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In vitro susceptibility of *Candida spp.* to fluconazole, itraconazole and voriconazole and the correlation between triazoles susceptibility: Results from a five-year study

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ABSTRACT

Candida spp. is a common cause of invasive fungal disease. The aim of this study was to examine the susceptibility of *Candida spp.* to fluconazole, itraconazole and voriconazole and explore the correlation between triazoles susceptibility. The antifungal susceptibility in the present study was measured by ATB Fungus 3 method, and the potential relationship was examined by obtaining the correlation of measured minimal inhibitory concentrations (MICs) of *Candida spp.* isolates. A total of 2099 clinical isolates of *Candida spp.* from 1441 patients were analyzed. The organisms included 1435 isolates of *Candida albicans*, 207 isolates of *Candida glabrata*, 65 isolates of *Candida parapsilosis*, 31 isolates of *Candida krusei*, 268 isolates of *Candida tropicalis*. Voriconazole and itraconazole were more active than fluconazole and against *Candida spp.* in vitro. The fluconazole, itraconazole and voriconazole MIC_{90} (MIC for 90% of the isolates) for all *Candida spp.* isolates was 4 mg/L, 1 mg/L and 0.25 mg/L, respectively. There was a moderate correlation between the fluconazole MIC_s for *Candida spp.* isolates and this for voriconazole ($R^2 = 0.475$; $P < 0.01$) and itraconazole ($R^2 = 0.431$; $P < 0.01$). Voriconazole MICs for the *Candida spp.* isolates also correlated with those for itraconazole ($R^2 = 0.401$; $P < 0.01$). These observations suggest that the in vitro susceptibility of *Candida spp.* to fluconazole, itraconazole and voriconazole exhibits a moderate correlation.

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1. Introduction

Candida spp. is currently the most common cause of invasive fungal disease, which is associated with considerable mortality [1–4]. Antifungal susceptibility testing has become an important method in the management of patients with invasive candidiasis (IC) [2,5], and this method is widely accepted and readily available in the department of laboratory. Given the increasing number of antifungal agents with activity against *Candida spp.*, it is recognized that antifungal susceptibility testing of these pathogens may be useful in guiding the selection of antifungal agents for the treatment of IC [2,6,7]. Clinically, fluconazole is frequently used to treat systemic infection caused by *Candida spp.* [8]. Itraconazole and voriconazole are used to treat invasive fungal disease caused by *Aspergillus spp.* and fluconazole-resistant *Candida spp.* [2]. However, few studies have investigated the correlation between triazoles susceptibility in a great number of clinical *Candida spp.* isolates. In this study, we examined the susceptibilities of 2099 *Candida spp.* isolates recovered from colonizing and invasive sites of patients to evaluate the epidemiology of *Candida* species and the clinical significance of triazole correlation between triazoles susceptibility in *Candida spp.* isolates.

2. Methods

2.1. Organisms

A single-centre clinical trial was conducted from December 2012 to August 2016 at the First Affiliated Hospital of Xi'an Jiaotong University. Patients who were diagnosed with a possible,

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probable or proven invasive fungal disease were enrolled. Invasive fungal diseases were defined by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) [9]. The isolates were obtained from all body sites, including blood, sputum, bronchoscopy, urine, ascitic fluid, bile and tissue biopsy specimens. During the 5-year period, a total of 2099 *Candida* clinical isolates obtained from 1441 patients were analyzed. The collection included the following numbers of isolates: 1435 isolates of *C. albicans*, 207 isolates of *C. glabrata*, 65 isolates of *C. parapsilosis*, 31 isolates of *C. krusei*, 268 isolates of *C. tropicalis*, 41 isolates of *C. guilliermondii*, 14 isolates of *C. sake*, 2 isolates of *C. dubliniensis*, 13 isolates of *C. lusitaniae*, 1 isolate of *C. colliculosa*, 3 isolates of *C. pelliculosa*, 1 isolate of *C. inconspicua*, 1 isolate of *C. lipolytica*, 3 isolates of *C. rugose*, 3 isolates of *C. intermedia*, 4 isolates of *C. catenulate*, 2 isolates of *Sporobolomyces*, 5 isolates of *C. famata*.

2.2. Susceptibility testing

Minimal inhibitory concentration (MIC) values were determined for all strains isolated. An ATB FUNGUS 3 strip contains five antifungal drugs at different concentrations, but only three antifungal agents were involved in the present study: fluconazole (1–128 mg/L), itraconazole (0.125–4 mg/L) and voriconazole (0.0625–8 mg/L). Testing on the ATB FUNGUS 3 strip was performed according to the manufacturer's instructions and ATB FUNGUS 3 strips were read visually. MIC endpoints of each isolate were determined after 24 h of incubation at 35 °C [10].

2.3. Quality control

Quality control was ensured by testing the following strains: *C. albicans* (ATCC90028), *C. glabrata* (ATCC 64677), and *C. krusei* (ATCC 6258).

2.4. Statistical method

We examined correlations between the MICs of each triazoles by using the univariate linear regression model. Stata software (version 14.0; Stata Corporation, College Station, TX, USA) was used for statistical analyses.

Table 2
The distribution of fluconazole, itraconazole and voriconazole MIC values for all *Candida spp.* isolates.

MIC (mg/L)	Cumulative frequency (%)		
	Fluconazole	Itraconazole	Voriconazole
0.0625	0	0	78.89
0.125	0	80.32	85.14
0.25	0	83.85	91.00
0.5	0	88.28	93.90
1	81.99	92.57	96.57
2	85.95	93.76	97.05
4	91.00	100	97.86
8	92.52	100	100
16	94.85	100	100
32	95.62	100	100
64	96.86	100	100
128	100	100	100

3. Results and discussion

Table 1 and Table 2 summarizes the in vitro susceptibilities of 2099 isolates of *Candida spp.* to fluconazole, itraconazole and voriconazole, respectively, as determined by ATB FUNGUS 3 method. Yeast cultures came form 19 species, and the most common species is *C. albicans* (*n* = 1435, 68.37%). The five most common *non-C. albicans* species are *C. glabrata* (*n* = 207, 9.86%), *C. parapsilosis* (*n* = 65, 3.10%), *C. krusei* (*n* = 31, 1.48%), *C. tropicalis* (*n* = 268, 12.77%) and *C. guilliermondii* (*n* = 41, 1.95%) (Table 1). Table 2 showed the distribution of fluconazole, itraconazole and voriconazole MIC values for all *Candida spp.* isolates. Isolates of *C. albicans, C. parapsilosis* and *C. tropicalis* remain highly susceptible to fluconazole (> 90% susceptible) in the present study. Table 1 also details the distribution of MIC_{50}s (MIC for 50% of the isolates), MIC_{90}s (MIC for 90% of the isolates) and MICs of fluconazole, itraconazole and voriconazole for each species of *Candida spp.* Fluconazole, itraconazole and voriconazole were highly active against *C. albicans* in vitro, with 90% of isolates inhibited at an MIC of 1 mg/L, 0.125 mg/L and 0.0625 mg/L, respectively. The fluconazole, itraconazole and voriconazole MIC_{50} values for all *Candida spp.* isolates was 1 mg/L, 0.125 mg/L and 0.0625 mg/L, respectively. The MIC_{90} value for fluconazole, itraconazole and voriconazole was 4 mg/L, 1 mg/L and 0.25 mg/L, respectively, which suggested that voriconazole and itraconazole were more active than fluconazole

Table 1
In vitro activities of fluconazole, itraconazole and voriconazole against *Candida spp.* by the ATB FUNGUS 3 method.

Isolates	MIC (range [MIC50] [MIC90]) (mg/L)			
	No.	Fluconazole	Itraconazole	Voriconazole
Candida albicans	1435	1–128 [1] [1]	0.125–4 [0.125] [0.125]	0.0625–8 [0.0625] [0.0625]
Candida glabrata	207	1–128 [2] [16]	0.25–4 [0.25] [4]	0.0625–8 [0.125] [1]
Candida parapsilosis	65	1–8 [1] [2]	0.25–4 [0.5] [1]	0.125–0.5 [0.125] [0.25]
Candida krusei	31	16–128 [16] [64]	0.125–4 [0.5] [1]	0.25–8 [0.25] [1]
Candida tropicalis	268	1–128 [1] [128]	0.125–4 [0.125] [4]	0.0625–4 [0.0625] [2]
Candida guilliermondii	41	2–32 [4] [4]	0.125–2 [0.5] [1]	0.0625–8 [0.125] [0.5]
Candida sake	14	1–32 [1] [2]	0.125–1 [0.125] [0.125]	0.0625–0.25 [0.0625] [0.125]
Candida dubliniensis	2	1–2	0.125	0.0625–2
Candida lusitaniae	13	1	0.125–2 [0.125] [2]	0.0625
Candida colliculosa	1	1	0.125	0.0625
Candida pelliculosa	3	1–2	0.125	0.0625–0.25
Candida inconspicua	1	1	0.125	0.0625
Candida lipolytica	1	2	0.25	0.0625
Candida rugosa	3	1	0.125	0.0625
Candida intermedia	3	1–16	0.125–4	0.125–8
Candida catenulata	4	1–128	0.125–0.25	0.0625–4
Sporobolomyces	2	32	2	2
Candida famata	5	1–8	0.125–1	0.0625–2
Overall isolates	2099	1–128 [1] [4]	0.125–4 [0.125] [1]	0.0625–8 [0.0625] [0.25]