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ORIGINAL RESEARCH

Resistance rates of non-*albicans Candida* infections in Taiwan after the revision of 2012 Clinical and Laboratory Standards Institute breakpoints

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Purpose: In 2012, the Clinical and Laboratory Standards Institute (CLSI) revised its breakpoints for drugs and species because of the increase in non-*albicans Candida* infections and their drug resistance. Following global trends, the non-*albicans* candidemia resistance rate has increased in Taiwan as well. To update the antifungal susceptibility of non-*albicans* candidemia isolates, we conducted a multicenter study using the revised break points.

Patients and methods: Patients with non-*albicans* candidemia infections were identified at five tertiary hospitals in Taiwan from July 1, 2011, to June 30, 2014. The broth microdilution method using a Sensititre YeastOne system was performed for the determination of minimum inhibitory concentration (MIC). The susceptibility was interpreted based on the guidelines of the CLSI (CLSI M27-S4 and M27-S3).

Results: *Candida tropicalis* was the predominant non-*albicans* candidemia pathogen (42.4%), and it showed increased fluconazole non-susceptibility (36.3%) when compared to the results from previous studies. In particular, *C. tropicalis* showed high cross-resistance to azole agents. *C. tropicalis* isolates that were found to be resistant to fluconazole also showed increased resistance to voriconazole (82.2%) and posaconazole (100%). The increased non-susceptibility of *Candida glabrata* to multiple antifungal agents, based on the revised break points, resulted from an increase in dose-dependent susceptibility (94.4%) rather than from an increase in resistance (5.6%).

Conclusion: The resistance rate of non-*albicans* candidemia isolates is increasing, particularly for *C. tropicalis* and *C. glabrata*.

Keywords: non-*albicans* candidemia, resistance, susceptibility

Introduction

Clinicians have used fluconazole to treat mucosal and invasive infections caused by *Candida*, *Cryptococcus*, and other opportunistic yeasts for nearly 30 years. In December 2012, the Clinical and Laboratory Standards Institute (CLSI), similar to the European Committee on Antimicrobial Susceptibility Testing (EUCAST), revised the antimicrobial break points for different species in CLSI M27-S4,[1] because resistance to fluconazole and echinocandins had been documented.[2–4] Accordingly, although *Candida albicans* is still the major pathogen responsible for candidiasis, many studies have reported the emergence of non-*albicans Candida* species.[5,6] The revised susceptibility tests are more sensitive at detecting resistant *Candida* strains.[7–9] The other species include *Candida glabrata* and *Candida tropicalis*, which have low susceptibility to azole antifungals. According to the CLSI M27-S4 guidelines,[1] most non-*albicans Candida* species, except for *Candida parapsilosis*, show decreased susceptibility to multiple antifungal agents.[1]

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The purpose of this study was to determine the resistance rates of non-*albicans Candida* species in Taiwan using the revised clinical break points defined by CLSI.

Patients and methods

Study design and setting

Candida specimens were obtained from adult patients who were positive for candidemia, from July 1, 2011, to June 30, 2014, at five tertiary hospitals in Taiwan: two in the south (Liouying Chi-Mei Medical Center, Kaohsiung Medical University), two in the central region (Changhua Christian Hospital, China Medical University Hospital), and one in the north (Taipei Veterans General Hospital). Non-duplicate samples were collected from abovementioned patients. The broth microdilution method was performed for the determination of minimum inhibitory concentration (MIC) according to the manufacturer's instructions using a Sensititre YeastOne system (Trek Diagnostic Systems Ltd., East Grinstead, UK). *Candida krusei* ATCC 6258 and *Candida parapsilosis* ATCC 22019 were used as quality control strains. All isolates were tested for in vitro susceptibility to fluconazole, voriconazole, posaconazole, itraconazole, anidulafungin, caspofungin, micafungin, flucytosine, and amphotericin B using CLSI guidelines. We interpreted susceptibility as it is defined in the CLSI editions, CLSI M27-S4 and CLSI M27-S3.[1,10] The designation of non-susceptibility included samples that were susceptible dose-dependent (SDD), intermediate, and resistant. The medical ethics committees of the five participating hospitals approved this study, and the informed consent was waived due to no intervention for the study population and difficulties in recontacting them. The whole process of collecting information from the participants was confidential. The privacy was maintained by using de-linking, and only the code appeared in the analyzed data. The authority to obtain the data was limited to the researchers ourselves.

Statistical analyses

Differences in results obtained using the 2008 and 2012 break points were assessed for significance by the Chi-squared or Fisher's exact test. A *P*-value of <0.05 was considered statistically significant.

Results

During the 3-year time frame of the study, 1,426 *Candida* samples were isolated from blood cultures. Of those, 815 were recognized as *C. albicans* and 611 as non-*albicans Candida*. The most common non-*albicans Candida* species were *C. tropicalis* (n=259; 42.4%), *C. glabrata* (n=213; 34.9%), *C. parapsilosis* (n=126; 20.6%), and *C. krusei* (n=13; 2.1%; Table 1). All other non-*albicans Candida* species were isolated infrequently (data not shown). MICs for the quality control strain of *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019 were 32 mg/L and 2 mg/L for fluconazole, 0.25 mg/L and 0.03 mg/L for voriconazole, 0.12 mg/L and 0.06 mg/L for posaconazole, 0.25 mg/L and 0.25 mg/L for itraconazole, 0.12 mg/L and 2 mg/L for micafungin, 0.25 mg/L and 0.5 mg/L for caspofungin, 0.12 mg/L and 2 mg/L for anidulafungin, 1 mg/L and 0.5 mg/L for amphotericin B, and 8 mg/L and 0.25 mg/L for flucytosine.

Table 1 summarizes the comparison of susceptibility rate according to CLSI criteria with different break points revised in 2008 (CLSI M27-S3)[10] and 2012 (CLSI M27-S4).[1] In this study, fluconazole susceptibility in non-*albicans* species was lower than 90% according to the 2012 revised break point, except for *C. parapsilosis*, of which the susceptibility was 92.1%. The three echinocandins were relatively effective in susceptibility tests against non-*albicans* species, except for *C. glabrata* and *C. krusei*, which showed 87.3% and 61.5% resistance to caspofungin, respectively.

According to the CLSI M27-S3 criteria,[10] *C. tropicalis* showed 100% susceptibility to the echinocandins (micafungin, caspofungin, and anidulafungin) and high susceptibility to the azoles (fluconazole: n=226, 87.3%; voriconazole: n=232, 89.6%). However, according to the CLSI M27-S4 criteria, a high percentage of isolates were found to be non-susceptible to azoles (Tables 1 and 2). In particular, 36.3% of isolates were not susceptible to fluconazole (SDD: 18.9%, n=49; R: 17.4%, n=45), and 61.0% were not susceptible to voriconazole (SDD: 46.7%, n=121; R: 14.3%, n=37). MIC_{50} and MIC_{90} of *C. tropicalis* for fluconazole in the present study were 2 mg/L and 32 mg/L, respectively, whereas for voriconazole, they were 0.25 mg/L and 2 mg/L, respectively (Table 1). MIC_{50} and MIC_{90} of *C. tropicalis* were 0.03 mg/L for micafungin, 0.06 mg/L and 0.25 mg/L for caspofungin, and 0.12 and 0.25 mg/L for anidulafungin, respectively (Table 1).

Among the isolates of *C. glabrata*, the rate of non-susceptibility, especially non-susceptible to fluconazole (SDD: 94.8%, n=202; R: 5.2%, n=11), increased when interpreted according to CLSI M27-S4[1] (Tables 1 and 2). The rate of *C. glabrata,* non-susceptible to fluconazole, was extremely high, based on the new break point, because of an increased number of dose-dependent strains, rather than because of an increased number of resistant strains. The break point for voriconazole was not reinterpreted in the new guidelines.

Table 1 MIC ranges, MIC 50%, MIC 90%, and numbers and percentages of isolates classified as susceptible (S), susceptible dose-dependent (SDD), intermediate (I), or resistant (R), based on the 2012 and CLSI M27-S3 break points for antifungal drugs

Candida species	Drug				CLSI M27-S3 break point			CLSI M27-S4 break point		
		MIC (mg/L)			Number (%) of isolates			Number (%) of isolates		
		Range	50	90	S	SDD (I)	R	S	SDD (I)	R
C. tropicalis (n=259)	Fluconazole	0.25–>256	2	32	226 (87.3)	17 (6.6)	16 (6.2)	165 (63.7)	49 (18.9)	45 (17.4)
	Voriconazole	≤0.008–>8	0.25	2	232 (89.6)	9 (3.5)	18 (6.9)	101 (39)	121 (46.7)	37 (14.3)
	Posaconazole	0.015–>8	0.25	0.5	–	–	–	–	–	–
	Itraconazole	0.06–>16	0.25	0.5	–	–	–	–	–	–
	Micafungin	0.015–2	0.03	0.03	259 (100)	0 (0)	0 (0)	254 (98.1)	2 (0.8)	3 (1.2)
	Caspofungin	0.015–>8	0.06	0.25	259 (100)	0 (0)	0 (0)	253 (97.7)	2 (0.4)	4 (1.9)
	Anidulafungin	0.03–2	0.12	0.25	259 (100)	0 (0)	0 (0)	255 (98.5)	1 (0.4)	3 (1.2)
	Amphotericin B	≤0.12–2	0.5	1	–	–	–	–	–	–
	Flucytosine	≤0.06–>64	≤0.06	0.12	257 (99.2)	0 (0)	2 (0.8)	–	–	–
C. glabrata (n=213)	Fluconazole	0.25–>256	16	32	96 (45.1)	106 (49.8)	11 (5.2)	–	202 (94.8)	11 (5.2)
	Voriconazole	≤0.008–4	0.5	1	206 (96.7)	5 (2.3)	2 (0.9)	–	–	–
	Posaconazole	≤0.008–>8	1	2	–	–	–	–	–	–
	Itraconazole	≤0.015–>16	0.5	1	–	–	–	–	–	–
	Micafungin	0.015–2	0.015	0.015	213 (100)	0 (0)	0 (0)	206 (96.7)	1 (0.5)	6 (2.8)
	Caspofungin	0.015–>8	0.12	0.25	213 (100)	0 (0)	0 (0)	186 (87.3)	25 (11.7)	2 (0.9)
	Anidulafungin	0.03–2	0.06	0.12	213 (100)	0 (0)	0 (0)	206 (96.7)	1 (0.5)	6 (2.8)
	Amphotericin B	≤0.12–4	0.5	1	–	–	–	–	–	–
	Flucytosine	≤0.06–1	≤0.06	≤0.06	213 (100)	0 (0)	0 (0)	–	–	–
C. parapsilosis (n=126)	Fluconazole	≤0.12–64	1	2	125 (99.2)	1 (0.8)	0 (0)	116 (92.1)	8 (6.3)	2 (1.6)
	Voriconazole	≤0.008–0.5	0.015	0.03	126 (100)	0 (0)	0 (0)	124 (98.4)	2 (1.6)	0 (0)
	Posaconazole	≤0.008–0.5	0.03	0.06	–	–	–	–	–	–
	Itraconazole	≤0.015–0.5	0.06	0.12	–	–	–	–	–	–
	Micafungin	0.015–4	1	2	125 (99.2)	0 (0)	1 (0.8)	125 (99.2)	1 (0.8)	0 (0)
	Caspofungin	0.03–1	0.5	0.5	126 (100)	0 (0)	0 (0)	126 (100)	0 (0)	0 (0)
	Anidulafungin	≤0.015–2	1	2	126 (100)	0 (0)	0 (0)	126 (100)	0 (0)	0 (0)
	Amphotericin B	≤0.12–1	0.5	0.5	–	–	–	–	–	–
	Flucytosine	≤0.06–>64	0.12	0.25	123 (97.6)	1 (0.8)	2 (1.6)	–	–	–
C. krusei (n=13)	Fluconazole	64–128	64	128	0 (0)	0 (0)	13 (100)	–	–	–
	Voriconazole	0.25–1	0.5	0.5	13 (100)	0 (0)	0 (0)	12 (92.7)	1 (7.7)	0 (0)
	Posaconazole	0.25–0.5	0.5	0.5	–	–	–	–	–	–
	Itraconazole	0.25–0.5	0.25	0.5	–	–	–	–	–	–
	Micafungin	0.06–0.12	0.12	0.12	13 (100)	0 (0)	0 (0)	13 (100)	0 (0)	0 (0)
	Caspofungin	0.12–0.5	0.25	0.5	13 (100)	0 (0)	0 (0)	8(61.5)	5(38.5)	0 (0)
	Anidulafungin	0.06–0.25	0.12	0.12	13 (100)	0 (0)	0 (0)	13 (100)	0 (0)	0 (0)
	Amphotericin B	0.5–1	0.5	1	–	–	–	–	–	–
	Flucytosine	8–16	16	16	0 (0)	13 (100)	0 (0)	–	–	–

Abbreviations: *C. glabrata, Candida glabrata; C. krusei, Candida krusei;* CLSI, Clinical and Laboratory Standards Institute; *C. parapsilosis, Candida parapsilosis; C. tropicalis, Candida tropicalis;* I, intermediate; MIC, minimum inhibitory concentration; R, resistant; S, susceptible; SDD, susceptible dose dependent.

According to the revised break points, the susceptibility of *C. glabrata* to anidulafungin and micafungin remained high (96.7% for each), although the susceptibility to caspofungin decreased from 100% (CLSI M27-S3) to 87.3% (CLSI M27-S4; Tables 1 and 2). MIC_{50} and MIC_{90} of *C. glabrata* were 16 mg/L and 32 mg/L for fluconazole and 0.5 mg/L and 1 mg/L for voriconazole, respectively. MIC_{50} and MIC_{90} were 0.015 mg/L for micafungin, 0.12 mg/L and 0.25 mg/L for caspofungin, and 0.06 mg/L and 0.12 mg/L for anidulafungin (Table 1).

There were no major differences in the drug susceptibility of *C. parapsilosis* isolates determined using the CLSI M27-S3 and CLSI M27-S4 break points (Tables 1 and 2). *C. krusei* is assumed to be intrinsically resistant to fluconazole.

However, this species showed significantly lower susceptibility (62%) to caspofungin based on the CLSI M27-S4 break point (P<0.039; Tables 1 and 2). MIC_{50} and MIC_{90} for the different non-*albicans Candida* species are listed in Table 1.

Table 3 summarizes the cross-resistance between fluconazole and echinocandins. According to the CLSI M27-S4 break points and epidemiological cutoff values,[11,12] our results indicate that *C. tropicalis* and *C. glabrata* showed cross-resistance between fluconazole and voriconazole. Among the *C. tropicalis* isolates (n=259), there were 45 fluconazole-resistant isolates. Of those, 80.0% (36/45) were also resistant to voriconazole (P<0.001). Regarding 11 isolates of *C. glabrata* with resistance to fluconazole, 90.9% (10/11) and 54.5% (6/11) were also resistant to voriconazole and posaconazole, respectively. Despite a strong correlation between fluconazole and voriconazole resistance in both *C. tropicalis* and *C. glabrata*, the susceptibility to echinocandins remained high (above 90%) in these two non-*albicans Candida* species.

Discussion

Our study showed that among all the *Candida* species that cause bloodstream infections, *C. albicans* remains the predominant pathogen in Taiwan (57.2%), in a similar fashion to studies conducted in other Asian countries such as Korea, Singapore, and Vietnam.[11] Of the non-*albicans* candidemia isolates, *C. tropicalis* was the most common species (42.4%), and this species distribution trend is likely as that reported in Asia or Taiwan from previous literatures.[12–15] In southern Taiwan, *C. albicans* was the most common *Candida* species (48.7%, 345/709) and *C. tropicalis* was the most common non-*albicans Candida* species (40.7%, 148/364).[15] In northern Taiwan, the percentages of *C. albicans* and *C. tropicalis* were 62.15% and 15.4%, respectively.[16] This divergence of species distribution among non-*albicans* candidemia between Asian and Western countries indicated the importance of comprehension and update about local epidemiology in each region around the world.

Using the revised CLSI guideline, we found that the susceptibility of *C. tropicalis* to fluconazole decreased from 87.3% to 63.7%, whereas the susceptibility to voriconazole decreased from 89.6% to 39.0%. On the other hand, it appeared that *C. glabrata* showed dose-dependent susceptibility to fluconazole in majority under the revised break points.

Table 2 Non-*albicans Candida* isolates non-susceptible to fluconazole, voriconazole, micafungin, caspofungin, and anidulafungin according to the CLSI M27-S4 and CLSI M27-S3 break points

Candida species	No. (%) of non-susceptible isolates									
	Fluconazole	*P*	Voriconazole	*P*	Anidulafungin	*P*	Caspofungin	*P*	Micafungin	*P*
C. tropicalis (n=259)										
CLSI M27-S3	33 (12.7)	<0.001	27 (10.4)	<0.001	0 (0)	0.124	0 (0)	0.030	0 (0)	0.061
CLSI M27-S4	94 (36.3)		158 (61.0)		4 (1.5)		6 (2.3)		5 (1.9)	
C. glabrata (n=213)										
CLSI M27-S3	117 (54.9)	<0.001	7 (3.3)	–	0 (0)	0.015	0 (0)	<0.001	0 (0)	0.015
CLSI M27-S4	213 (100)		–		7 (3.3)		27 (12.7)		7 (3.3)	
C. parapsilosis (n=126)										
CLSI M27-S3	1 (0.8)	0.014	0 (0)	0.498	0 (0)	1.000	0 (0)	1.000	1 (0.8)	1.000
CLSI M27-S4	10 (7.9)		2 (1.6)		0 (0)		0 (0)		1 (0.8)	
C. krusei (n=13)										
CLSI M27-S3	13 (100)	–	0 (0)	1.000	0 (0)	1.000	0 (0)	0.039	0 (0)	1.000
CLSI M27-S4	–		1 (7.7)		0 (0)		5 (38.5)		0 (0)	

Abbreviations: *C. glabrata, Candida glabrata; C. krusei, Candida krusei;* CLSI, Clinical and Laboratory Standards Institute; *C. parapsilosis, Candida parapsilosis; C. tropicalis, Candida tropicalis.*

Table 3 Cross-resistance to azole and echinocandin drugs among fluconazole-resistant isolates of *C. tropicalis* and *C. glabrata*

Drugs	*C. tropicalis* (n=45)			*C. glabrata* (n=11)		
	S n (%)	SDD n (%)	R n (%)	S n (%)	SDD n (%)	R n (%)
Voriconazole	1 (2.2)	8 (17.8)	36 (80.0)			
Anidulafungin	43 (95.6)	0 (0)	2 (4.4)	11 (100)	0 (0)	0 (0)
Caspofungin	42 (93.3)	1 (2.2)	2 (4.4)	10 (90.9)	1 (9.1)	0 (0)
Micafungin	43 (95.6)	1 (2.2)	1 (2.2)	10 (90.9)	1 (9.1)	0 (0)

Abbreviations: *C. glabrata, Candida glabrata; C. tropicalis, Candida tropicalis;* R, resistant; S, susceptible; SDD, susceptible-dose dependent.

Although our results have shown that the susceptibility of *C. tropicalis* to fluconazole has decreased according to these revised break points, this trend is not confirmed in other studies conducted in Taiwan. Chen et al[15] reported that the susceptibility of *C. tropicalis* to fluconazole was as high as 85.8%. Yang et al[17] reported that the susceptibility to fluconazole and voriconazole was 99.6% and 100%, respectively. However, these studies did not exclusively consider bloodstream infections, but they also included other sterile site specimens. Huang et al[18] reported the susceptibility of *C. tropicalis* to fluconazole and voriconazole to be 86.7% and 78.6%, respectively. When comparing to our results, the higher susceptibility of *C. tropicalis* observed in previous studies could be explained by the fact that these authors only considered one hospital during their researches. The disparity of our study method with the Taiwan Surveillance of Antimicrobial Resistance of Yeasts (TSARY)[17] resulted in different susceptibility results. Among the five hospitals in this study, there was only one hospital in which *C. tropicalis* susceptibility to fluconazole attained 70%. In addition, none of *C. tropicalis* samples tested were susceptible to voriconazole beyond 50%. In this study, we found that the resistance rate of *C. glabrata* to fluconazole under the revised break points did not vary compared to that under the former break points. We noticed that the non-susceptible rate changes were mostly due to the increase in the SDD *C. glabrata* strains. The susceptibility test of *C. parapsilosis* to fluconazole had minor variation and was similar to the previous break points.

Caspofungin susceptibility significantly decreased when using the new break points of each species (Tables 1 and 2). In the study by Espinel-Ingroff et al,[19] caspofungin susceptibility had interlaboratory variation against each species, except for *C. parapsilosis* and *Candida guilliermondii*. Therefore, there was no MIC used to perform this test.

As *C. tropicalis* isolates were resistant to fluconazole in our study, those were 80.0% resistant to voriconazole and 100% resistant to posaconazole. However, their susceptibilities to echinocandin were excellent (>93%). In the same way, although *C. glabrata* was resistant to fluconazole, the susceptibility rate to echinocandins (>90%) was shown to be similar as that of *C. tropicalis. Candida* resistance mechanisms have mainly been described to include increased efflux of the azole drug, overexpression of the ERG11 gene, or a point mutation in the ERG11 sequence. Regarding *C. tropicalis*, changes in the permeability of the fungal membrane may be associated with the function of Erg11p and result in cross-resistance to azole agents.[20] Empirical antifungal agents should be used with prudence after the revision of the break points. Pfaller et al[21] used fluconazole to predict susceptibility and resistance to voriconazole. In this study, we showed a similar pattern, because when *C. tropicalis* was found to be resistant to fluconazole, it was likely to be resistant to voriconazole as well.

Conclusion

This is the first epidemiological study of candidemia in Taiwan, which included susceptibility tests. In our study, *C. tropicalis* was the predominant non-*albicans Candida* species detected, similar to other Asian countries. However, non-susceptibility of non-*albicans Candida* species to azoles increased after the break point revision and it was widely different compared to the reports from Western countries. The cross-resistance to azoles is a concern in non-*albicans Candida*. A high resistance rate to voriconazole (80%) was observed if the sensitivity test of *C. tropicalis* showed resistance to fluconazole; the results of sensitivity test in echinocandins were similar for *C. tropicalis* and *C. glabrata* when the isolates of these two non-*albicans Candida* species were resistant to fluconazole. There was no genetic analysis of the species in this study, and there was no correlation of the data with the clinical outcomes; these are the limitations of this paper.

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Disclosure

The authors report no conflicts of interest in this work.

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