Mycopathologia
https://doi.org/10.1007/s11046-018-0305-2

ORIGINAL PAPER

Antifungal Susceptibility Profile of *Candida Albicans* Isolated from Vulvovaginal Candidiasis in Xinjiang Province of China

Liang Yan · Xiao-dong Wang · Seyedmojtaba Seyedmousavi · Juan-na Yuan · Palida Abulize · Wei-hua Pan · Nong Yu · Ya-li Yang · Hai-qing Hu · Wan-qing Liao · Shu-wen Deng

Received: 26 April 2018 / Accepted: 30 October 2018

Abstract We investigated the antifungal susceptibility profiles of 207 independent *Candida albicans* strains isolated from patients with vulvovaginal candidiasis (VVC) in Xinjiang Province of China. Using CLSI M27-A3 and M27-S4 guidelines, anidulafungin and micafungin were the most active drugs against *C. albicans* showing an MIC_{50}/MIC_{90} corresponding to 0.016/0.0313 μg/mL, followed by caspofungin (0.25/0.25 μg/mL), posaconazole (0.125/0.5 μg/mL), ravuconazole (0.063/1 μg/mL), itraconazole (0.125/1 μg/mL), amphotericine B (0.5/1 μg/mL), isavuconazole (0.063/2 μg/mL), 5-flucytosine (1/2 μg/mL), voriconazole (0.125/4 μg/mL), and fluconazole (0.5/4 μg/mL). 96.1% (199)–100.0% (207) isolates were sensitive to the three echinocandins tested, amphotericine B and 5-flucytosine. The in vitro activity of triazoles against all isolates tested was variable; itraconazole and voriconazole had reduced the activity to almost half of the isolates (55.1% (114) and 51.2% (106) susceptible, respectively). Fluconazole was active against 76.3% (158) isolates tested. The new triazoles ravuconazole, isavuconazole and posaconazole showed good in vitro potency against 89.9% (186)–95.2% (197) of isolates with the geometric mean MIC (μg/mL) of 0.10, 0.12 and 0.14 μg/mL, respectively. In conclusion, our study indicates that for effective management of systemic candidiasis

Liang Yan and Xiao-dong Wang have contributed equally to this work.

Handling Editor: Yuping Ran.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11046-018-0305-2) contains supplementary material, which is available to authorized users.

N. Yu · S. Deng (✉)
The People's Hospital of Suzhou National New & Hi-Tech Industrial Development Zone, Suzhou, Jiangsu, China
e-mail: danyanghhh@qq.com

L. Yan · J. Yuan · W. Pan · Y. Yang · W. Liao (✉)
Shanghai Key Laboratory of Medical Molecular Mycology & PLA Key Laboratory of Fungal Disease, Department of Dermatology, Changzheng Hospital, Second Military Medical University, Shanghai, China
e-mail: liaowanqing@smmu.edu.cn

L. Yan
Wuhan General Hospital of Chinese PLA, Wuhan, Hubei, China

X. Wang · P. Abulize
The First Affiliated Hospital of Xinjiang Medical University, Ürümqi, Xinjiang, China

S. Seyedmousavi
Molecular Microbiology Section, Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA

Published online: 09 April 2019

in Xinjiang Province of China, it is important to determine the susceptibility profiles of isolated *C. albicans* from patients with VVC.

Keywords Antifungal susceptibility · *Candida albicans* · Vulvovaginal candidiasis · Xinjiang Province

Introduction

Vulvovaginal candidiasis (VVC) poses a serious challenge to public health. 70–75% of women suffer at least one VVC episode during their lives, and half of them will experience a recurrence [1]. Evidence shows that disease is recurrent in almost 8% of women aged 15–50 years old. Recurrent vulvovaginal candidiasis (RVVC) is defined as four or more episodes of disease per year [2]. Several studies reported that *C. albicans* remains the most frequently isolated species from VVC (76–89%) [2], followed by *C. glabrata* (7–16%) [2], *C. parapsilosis*, *C. tropicalis*, and *C. krusei* [3]. An increasing prevalence of fungal resistance is also reported in global and local antifungal surveillance studies [4–23]. The increased RVVC incidence and drug resistances causes an important public health issue and poses significant challenges to implement appropriate and effective management strategies. Antifungal susceptibility testing of isolated *Candida* strains therefore plays a useful role in managing *Candida* infections.

Despite previous reports on antifungal susceptibility of *C. albicans* causing VVC in Beijing, Shanghai, Shenzhen and Zhanjiang [4, 14, 19–22], there are limited data regarding the antifungal resistance of *C. albicans* isolated from VVC in Xinjiang Province of China, a multi-ethnic area with different climates and under developed economies compared to the rest of country. In the current study, we therefore investigated the antifungal susceptibility profile of a large collection of *C. albicans* isolates obtained from VVC patients in Xinjiang Province.

Materials and Methods

Isolates and Identification

We investigated a collection of 207 *C. albicans* strains isolated from 207 adult women between October 2015 and February 2017 at the First Hospital of Xinjiang Medical University, Xinjiang, China. During examination, all patients showed signs and/or symptoms suggestive of vaginitis, including pruritus vulvae, vulvar burning, vaginal soreness and irritation, dyspareunia, pain or discomfort during urination and abnormal vaginal discharge, which could be diagnosed with VVC along with culture-positive vaginal secretion. Approval of the research was acquired from the Research Ethics Committee of the hospital, and written consent was gained from all patients involved.

All samples were collected with sterilized vaginal swabs. Swabs were cultured on CHROM agar *Candida* and incubated for 48 h at 35–37 °C. All isolates were identified to the species level by sequencing 26S ribosomal DNA gene D1/D2 domains with primer pairs NL-1 (5′-GCATATCAATAAGCGGAGGAAAAG) and NL-4 (5′- GGTCCGTGTTTCAAGACGG), as described previously [24]. The obtained sequences were compared to the NCBI nucleotide database (https://blast.ncbi.nlm.nih.gov/Blast.cgi) to verify species-level identity of each isolate. The geographical origin, clinical data and GenBank accession numbers for the generated D1/D2 sequences are listed in Supplementary Table S1.

Antifungal Susceptibility Testing

All isolates were tested for in vitro antifungal susceptibility to 11 antifungal agents according to the CLSI reference guideline M27-A3 and M27-S4 [25, 26]. Antifungal drugs tested were anidulafungin (ANF),

S. Seyedmousavi
Center of Expertise in Microbiology, Infection Biology and Antimicrobial Pharmacology, Tehran, Iran

S. Seyedmousavi
Invasive Fungi Research Center, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

J. Yuan
The Second Affiliated Hospital of Guangzhou University of Chinese Medicine Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, Guangdong, China

H. Hu
Department of Laboratory Medicine, Changzheng Hospital, Second Military Medical University, Shanghai, China

caspofungin (CAS), micafungin (MFG), amphotericin B (AmB), 5-flucytosine (5-FC), fluconazole (FLC), itraconazole (ITC), voriconazole (VRC), posaconazole (POS), isavuconazole (ISA), and ravuconazole (RAV). Anidulafungin, voriconazole, isavuconazole purchased from Toronto Research Chemicals Inc., micafungin provided by Astellas Pharma, and remaining antifungal were obtained from Sigma-Aldrich). *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258 were used as control strains for all experiments. All isolates were sub-cultured onto Sabouraud Dextrose Agar at 35 °C for almost 24 h for viability and purity. Colonies were suspended in sterile saline, and the final inoculum concentration of the suspension was adjusted to 0.5–2.5 $\times$ 10^3 CFU mL^{-1} with RPMI 1640 broth medium. The 96-well plates were incubated for 24 or 48 h at 35 °C, and minimum inhibitory concentrations (MIC) were determined visually.

Drug concentration ranges, time of MIC reading and interpretive breakpoints used for 11 antifungal agents are listed in Table 1. Although interpretive criteria for the susceptibility to amphotericin B remain elusive, we here classified MIC $\leqq$ 1 μg/mL as susceptible and MIC $\geqq$ 2 μg/mL as resistant referring to previous studies [8–10, 13, 16–18]. There are no interpretive breakpoints for posaconazole, isavuconazole and ravuconazole yet.

Results

MIC distribution, MIC_{50}/MIC_{90}, geometric mean values (GM), susceptibility rate (*S*%), susceptible-dose dependent rate (SDD%) and resistant rate (*R*%) of 207 *C. albicans* isolates tested to 11 antifungal agents are summarized in Table 2.

The values of MIC_{50}/MIC_{90} for all isolates used in this study are as follows (in increasing order): anidulafungin and micafungin were the most active drugs against *C. albicans* as they had the lowest MIC_{50}/MIC_{90} (0.016/0.0313 μg/mL), followed by caspofungin (0.25/0.25 μg/mL), posaconazole (0.125/0.5 μg/mL), ravuconazole (0.063/1 μg/mL), itraconazole (0.125/1 μg/mL), amphotericine B (0.5/1 μg/mL), isavuconazole (0.063/2 μg/mL), 5-flucytosine (1/2 μg/mL), voriconazole (0.125/4 μg/mL), fluconazole (0.5/4 μg/mL).

According to the CLSI M27-S4 guideline, of the 207 *C. albicans* isolates, 96.1% (199)–100.0% (207) isolates were susceptible to the three echinocandins tested, and the MIC_{50}/MIC_{90} of both micafungin and anidulafungin were 0.016/0.0313 μg/mL, which were tenfolds less than that of caspofungin (0.25/0.25 μg/mL) (Table 2).

The in vitro activity of triazoles against 207 isolates of *C. albicans* was variable; itraconazole and voriconazole had reduced activity to approximately half of the isolates (susceptibility rate 55.1% (114) and

Table 1 Drug concentration range, time of MIC reading, and interpretive breakpoints for 11 antifungal agents

Antifungal agent	Drug concentration range (μg/ml)	Time of MIC reading (h)	MIC ranges (μg/ml)		
			S	SDD	*R*
Anidulafungin	0.016–8	24	$\leqq$ 0.25	0.5	$\geqq$ 1
Caspofungin	0.016–8	24	$\leqq$ 0.25	0.5	$\geqq$ 1
Micafungin	0.016–8	24	$\leqq$ 0.25	0.5	$\geqq$ 1
Amphotericine B	0.0313–16	24	$\leqq$ 1	–	$\geqq$ 2
5-Flucytosine	0.125–64	48	$\leqq$ 4	8–16	$\geqq$ 32
Itraconazole	0.016–8	48	$\leqq$ 0.125	0.25–0.5	$\geqq$ 1
Voriconazole	0.016–16	48	$\leqq$ 0.125	0.25–0.5	$\geqq$ 1
Fluconazole	0.0313–64	24	$\leqq$ 2	4	$\geqq$ 8
Posaconazole	0.0313–16	48	NA[a]	NA	NA
Isavuconazole	0.0313–16	48	NA	NA	NA
Ravuconazole	0.0313–16	48	NA	NA	NA

a Not applicable

S susceptible, *SDD* susceptible-dose dependent, *R* resistant

Table 2 MIC distribution, MIC_{50}/MIC_{90}, GM, SDD%, R% of 207 *C. albicans* isolates from VVC to 11 antifungal agents

Antifungal agent	Cumulative % of isolates with MIC (μg/mL) of											MIC_{50}/MIC_{90}	GM	SDD (%)	*R* (%)
	0.016	0.0313	0.063	0.125	0.25	0.5	1	2	4	8	16	32	≥ 64				
Micafungin	53.6	92.3	95.7	99.5	100	100	100	100	100	100	100	100	100	0.016/0.0313	0.02	0.0	0.0
Anidulafungin	78.3	96.6	99.0	99.5	99.5	99.5	100	100	100	100	100	100	100	0.016/0.0313	0.02	0.0	0.5
Caspofungin	0.0	0.0	0.5	42.5	96.1	99.5	100	100	100	100	100	100	100	0.25/0.25	0.19	3.4	0.5
Fluconazole	0.0	0.5	1.9	14.5	40.6	51.2	59.9	76.3	91.8	99.0	99.5	99.5	100	0.5/4	0.79	15.5	8.2
Itraconazole	2.9	20.8	41.1	55.1	70.5	89.9	97.1	98.6	99.0	99.0	100	100	100	0.125/1	0.15	34.8	10.1
Voriconazole	1.4	30.4	44.0	51.2	58.5	68.1	80.7	89.9	95.7	97.6	98.1	100	100	0.125/4	0.22	16.9	31.9
Posaconazole	0.0	15.9	39.6	61.8	82.1	91.8	95.2	97.1	98.1	99.0	99.0	100	100	0.125/0.5	0.14	–	–
Isavuconazole	0.0	43.5	54.6	67.1	76.3	84.5	89.9	94.2	98.1	99.5	99.5	100	100	0.063/2	0.12	–	–
Ravuconazole	0.0	42.0	57.0	72.5	84.1	88.4	93.7	96.1	100	100	100	100	100	0.063/1	0.10	–	–
Amphotericine B	0.0	0.0	0.0	0.0	13.0	79.7	100	100	100	100	100	100	100	0.5/1	0.52	–	0.0
5-Flucytosine	0.0	0.0	0.5	15.5	35.3	41.1	67.1	93.2	97.1	97.1	97.1	97.1	100	1/2	0.75	0.0	2.9

GM geometric mean values, *SDD%* susceptible-dose dependent rate, *R%*, resistant rate

51.2% (106), respectively). Furthermore, 34.8% (72) isolates were susceptible-dose-dependent (SDD) and 10.1% (21) isolates were resistant to itraconazole; for voriconazole, 16.9% (35) isolates were SDD and 31.9% (66) were resistant. Fluconazole was active against 76.3% (158) isolates tested. The triazoles, posaconazole, isavuconazole and ravuconazole showed good in vitro potency with MICs less than 1 μg/mL against 89.9% (186)–95.2% (197) *C. albicans* isolates tested.

As expected, all *C. albicans* isolates tested were susceptible to amphotericin B. Six isolates showed resistance to 5-flucytosine, but remained sensitive to the remaining list of antifungals tested.

Discussion

Candida species contribute to a significant percentage of women's healthcare-related fungal infections worldwide [3]. In order to find a way to prevent and control such infections, it is important to select as early as possible the antifungal treatment of choice, and understand the resistance profile of causative agents to various antifungals.

We investigated the antifungal susceptibility of 207 *C. albicans* isolates obtained from the patients with VVC in Xinjiang province, which is the largest and most westerly province in China with the population consisting of Han Chinese and Muslims, and separated from the densely populated areas of the country. Table 3 was summarized data on susceptibility of VVC *C. albicans* isolates to five common antifungal drugs in different studies from 2003 to 2017 [4–22]. To the best of our knowledge, our report is the first study addressing the antifungal susceptibility of *C. albicans* isolates from VVC patients to 11 antifungals in Xinjiang province. Our findings would be helpful in guiding effective clinical therapy regimes.

The echinocandins have been widely used clinically for candidemia and invasive candidiasis due to their negligible toxicities, generally fungicidal activities and lack of cross-resistance with azoles [27, 28]. Our results showed good activity of the three echinocandins against the majority of *C. albicans* isolates tested. Of note, micafungin and anidulafungin (MIC_{50}/MIC_{90}: 0.016/0.0313 μg/mL) showed higher potency than caspofungin (MIC_{50}/MIC_{90}: 0.25/0.25 μg/mL). Several studies investigated the

Table 3 Summarized data on susceptibility of *C. albicans* from VVC patients to 5 antifungal agents in different studies from 2003–2017[4–22]

Test method	Fluconazole				Itraconazole				Voriconazole			
	MIC_{50}/MIC_{90}	*S* (%)	SDD (%)	*R* (%)	MIC_{50}/MIC_{90}	*S* (%)	SDD (%)	*R* (%)	MIC_{50}/MIC_{90}	*S* (%)	SDD (%)	*R* (%)
M27-A3 S4	0.5/4	76.3	15.5	8.2	0.125/1	55.1	34.8	10.1	0.125/4	51.2	16.9	31.9
ATB fungus3		83.0	10.0	7.0						81.0	5.0	14.0
M27-A3 S4	/4	90.3	3.9	5.8	/0.25							
M27-A3 S4	0.25/1				0.06/0.12							
M27-A3 S3		82.8	12.0	5.2		70.7	22.4	6.9				
M27-A	0.125/0.25	98.5	0.0	1.5								
M27-A3 S3	0.5/2	95.0	5.0	0.0	0.25/0.5	80.0	16.0	4.0				
M27-A3 S3	0.5/2	96.0	4.0	0.0	0.25/0.5	83.0	13.0	4.0				
M27-A2		32.4	10.8	56.8		21.6	24.3	54.1				
M27-A2		100.0	0.0	0.0		99.5	0.5	0.0				
M27-A2		94.8	5.2	0.0		82.8	6.9	10.3		98.3	1.7	0.0
M27-A2		98.1	1.9	0.0		62.1	35.9	1.9				
M27-A2		88.3	7.0	4.7								
M27-A2	0.25/2	97.7	0.0	2.3	0.06/0.4				0.008/0.25			
M27-A2	0.25/0.5				0.03/0.06							
M27-A2	0.25/4				< 0.03/1							
M44-A		92.7	6.8	0.5		85.0	15.0	0.0				
M44-A		81.8	17.1	1.1		90.6	7.2	2.2				
Rosco		70.8	12.5	16.6		46.5	2.0	51.5				
Rosco		72.4	15.3	12.3		48.8	44.1	7.1		81.2	11.2	7.6

Table 3 continued

Test method	Amphotericine B			5-fluorocytosine				Number of strains	References
	MIC_{50}/MIC_{90}	*S* (%)	*R* (%)	MIC_{50}/MIC_{90}	*S* (%)	SDD (%)	*R* (%)		
M27-A3 S4	0.5/1	100.0	0.0	1/2	97.1	0.0	2.9	207	This paper
ATB fungus3								115	Ying [4]
M27-A3 S4	/0.25							103	Gamarra [5]
M27-A3 S4								54	Nagashima [6]
M27-A3 S3								58	Güzel [7]
M27-A	0.5/0.5	98.5	1.5					69	De Pádua [8]
M27-A3 S3	0.5/1	100.0	0.0	0.25/4	90.0	10.0	0.0	38	Kalkanci [9]
M27-A3 S3	0.03/0.12	100.0	0.0	0.25/4	96.0	4.0	0.0	46	Kalkanci [10]
M27-A2								37	Brandolt [11]
M27-A2					96.7	0.0	3.3	420	Richter [12]
M27-A2		98.3	1.7					58	Dota [13]
M27-A2								103	Ge [14]
M27-A2								529	Zhang [15]
M27-A2	0.125/0.25			0.125/1				303	Asticcioli [16]
M27-A2	0.06/0.12							51	Dias [17]
M27-A2	< 0.03/< 0.03							21	Ozcan [18]
M44-A								206	Fan [19]
M44-A								1612	Liu [20]
Rosco								1775	Wang [21]
Rosco								170	Shi [22]

S% susceptible rate, *SDD*% susceptible-dose dependent rate, *R*% resistant rate

in vitro efficacy of echinocandins against *C. albicans* obtained from VVC. Shi et al. [22] reported that caspofungin showed good activity to the vaginal *C. albicans* isolates in southern China. Kalkanci et al. [10] reported MIC values of caspofungin against 46 *C. albicans* isolates from acute VVC in Turkey (MIC_{50}/MIC_{90}: 0.25/0.5 μg/mL). Boikov et al. [29] also showed that caspofungin, micafungin and anidulafungin showed good activity against 60 *C. albicans* strains isolated from VVC with a MIC_{50}/MIC_{90} of 0.25/0.5 μg/mL, 0.008/0.008 μg/mL and 0.008/0.008 μg/mL, respectively. More recently, Sharifynia et al. [30] also reported that caspofungin (geometric means: 0.27 μg/mL) was the most active antifungal against 26 *C. albicans* strains isolated from RVVC patients in Iran.

Furthermore, in our study all vaginal *C. albicans* isolates were susceptible to micafungin, which was in agreement with that reported on *C. albicans* isolates causing systemic *Candida* infections [31]. Activity of anidulafungin to *C. albicans* isolates from VVC was similar to that of micafungin except one isolate showing resistance. Similarly, Pfaller et al. presented similar results on anidulafungin against *C. albicans* causing invasive infections [32].

As shown in Table 3, fluconazole (the recommended drug of choice for VVC) was active against most *C. albicans* isolates from VVC in the majority of previous reports [4–22] (Table 3). Multiple studies in Argentina, Brazil, Turkey, America, Italy, showed the susceptibility rate of 90–100% on fluconazole against *C. albicans* isolates from VVC [5, 8–10, 12, 13, 16]. In China, except two reports from Shenzhen with similar susceptibility rate (98.1% *S* and 88.3% *S*) (Ge et al. [14], Zhang JY et al. [15]) to western countries, most reports presented lower susceptibility rate (70–83% S, Table 3) in Shenzhen [20], Shanghai [4] and Beijing [21]. The data shown in our study (76.3% *S*) were in agreement with previously published reports from China.

Studies in Turkey [7, 9, 10], Brazil [13], and America [12], also indicated good in vitro activity of itraconazole (70.7–99.5% S, Table 3) against *C. albicans* isolates from VVC. However, in China, itraconazole was active against only half isolates in the most reports (62.1% *S*, 46.5% *S*, 48.8% *S*, Table 3) [14, 21, 22], except two studies in Shenzhen (85.0% *S* and 90.6% *S*, Table 3) [19, 20]. In our results, susceptibility of *C. albicans* isolates from VVC to itraconazole (55.1% *S*) in Xinjiang province was the same as those at other areas of China. Of note, 34.8% isolates were SDD and 10.1% were resistant to itraconazole. The less antifungal activity of itraconazole was likely associated with relatively high-frequency use in clinical setting in China [33], requiring the attention of clinicians in this situation in China.

Higher susceptibility rate (98.3% *S*) of *C. albicans* isolates from VVC to voriconazole had been reported by Dota et al. [13]. In China, two studies from Shanghai and Zhanjiang reported the susceptibility rate of *C. albicans* isolates from VVC to voriconazole were 81.0 and 81.2%, respectively [4, 22]. The susceptibility rate shown in our study (51.2% *S*) was however relatively lower, and notably, 31.9% isolates were resistant and 16.9% isolates were SDD in Xinjiang province which were much higher than those in previous reports from Ying C et al., Dota KFD et al. and Shi et al. (14.0% and 5.0%; 0.0% and 1.7%; 7.6% and 11.2%; respectively, Table 3) [4, 13, 22]. It is not known exactly what lead to the regional disparity, but different ethnic compositions, climates and clinical uses of antifungal drugs between Shanghai and Xinjiang possibly contribute to the distinction in susceptibility. Nevertheless, it will remind of clinicians of caution when choosing voriconazole as the therapy for VVC in Xinjiang province.

The *Candida* surveillance study demonstrated that resistance to fluconazole was highly predictive for resistance to voriconazole [34]. Our results also showed that 14 of 17 fluconazole-resistant isolates were resistant to voriconazole. In addition, isolates with reduced susceptibility to fluconazole showed cross-resistance to itraconazole and voriconazole. Seven isolates were resistant to both of fluconazole and itraconazole, and 14 isolates were resistant to both of fluconazole and voriconazole. Moreover, 5 isolates were resistant to fluconazole, itraconazole and voriconazole.

The good in vitro activity of members of new triazoles (posaconazole, isavuconazole and ravuconazole) against *C. albicans* isolates resulting in invasive infections has been documented by many studies [35–39]. For VVC, however, there are limited data on vaginal *C. albicans* isolates. In the present study, the three new triazoles showed good in vitro activity against all *C. albicans* isolates from VVC patients in Xinjiang province. Approximately, 90% isolates were

inhibited by within 1 μg/mL of posaconazole, isavuconazole and ravuconazole (1 μg/mL regarded as the breakpoint of susceptibility for the new triazoles [40–45]). Our finding is in agreement with reports from Northern America [46] and Kuwait [47] which showed good activity of posaconazole against *C. albicans* isolates from VVC (MIC_{90}: 0.03 μg/mL and 0.064 μg/mL, respectively). However, there are no data available on isavuconazole and ravuconazole about the in vitro susceptibility of *C. albicans* isolates from VVC currently. For isavuconazole, compared with the results reported in studies on *Candida* bloodstream isolates (MIC_{50}/MIC_{90}: 0.002/0.004 μg/mL [35] and 0.015/0.03 μg/mL [36], respectively), our results (MIC_{50}/MIC_{90}: 0.063/2 μg/mL) were significantly higher. Ravuconazole showed good effectiveness against *C. albicans* isolated from VVC (MIC_{50}/MIC_{90}: 0.063/1 μg/mL), although it had higher MIC values compared to that in the studies against *Candida* bloodstream isolates (MIC_{50}/MIC_{90}: 0.007/0.03 μg/mL [40] and 0.016/0.125 μg/mL [48]). And the differences of MIC values for isavuconazole and ravuconazole were both above 2 $\log_2$ dilution steps, suggesting that isolates from VVC are less susceptible than isolates from invasive infections to isavuconazole and ravuconazole.

Our study also confirmed the good in vitro activity of amphotericin B and 5-flucytosine against *C. albicans* isolates from VVC again (Table 3) [8–10, 12, 13]. Hundred percentage of the isolates tested were susceptible to amphotericin B which agreed with previous studies [9, 10]. Over 95% of isolates were susceptible to 5-flucytosine, which was consistent with the previous studies [10, 12]. The isolates resistant to 5-flucytosine did not have cross-resistance to 10 other antifungal drugs, which was in agreement with previous study by Ribeiro et al. [49].

In conclusion, our finding suggests that antifungal susceptibility testing in Xinjiang province should be performed routinely to help clinicians to develop appropriate therapies with high probability of successfully treating VVC.

Acknowledgements This study was supported by Suzhou New & Hi-Tech IDZ grant 2017Z008, in part by Shanghai Science Foundation of China under Grant 16DZ0500401. Seyedmojtaba Seyedmousavi is presently supported by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda, MD, USA.

Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

References

1. Hurley R, de Louvois J. *Candida* vaginitis. Postgrad Med J. 1979;55:645.
2. Achkar JM, Fries BC. *Candida* infections of the genitourinary tract. Clin Microbiol Rev. 2010;23:253–73.
3. Sobel JD. Vulvovaginal candidosis. Lancet. 2007;369:1961–71.
4. Ying C, Zhang H, Tang Z, Chen H, Gao J, Yue C. Antifungal susceptibility and molecular typing of 115 *Candida albicans* isolates obtained from vulvovaginal candidiasis patients in 3 Shanghai maternity hospitals. Med Mycol. 2016;54:394–9.
5. Gamarra S, Morano S, Dudiuk C, Mancilla E, Nardin ME, de los Angeles Méndez E, et al. Epidemiology and antifungal susceptibilities of yeasts causing vulvovaginitis in a teaching hospital. Mycopathologia. 2014;178:251–8.
6. Nagashima M, Yamagishi Y, Mikamo H. Antifungal susceptibilities of *Candida* species isolated from the patients with vaginal candidiasis. J Infect Chemother. 2016;22:124–6.
7. Güzel A, Küçükgöz-Güleç Ü, Aydin M, Gümral R, Kalkanci A, Ilkit M. *Candida* vaginitis during contraceptive use: the influence of methods, antifungal susceptibility and virulence patterns. J Obstet Gynaecol. 2013;33:850–6.
8. De Pádua RF, Guilhermetti E, Svidzinski TE. *In vitro* activity of antifungal agents on yeasts isolated from vaginal secretion. Acta Scientiarum. 2003;25:51–4.
9. Kalkanci A, Güzel A, Jabban I, Aydin M, Ilkit M, Kuştimur S. *Candida* vaginitis in non-pregnant patients: a study of antifungal susceptibility testing and virulence factors. J Obstet Gynaecol. 2013;33:378–83.
10. Kalkanci A, Güzel AB, Khalil IIJ, Aydin M, Ilkit M, Kuştimur S. Yeast vaginitis during pregnancy: susceptibility testing of 13 antifungal drugs and boric acid and the detection of four virulence factors. Med Mycol. 2012;50:585–93.
11. Brandolt TM, Klafke GB, Gonçalves CV, Bitencourt LR, Martinez AMBd, Mendes JF, et al. Prevalence of *Candida spp.* in cervical-vaginal samples and the in vitro susceptibility of isolates. Braz. J Microbiol. 2017;48:145–50.
12. Richter SS, Galask RP, Messer SA, Hollis RJ, Diekema DJ, Pfaller MA. Antifungal susceptibilities of *Candida* species causing vulvovaginitis and epidemiology of recurrent cases. J Clin Microbiol. 2005;43:2155–62.
13. Dota KFD, Consolaro MEL, Svidzinski TIE, Bruschi ML. Antifungal activity of Brazilian propolis microparticles against yeasts isolated from vulvovaginal candidiasis. Evid-Based Complement Altern. 2011;2011:201953.
14. Ge SH, Wan Z, Li J, Xu J, Li RY, Bai FY. Correlation between azole susceptibilities, genotypes, and ERG11 mutations in *Candida albicans* isolates associated with

vulvovaginal candidiasis in China. Antimicrob Agents Chemother. 2010;54:3126–31.
15. Zhang JY, Liu JH, Liu FD, Xia YH, Wang J, Liu X, et al. Vulvovaginal candidiasis: species distribution, fluconazole resistance and drug efflux pump gene overexpression. Mycoses. 2014;57:584–91.
16. Asticcioli S, Sacco L, Daturi R, Matti C, Nucleo E, Zara F, et al. Trends in frequency and in vitro antifungal susceptibility patterns of *Candida* isolates from women attending the STD outpatients clinic of a tertiary care hospital in Northern Italy during the years 2002-2007. New Microbiol. 2009;32:199–204.
17. Dias LB. Melhem MdSC, Szeszs MW, Meirelles Filho J, Hahn RC. Vulvovaginal candidiasis in Mato Grosso, Brazil: pregnancy status, causative species and drugs tests. Braz. J Microbiol. 2011;42:1300–7.
18. Ozcan SK, Budak F, Yucesoy G, Susever S, Willke A. Prevalence, susceptibility profile and proteinase production of yeasts causing vulvovaginitis in Turkish women. APMIS. 2006;114:139–45.
19. Fan SR, Liu XP, Li JW. Clinical characteristics of vulvovaginal candidiasis and antifungal susceptibilities of *Candida* species isolates among patients in southern China from 2003 to 2006. J Obstet Gynaecol Res. 2008;34:561–6.
20. Liu X, Fan S, Peng Y, Zhang H. Species distribution and susceptibility of *Candida* isolates from patient with vulvovaginal candidiasis in Southern China from 2003 to 2012. J Mycol Med. 2014;24:106–11.
21. Wang FJ, Zhang D, Liu ZH, Wu WX, Bai HH, Dong HY. Species distribution and in vitro antifungal susceptibility of vulvovaginal *Candida* isolates in China. Chin Med J Peking. 2016;129:1161–5.
22. Shi XY, Yang YP, Zhang Y, Li W, Wang JD, Huang WM. Molecular identification and antifungal susceptibility of 186 *Candida* isolates from vulvovaginal candidiasis in southern China. J Med Microbiol. 2015;64:390–3.
23. Pfaller MA, Diekema DJ. Progress in antifungal susceptibility testing of Candida spp. by use of Clinical and Laboratory Standards Institute broth microdilution methods 2010 to 2012. J Clin Microbiol. 2010;2012(50):2846–56.
24. Kurtzman C, Robnett C. Identification of clinically important ascomycetous yeasts based on nucleotide divergence in the 5′end of the large-subunit (26S) ribosomal DNA gene. J Clin Microbiol. 1997;35:1216–23.
25. Clinical and Laboratory Standards Institute. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts, 3rd edition; Document M27-A3. 2008.
26. Clinical and Laboratory Standards Institute. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts: 4th Informational Supplement-CLSI Document M27-S4-Wayne, PA. 2012.
27. Katiyar S, Pfaller M, Edlind T. *Candida albicans* and *Candida glabrata* clinical isolates exhibiting reduced echinocandin susceptibility. Antimicrob Agents Chemother. 2006;50:2892–4.
28. Pappas PG, Kauffman CA, Andes D, Benjamin DK, Calandra TF, Edwards JE, et al. Clinical practice guidelines for the management candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;48:503–35.
29. Boikov DA, Locke JB, James KD, Bartizal K, Sobel JD. *In vitro* activity of the novel echinocandin CD101 at pH 7 and 4 against *Candida spp.* isolates from patients with vulvovaginal candidiasis. J Antimicrob Chemother. 2017;72:1355–8.
30. Sharifynia S, Rezaie S, Mohamadnia A, Mortezaee V, Hadian A, Seyedmousavi S. Genetic diversity and antifungal susceptibility of *Candida albicans* isolated from Iranian patients. Med Mycol. 2019;57:127–31.
31. Pfaller M, Boyken L, Hollis R, Messer S, Tendolkar S, Diekema D. Global surveillance of in vitro activity of micafungin against *Candida*: a comparison with caspofungin by CLSI-recommended methods. J Clin Microbiol. 2006;44:3533–8.
32. Pfaller M, Boyken L, Hollis R, Kroeger J, Messer S, Tendolkar S, et al. In vitro susceptibility of invasive isolates of *Candida spp.* to anidulafungin, caspofungin, and micafungin: six years of global surveillance. J Clin Microbiol. 2008;46:150–6.
33. Lin XY, Wang SL, Duan XL, Lan CG, Chen XJ, Xue J, et al. Review of clinical experience in itraconazole therapy for 10 years in China. J Clin Dermatol. 2003;32:429–30 **(in Chinese)**.
34. Lyon GM, Karatela S, Sunay S, Adiri Y. Antifungal susceptibility testing of *Candida* isolates from the *Candida* surveillance study. J Clin Microbiol. 2010;48:1270–5.
35. Seifert H, Aurbach U, Stefanik D, Cornely O. *In vitro* activities of isavuconazole and other antifungal agents against *Candida* bloodstream isolates. Antimicrob Agents Chemother. 2007;51:1818–21.
36. Castanheira M, Messer SA, Rhomberg PR, Dietrich RR, Jones RN, Pfaller MA. Isavuconazole and nine comparator antifungal susceptibility profiles for common and uncommon *Candida* species collected in 2012: application of new CLSI clinical breakpoints and epidemiological cutoff values. Mycopathologia. 2014;178:1–9.
37. Pfaller M, Diekema D, Messer S, Boyken L, Huynh H, Hollis R. Clinical evaluation of a frozen commercially prepared microdilution panel for antifungal susceptibility testing of seven antifungal agents, including the new triazoles posaconazole, ravuconazole, and voriconazole. J Clin Microbiol. 2002;40:1694–7.
38. Pfaller M, Messer S, Hollis R, Jones R, Diekema D. *In vitro* activities of ravuconazole and voriconazole compared with those of four approved systemic antifungal agents against 6,970 clinical isolates of *Candida spp*. Antimicrob Agents Chemother. 2002;46:1723–7.
39. Sims CR, Paetznick VL, Rodriguez JR, Chen E, Ostrosky-Zeichner L. Correlation between microdilution, E-test, and disk diffusion methods for antifungal susceptibility testing of posaconazole against *Candida spp*. J Clin Microbiol. 2006;44:2105–8.
40. Pfaller M, Diekema D, Jones R, Sader HS, Fluit A, Hollis R, et al. International surveillance of bloodstream infections due to *Candida* species: frequency of occurrence and in vitro susceptibilities to fluconazole, ravuconazole, and voriconazole of isolates collected from 1997 through 1999 in the SENTRY antimicrobial surveillance program. J Clin Microbiol. 2001;39:3254–9.
41. Pfaller M, Messer S, Boyken L, Rice C, Tendolkar S, Hollis R, et al. Cross-resistance between fluconazole and ravuconazole and the use of fluconazole as a surrogate marker to

predict susceptibility and resistance to ravuconazole among 12,796 clinical isolates of *Candida spp*. J Clin Microbiol. 2004;42:3137–41.
42. Pfaller MA, Messer SA, Rhomberg PR, Jones RN, Castanheira M. *In vitro* activity of isavuconazole and comparator antifungal agents tested against a global collection of opportunistic yeasts and moulds. J Clin Microbiol. 2013;51:2608–16.
43. Guinea J, Peláez T, Recio S, Torres-Narbona M, Bouza E. *In vitro* antifungal activities of isavuconazole (BAL4815), voriconazole, and fluconazole against 1,007 isolates of Zygomycete, *Candida*, *Aspergillus*, *Fusarium*, and *Scedosporium* species. Antimicrob Agents Chemother. 2008;52:1396–400.
44. Marcos Arias C, Eraso E, Madariaga L, Carrillo Muñoz AJ, Quindós G. *In vitro* activities of new triazole antifungal agents, posaconazole and voriconazole, against oral *Candida* isolates from patients suffering from denture stomatitis. Mycopathologia. 2012;73:35–46.
45. Pfaller M, Messer S, Boyken L, Hollis R, Rice C, Tendolkar S, et al. In vitro activities of voriconazole, posaconazole, and fluconazole against 4,169 clinical isolates of *Candida spp.* and *Cryptococcus neoformans* collected during 2001 and 2002 in the ARTEMIS global antifungal surveillance program. Diagn Microbiol Infect Dis. 2004;48:201–5.
46. Danby CS, Boikov D, Rautemaa-Richardson R, Sobel JD. Effect of pH on in vitro susceptibility of *Candida glabrata* and *Candida albicans* to 11 antifungal agents and implications for clinical use. Antimicrob Agents Chemother. 2012;56:1403–6.
47. Alfouzan W, Dhar R, Ashkanani H, Gupta M, Rachel C, Khan Z. Species spectrum and antifungal susceptibility profile of vaginal isolates of *Candida* in Kuwait. J Mycol Med. 2015;25:23–8.
48. Laverdiere M, Hoban D, Restieri C, Habel F. *In vitro* activity of three new triazoles and one echinocandin against *Candida* bloodstream isolates from cancer patients. J Antimicrob Chemother. 2002;50:119–23.
49. Ribeiro M, Dietze R, Paula C, Da Matta D, Colombo A. Susceptibility profile of vaginal yeast isolates from Brazil. Mycopathologia. 2001;151:5–10.