated.
ICU = intensive care unit.
*p was statistically significant.

azole-resistant *Candida* species (e.g., *C. glabrata*), was not investigated here. We will address these limitations in our future work.

In conclusion, this study showed the epidemiology and antifungal susceptibilities of invasive *Candida* species isolated from the First Affiliated Hospital of Chongqing Medical University between 2011 and 2013, and the difference in risk factors between *C. albicans* and *C. non-albicans* species. *C. albicans* was the most common species, compared with the *C. non-albicans* species. *C. albicans*, *C. tropicalis*, and *C. parapsilosis* had a high susceptibility to the five antifungal agents, whereas *C. glabrata* showed decreased

Table 4 Multivariate logistic regression analyses of risk factors associated with *Candida albicans* infections

Variables	OR	95% CI		*p*
		Lower	Upper	
Elderly (≥60 y)	1.423	0.818	2.476	0.212
Hospital length of stay	0.991	0.977	1.005	0.211
Corticosteroids	0.857	0.428	1.715	0.633
Duration on corticosteroids	0.94	0.84	1.052	0.280
Chemotherapy	0.422	0.079	2.242	0.311
Solid tumor	1.791	0.862	3.72	0.118
Hematologic malignancy	3.345	0.342	32.744	0.300
Hypoproteinemia	2.133	1.164	3.908	0.014*
Neutropenia	0	0	—	0.999
Glycopeptides	0.526	0.268	1.031	0.061

CI = confidence interval; OR = odds ratio.
*p was statistically significant.

susceptibility to fluconazole and itraconazole. Amphotericin B is highly effective *in vitro* against all *Candida* species. We differentiated several clinical risk factors for IC due to *C. albicans* (older age, solid tumor, and hypoproteinemia) and *C. non-albicans* spp. (long stay in hospital, chemotherapy, hematologic malignancy, neutropenia, long-term use of corticosteroids, and usage of glycopeptides).

Conflicts of interest

All contributing authors declare no conflicts of interest.

Acknowledgments

This work was supported in part by National Key Clinical Specialties Construction Program of China, the National Science Foundation of China (Grant No. 81101304).

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