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Antifungal Susceptibility to Amphotericin B, Fluconazole, Voriconazole, and Flucytosine in *Candida* Bloodstream Isolates from 15 Tertiary Hospitals in Korea

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The *in vitro* antifungal susceptibility of 636 *Candida* bloodstream isolates collected from 15 tertiary hospitals in Korea was determined using the Vitek-2 yeast susceptibility system (bioMérieux, France). Overall susceptibility rates were 98.1%, 95.9%, 99.1%, and 97.3% for amphotericin B, fluconazole, voriconazole, and flucytosine, respectively. The results show that the rates of resistance to 4 antifungal drugs remain low among *Candida* bloodstream isolates in Korea.

Key Words: *Candida*, Amphotericin B, Flucytosine, Fluconazole, Voriconazole

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The Vitek-2 yeast susceptibility system (bioMérieux, Marcy l'Étoile, France) is a fully automated commercial method that allows determination of the minimal inhibitory concentration (MIC) of 4 antifungal agents, i.e., amphotericin B, fluconazole, voriconazole, and flucytosine [1, 2]. This system has demonstrated a high level of reproducibility and has an excellent categorical agreement with the CLSI microdilution reference method [1-3]. Moreover, a recent study showed that the Vitek-2 system is superior to the CLSI or the European Committee on Antimicrobial Susceptibility Testing (EUCAST) broth microdilution method for detecting amphotericin B-resistant *Candida* isolates [4]. Because of its advantages, including a significant reduction in technologist hands-on time and turnaround time [1, 2], this system has become one of the most widely used antifungal susceptibility testing systems in Korean clinical laboratories. However, nationwide data for the *in vitro* antifungal susceptibility of *Candida* bloodstream infection (BSI) isolates as determined by the Vitek-2 system are still lacking in Korea. In this study, we investigated the *in vitro* activity of 4 antifungal agents using the Vitek-2 system against *Candida* BSI isolates recovered from 15 tertiary hospitals in Korea.

During the study period (September 2007 to August 2008), 636 *Candida* BSI isolates were collected from 636 patients among the 15 tertiary hospitals in Korea. Antifungal susceptibility testing

with the Vitek-2 system was performed according to the manufacturer's instructions [1, 2]. The categorical result was obtained according to the breakpoints provided by the Vitek-2 system for amphotericin B (susceptible [S], ≤1 μg/mL; intermediate, 2 μg/mL; resistant [R], ≥4 μg/mL), fluconazole (S, ≤8 μg/mL; susceptible dose dependence [SDD], 16 to 32 μg/mL; R, ≥64 μg/mL), and voriconazole (S, ≤1 μg/mL; SDD, 2 μg/mL; R, ≥4 μg/mL), and flucytosine (S, ≤4 μg/mL; intermediate, 8-16 μg/mL; R, ≥32 μg/mL).

Table 1 summarizes the *in vitro* antifungal susceptibilities of the 636 *Candida* BSI isolates to 4 antifungal agents as determined by using the Vitek-2 system. For all 636 *Candida* BSI isolates combined, the activity of each agent (μg/mL), expressed as the MIC_{50}/MIC_{90} (and the percentage of susceptible isolates) was as follows: amphotericin, 0.5/0.5 (98.1%); fluconazole, ≤1/2 (95.9%); voriconazole, ≤0.12/≤0.12 (99.1%); and flucytosine, ≤1/≤1 (97.3%). These results represent the updated nationwide data, which show that the majority of *Candida* BSI isolates was susceptible to all 4 fungal agents tested.

In our previous multicenter study, nearly all isolates (99.7%) had a MIC ≤1 μg/mL for amphotericin B [5]. In the present study, resistance to amphotericin B was found in 5 *Candida* isolates; whereas intermediate resistance was found in 7 isolates. These Vitek-2 results produced no major errors when the E test

Table 1. *In vitro* antifungal susceptibilities of 636 isolates of *Candida* species to fluconazole, voriconazole, amphotericin B, and flucytosine, as determined by using the Vitek-2 system

Species (N of isolates)	Antifungal agents	MIC (μg/mL)			SDD/I* (%)	R* (%)
		Range	MIC_{50}	MIC_{90}		
C. albicans (252)	Amphotericin B	≤0.25-1	0.5	0.5		
	Fluconazole	≤1-32	≤1	≤1	3 (1.2)	
	Voriconazole	≤0.12-4	≤0.12	≤0.12		1 (0.4)
	Flucytosine	≤1-≥64	≤1	≤1		8 (3.2)
C. tropicalis (149)	Amphotericin B	≤0.25-0.5	≤0.25	0.5		
	Fluconazole	≤1-16	≤1	≤1	1 (0.7)	
	Voriconazole	≤0.12-1	≤0.12	≤0.12		
	Flucytosine	≤1-≥64	≤1	≤1		
C. parapsilosis (132)	Amphotericin B	≤0.25-8	0.5	0.5	1 (0.8)	1 (0.8)
	Fluconazole	≤1-≥64	≤1	2		2 (1.5)
	Voriconazole	≤0.12-0.5	≤0.12	≤0.12		
	Flucytosine	≤1-≥64	≤1	≤1		2 (1.5)
C. glabrata (72)	Amphotericin B	≤0.25-8	0.5	1	6 (8.3)	2 (2.8)
	Fluconazole	≤1-≥64	8	16	13 (18.1)	3 (4.2)
	Voriconazole	≤0.12-8	≤0.12	1		5 (6.9)
	Flucytosine	≤1-≥64	≤1	≤1	1 (1.4)	1 (1.4)
Others (31)†	Amphotericin B	≤0.25-≥16	≤0.25	0.5		2 (6.5)
	Fluconazole	≤1-16	2	8		4 (12.9)‡
	Voriconazole	≤0.12-0.25	≤0.12	0.25		
	Flucytosine	≤1-32	≤1	8	4 (12.9)	1 (3.2)
Total (636)	Amphotericin B	≤0.25-≥16	0.5	0.5	7 (1.1)	5 (0.8)
	Fluconazole	≤1-≥64	≤1	2	17 (2.7)	9 (1.4)
	Voriconazole	≤0.12-8	≤0.12	≤0.12		6 (0.9)
	Flucytosine	≤1-≥64	≤1	≤1	5 (0.8)	12 (1.9)

*SDD, I and R (susceptible-dose dependent, intermediate and resistant, respectively), using the Vitek-2 interpretive breakpoint criteria; †Includes *Candida guilliermondii* (10 isolates), *C. famata* (6 isolates), *C. krusei* (4 isolates), *C. pelliculosa* (4 isolates), *C. utilis* (3 isolates), *C. pseudohaemulonii* (2 isolates), *C. lusitaniae* (1 isolate), and *C. intermedia* (1 isolate); ‡All 4 *C. krusei* isolates are considered to be resistant to fluconazole, irrespective of the minimum inhibitory concentration (MIC).

was used as reference standard, supporting our previous report that Vitek-2 is more sensitive for detecting amphotericin B resistance among *Candida* species than the CLSI method [4].

According to the SENTRY Antimicrobial Surveillance Program [6], the percentages of *Candida* BSI isolates with resistance to fluconazole and voriconazole are 2.5% and 1.2%, respectively. In the present study, resistance to fluconazole was found in 1.4% (9/636) of the *Candida* isolates (4 *C. krusei*, 3 *C. glabrata*, and 2 *C. parapsilosis*) and resistance to voriconazole was found in 0.9% (6/636) of the *Candida* isolates (1 *C. albicans* and 5 *C. glabrata*), which was comparable with our previous report [5].

Until now, nationwide data on the *in vitro* antifungal activity of flucytosine against *Candida* BSI isolates were not available in Korea. Results from the global SENTRY Antimicrobial Surveillance Program (2008) showed that 95.5% of the 1,201 *Candida* BSI isolates from 5 continents are susceptible to flucytosine [6]. Resistance to flucytosine was noted in 2.4% of *C. albicans*, 0% of *C. glabrata*, 0.5% of *C. parapsilosis*, and 10.3% of *C. tropicalis* isolates [6]. In this study, we showed, for the first time, that 97.3% of *Candida* BSI isolates from Korea were susceptible to flucytosine, as determined by using the Vitek-2 system. Only 3.2% of *C. albicans*, 1.5% of *C. parapsilosis*, 1.4% of *C. glabrata*, and 0% of *C. tropicalis* isolates were resistant to this agent. Again, our results show that the low rates of resistance to flucytosine are consistent with reports from other countries.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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