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Invasive candidiasis in intensive care units in China: *in vitro* antifungal susceptibility in the China-SCAN study

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Objectives: The objectives of this study were to determine species distribution and *in vitro* antifungal susceptibility of *Candida* isolates identified in the multicentre China-SCAN study of invasive *Candida* infection (ICI) in intensive care units (ICUs) across China.

Methods: *Candida* isolates from patients in the China-SCAN study with documented ICI were evaluated by a central laboratory. Species were identified using chromogenic culture media or the API 20C AUX kit. Susceptibility to fluconazole, voriconazole, itraconazole, caspofungin and amphotericin B was determined using the CLSI broth microdilution method (M27-A3) and updated clinical breakpoints or epidemiological cut-off values.

Results: A total of 389 isolates from 244 patients were analysed. Species identified most frequently were *Candida albicans* (40.1%), *Candida parapsilosis* (21.3%), *Candida tropicalis* (17.2%) and *Candida glabrata* (12.9%). Rarer species such as *Lodderomyces elongisporus* and *Candida ernobii* were also identified. Fluconazole susceptibility was evident in 85.9% (134/156) of *C. albicans*, 62.7% (42/67) of *C. tropicalis* and 48.2% (40/83) of *C. parapsilosis* isolates. Susceptibility to voriconazole was ≥90% among all species. All isolates were susceptible to amphotericin B and caspofungin except *C. glabrata* [86.0% (43/50) susceptible to caspofungin]. Cross-resistance between fluconazole and voriconazole was observed for *C. parapsilosis* and *C. glabrata*.

Conclusions: Although *C. albicans* was the predominant single species, non-*albicans* species constituted >50% of isolates. Fluconazole susceptibility was lower in most non-*albicans* species, indicating that fluconazole resistance should be closely monitored. Susceptibility to voriconazole, amphotericin B and caspofungin is encouraging. Differences between these data and those from other regions emphasize the importance of assessing regional variations.

Keywords: *Candida*, *albicans*, non-*albicans*, azoles, resistance

Introduction

Invasive *Candida* infection (ICI) is well-recognized among critically ill patients, who are at increased risk of infection due to severe underlying disease and immunocompromise.[1] This raises concern due to the associated mortality rate of up to 80% in this severely ill population.[2,3] *Candida albicans* is the most common causative species, accounting for 40%–82% of ICI cases in various geographical regions.[2,4–6] Retrospective studies in intensive care units (ICUs) in China suggest *C. albicans* prevalence rates between 29% and 67%;[7,8] however, several were methodologically flawed. In recent years, the incidence of non-*albicans* infection has increased in multiple geographical regions,[2,4] including China.[5,9]

The large, prospective China Survey of Candidiasis (China-SCAN) assessed the epidemiology, microbiology, management and outcomes of ICI in 67 ICUs across China; results are reported elsewhere.[10] Here we describe the distribution of *Candida* species and patterns of *in vitro* antifungal susceptibility in the China-SCAN population.

Methods

The China-SCAN study methods, including eligibility criteria, were published previously.[10] Isolated *Candida* samples obtained after documentation of ICI were sent to the Research Center for Medical Mycology, Peking University First Hospital, Beijing, China ('central laboratory') for species identification and *in vitro* susceptibility testing. Species were identified using chromogenic culture media (CHROMagar, Paris, France) and the API 20C AUX yeast identification kit (bioMérieux SA, Marcy l'Étoile, France). When necessary, large-subunit (26S) ribosomal rRNA gene D1/D2 domain sequencing was undertaken; *Candida haemulonii*, *Candida pelliculosa*, *Candida ernobii*, *Candida norvegensis*, *Candida metapsilosis* and *Lodderomyces elongisporus* were identified by sequencing.[11,12]

Antifungal susceptibility testing was performed using the CLSI M27-A3 microbroth dilution method.[13] Fluconazole (Shouguang Fukang Pharmaceutical Ltd, Shan Dong, China; purity 99.5%), caspofungin (Merck & Co., Inc., Whitehouse Station, NJ, USA; purity 99%), itraconazole (Shouguang Fukang Pharmaceutical Ltd, Shan Dong, China; purity 99.3%), voriconazole (Shouguang Fukang Pharmaceutical Ltd; purity 99.3%) and amphotericin B (Sigma Chemical Co., St Louis, MO, USA; purity 80%) were prepared according to CLSI methods described previously.[13]

MICs were determined after growth at 35°C for 24 h for all antifungal agents.[14] MICs were read as the lowest drug concentration producing a prominent decrease in turbidity translating to ~50% (fluconazole, voriconazole, itraconazole, caspofungin) or 100% (amphotericin B) growth reduction compared with the drug-free control.

The recently revised clinical breakpoints for azoles and echinocandins were used for *C. albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, *Candida krusei* and *Candida guilliermondii*.[15] Epidemiological cut-off values (ECVs) were used for amphotericin B and some azoles.[15]

Results

Species distribution

A total of 389 isolates from 244 patients were analysed (Table 1). The most commonly identified species was *C. albicans* (40.1%), followed by *C. parapsilosis* (21.3%). Taken together, *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, *C. haemulonii* and *C. guilliermondii* constituted 96.9% of isolates. Species identified infrequently were *C. pelliculosa*, *Lodderomyces elongisporus*, *Candida lipolytica*, *C. krusei*, *C. ernobii* and *C. norvegensis*.

Antifungal susceptibility

Susceptibility patterns are presented in Table 1. Overall susceptibility/wild-type (WT) among the four species that accounted for 90.0% of all isolates (*C. albicans*, *C. parapsilosis*, *C. tropicalis* and *C. glabrata*) was high for voriconazole (92.4%), caspofungin (98.0%) and amphotericin B (100.0%) and lower for fluconazole (60.7%) and itraconazole (42.0%). In total, 134/156 *C. albicans* isolates (85.9%) were susceptible to fluconazole and >90% were susceptible/WT to voriconazole, caspofungin and amphotericin B. Only 3.9% of *C. albicans* were susceptible to itraconazole. The only species that retained a high degree of susceptibility to itraconazole was *C. glabrata* (96.0% WT), with 94.0% also WT to voriconazole. All isolates were susceptible to caspofungin and amphotericin B except *C. glabrata*, where 43/50 (86.0%) of isolates remained susceptible and 7/50 (14%) were susceptible–dose dependent (SDD) to caspofungin.

Among 39/363 isolates that were resistant/non-WT to fluconazole and had breakpoints or ECV available for the three azoles (fluconazole, voriconazole and itraconazole), 29 (74.4%) and 5 (12.8%) were also resistant/non-WT to itraconazole and voriconazole, respectively. Six isolates (three *C. parapsilosis*; three *C. glabrata*) were resistant to voriconazole, of which five were also resistant to fluconazole (MIC 64 mg/L) and one (*C. glabrata*) was SDD to fluconazole (MIC 32 mg/L). All six (100%) were resistant to itraconazole. In total, four isolates (three *C. parapsilosis* and one *C. glabrata*) were resistant to all three azoles.

Discussion

The China-SCAN study is, to our knowledge, the largest prospective study of ICI in ICUs in China, and possibly anywhere, and also one of the first to report data from China using the revised clinical breakpoints and ECVs.

The most commonly isolated species was *C. albicans* (40%). This rate concurs with recent reports of ICI in ICUs in China and elsewhere,[5–8,16,17] but is considerably lower than that in the ARTEMIS DISK Global Antifungal Surveillance Study (64%–67%), which surveyed the Asia-Pacific region between 2001 and 2007,[9] or the study of Holley *et al.*[6] at a similar time in four geographically diverse ICUs (56.0%). Potential reasons for this discrepancy include different specimen types and locations: for example, *Candida* strains were isolated from many specimen types in multiple hospital departments during the ARTEMIS DISK study,[9] whereas we collected fewer specimen types, only in ICU patients.

The most commonly identified non-*albicans* species were *C. parapsilosis*, *C. tropicalis* and *C. glabrata*, which together constituted 51.4% of isolates, compared with 32% in the ARTEMIS DISK study[9] and 39% in the study by Holley *et al.*[6] Our data may reflect the decreasing prevalence of *C. albicans* over time, made possible by low-cost fluconazole and resulting in a higher relative proportion of non-*albicans* strains. Although *C. tropicalis* was the second most common cause of ICI in the Asia-Pacific region in the ARTEMIS DISK study,[9] we identified *C. parapsilosis* slightly more frequently than *C. tropicalis* (21% versus 17% of isolates, respectively), and much more frequently than in other Chinese ICU studies[7,8] (21.3% compared with 5.0%–12.6%, respectively); in this respect, the distributions of *C. albicans* and non-*albicans* species in our study align with those of Bassetti *et al.*[17] in an Italian ICU.

Rarer species identified in this study were *C. haemulonii*, *C. pelliculosa*, *C. lipolytica*, *C. ernobii*, *C. norvegensis* and *Lodderomyces elongisporus* (commonly misidentified as *C. parapsilosis*),[18] some of which are newly reported in China. For example, this may be the first *C. ernobii* infection reported in humans. The patient was a 50-year-old female with acute pancreatitis in whom ICI was diagnosed by peripheral blood culture 23 days after hospitalization (4 days after ICU admission). After misdiagnosis (*C. krusei*) in the hospital laboratory, the central laboratory confirmed *C. ernobii* infection. The patient received fluconazole and micafungin, but chose to discontinue treatment when discharged 9 days after

Table 1. Susceptibility of 389 *Candida* isolates to antifungal agents in 244 patients with ICI

Species	Isolates, *n* (%)	Agent	MIC (mg/L)			Susceptible, *n* (%)	SDD, *n* (%)	Resistant, *n* (%)	ECV (mg/L)	
			range	50%	90%				WT	non-WT
Candida albicans	156 (40.1)	fluconazole	0.06–64	1	4	134 (85.9)	7 (4.5)	15 (9.6)		
		voriconazole	0.03–0.5	0.03	0.03	145 (93.0)	11 (7.1)	0 (0.0)		
		itraconazole	0.06–4	0.06	1	6 (3.9)	125 (80.1)	25 (16.0)		
		caspofungin	0.03–0.25	0.06	0.125	156 (100.0)	0 (0.0)	0 (0.0)		
		amphotericin B	0.25–1	0.5	0.5				156 (100.0)	0 (0.0)
Candida parapsilosis	83 (21.3)	fluconazole	0.125–64	4	8	40 (48.2)	27 (32.5)	16 (19.3)		
		voriconazole	0.03–2	0.03	0.125	77 (92.8)	3 (3.6)	3 (3.6)		
		itraconazole	0.06–2	0.5	1				50 (60.2)	33 (39.8)
		caspofungin	0.03–0.5	0.25	0.25	83 (100.0)	0 (0.0)	0 (0.0)		
		amphotericin B	0.25–1	0.5	0.5				83 (100.0)	0 (0.0)
Candida tropicalis	67 (17.2)	fluconazole	0.25–64	2	4	42 (62.7)	21 (31.3)	4 (6.0)		
		voriconazole	0.03–0.5	0.03	0.25	60 (89.6)	7 (10.4)	0 (0.0)		
		itraconazole	0.03–4	0.5	2				46 (68.7)	21 (31.3)
		caspofungin	0.03–0.25	0.06	0.125	67 (100.0)	0 (0.0)	0 (0.0)		
		amphotericin B	0.25–1	0.5	1	67 (100.0)[a]		0 (0.0)[a]		
Candida glabrata	50 (12.9)	fluconazole	0.5–64	4	32	0 (0.0)	48 (96.0)	2 (4.0)		
		voriconazole	0.03–2	0.06	0.125				47 (94.0)	3 (6.0)
		itraconazole	0.5–4	1	2	0 (0.0)			48 (96.0)	2 (4.0)
		caspofungin	0.03–0.25	0.125	0.25	43 (86.0)	7 (14.0)	0 (0.0)		
		amphotericin B	0.03–1	0.5	0.5	50 (100.0)[a]		0 (0.0)[a]		
Candida haemulonii	15 (3.9)	fluconazole	1–64	16	16	—		—		
		voriconazole	0.03–4	0.25	0.5	—		—		
		itraconazole	0.5–2	1	2	—		—		
		caspofungin	0.06–0.125	0.06	0.06	—		—		
		amphotericin B	0.5–1	0.5	1	—		—		
Candida guilliermondii	6 (1.5)	fluconazole	8–64	8	64				4 (66.7)	2 (33.3)
		voriconazole	0.03–0.25	0.03	0.25				6 (100.0)	0 (0.0)
		itraconazole	0.5–4	1	4				3 (50.0)	3 (50.0)
		caspofungin	0.06–0.5	0.25	0.5	6 (100.0)	0 (0.0)	0 (0.0)		
		amphotericin B	0.25–0.5	0.5	0.5				6 (100.0)	0 (0.0)
Candida pelliculosa	5 (1.3)	fluconazole	8–16	16	16				0 (0.0)	5 (100.0)
		voriconazole	0.03–0.125	0.125	0.125				5 (100.0)	0 (0.0)
		itraconazole	0.5–2	1	2	—		—		
		caspofungin	0.06–0.125	0.06	0.125				5 (100.0)	0 (0.0)
		amphotericin B	0.25	0.25	0.25	—		—		
Lodderomyces elongisporus	2 (0.52)	fluconazole	2	2	2	—		—		
		voriconazole	0.03	0.03	0.03	—		—		

		itraconazole	0.5–1	0.05	1	—		—		
		caspofungin	0.06	0.06	0.06	—		—		
		amphotericin B	0.25–1	0.25	1	—		—		
Candida lipolytica	2 (0.52)	fluconazole	2			—		—		
		voriconazole	0.03–0.125			—		—		
		itraconazole	0.5			—		—		
		caspofungin	0.125–0.25			—		—		
		amphotericin B	0.25			—		—		
Candida krusei	1 (0.26)	fluconazole	1	△	△				1 (100.0)	0 (0.0)
		voriconazole	0.03	△	△	1 (100.0)	0 (0.0)	0 (0.0)		
		itraconazole	0.25	△	△				1 (100.0)	0 (0.0)
		caspofungin	0.25	△	△	1 (100.0)	0 (0.0)	0 (0.0)		
		amphotericin B	0.5	△	△				1 (100.0)	0 (0.0)
Candida ernobii	1 (0.26)	fluconazole	4	△	△	—		—		
		voriconazole	0.25	△	△	—		—		
		itraconazole	2	△	△	—		—		
		caspofungin	0.06	△	△	—		—		
		amphotericin B	0.25	△	△	—		—		
Candida norvegensis	1 (0.26)	fluconazole	1	△	△	—		—		
		voriconazole	0.03	△	△	—		—		
		itraconazole	0.5	△	△	—		—		
		caspofungin	0.06	△	△	—		—		
		amphotericin B	0.5	△	△	—		—		

△, MIC_{50} or MIC_{90} unavailable.
—, breakpoints unavailable.
Susceptible/SDD/resistant is defined as an MIC ≤2/4/≥8 mg/L of fluconazole for *C. albicans*, *C. tropicalis* and *C. parapsilosis*, and an MIC of 32 and ≥64 mg/L of fluconazole is defined as SDD and resistant for *C. glabrata*, respectively.
Susceptible/SDD/resistant is defined as an MIC ≤0.125/0.25–0.5/≥1 mg/L of voriconazole for *C. albicans*, *C. tropicalis* and *C. parapsilosis*, and an MIC ≤0.5/1/≥2 mg/L of voriconazole for *C. krusei*.
Susceptible/SDD/resistant is defined as an MIC ≤0.125/0.25–0.5/≥1 mg/L of itraconazole for *C. albicans*.
Susceptible/intermediate/resistant is defined as an MIC ≤0.25/0.5/≥1 mg/L of caspofungin for *C. albicans*, *C. tropicalis* and *C. krusei*, an MIC ≤2/4/≥8 mg/L of caspofungin for *C. parapsilosis* and *C. guilliermondii*, and an MIC ≤0.125/0.25/≥0.5 mg/L of caspofungin for *C. glabrata*.
In lieu of clinical breakpoints for voriconazole for *C. glabrata*, the ECV of >0.5 mg/L was used to identify non-WT isolates; ECV >0.25 was used to identify non-WT *C. guilliermondii* and *C. pelliculosa*. Fluconazole ECVs were used to identify non-WT isolates of *C. krusei* (ECV >64 mg/L), *C. guilliermondii* (ECV >8 mg/L) and *C. pelliculosa* (ECV >4 mg/L). Itraconazole ECVs were used to identify non-WT isolates of *C. tropicalis and C. parapsilosis* (ECV >0.5 mg/L), *C. glabrata* (ECV >2 mg/L), *C. krusei* and *C. guilliermondii* (ECV >1 mg/L). Caspofungin ECVs were used to identify non-WT isolates of *C. pelliculosa* (ECV >0.12 mg/L). Amphotericin B ECVs were used to identify non-WT isolates of *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, *C. krusei* and *C. guilliermondii* (ECV >2 mg/L).[15]
[a]ECV was used since no clinical breakpoints were available.[15]

diagnosis. In another example, *L. elongisporus* infection (initially misidentified as *C. albicans*) was diagnosed 64 days after hospital admission in a 78-year-old man with chronic obstructive pulmonary disease and respiratory failure. Initial fluconazole treatment was switched to voriconazole, but the patient died 23 days after diagnosis. *L. elongisporus* infection in humans has been reported in Asia and Mexico before.[18] Diagnosis of ICI from rarer species was based on clinical signs of infection and peripheral blood culture results, as described in the main China-SCAN paper.[10]

Approximately 86% of *C. albicans* isolates were susceptible to fluconazole, but susceptibility among non-*albicans* species was considerably lower. Among *C. glabrata*, 96% of isolates were SDD and the remaining 4% were resistant. Resistance to fluconazole among *C. tropicalis* (6.0%) was similar to that in the ARTEMIS Disk study (6.5%).[9] More than 90% of species (and 100% of some rarer species) in China-SCAN were susceptible/WT to voriconazole. Susceptibility/WT to itraconazole varied widely from <4% of *C. albicans* to 96% of *C. glabrata*.

Some common non-*albicans* strains, particularly *C. glabrata* and *C. parapsilosis*, had higher rates of resistance (4.0% and 19.3%, respectively) or SDD (96.0% and 32.5%) to fluconazole than other antifungals, as did the less common *C. pelliculosa* and *C. guilliermondii* (100.0% and 33.0% resistant, respectively). This should prompt reconsideration of fluconazole for first-line therapy in areas where these strains are common. Furthermore, the high cross-resistance rate between azoles, including 4/39 (10.1%) isolates (3 *C. parapsilosis*, 1 *C. glabrata*) that were resistant to all three agents, highlights the importance of susceptibility monitoring and use of effective non-azole antifungals in patients with probable or proven azole resistance. In this regard, our finding that all *Candida* species, including those that demonstrated SDD or resistance to azoles, were susceptible (or SDD in the case of *C. glabrata*) to caspofungin and amphotericin B is encouraging. ICI surveillance data show many species with MICs substantially below the breakpoint for caspofungin.[19] Amphotericin B remains highly effective, but is more toxic than azoles and echinocandins.[20]

Data from this and other studies highlight the importance of regional data and resistance monitoring, particularly among non-*albicans* strains. There was a sufficient degree of cross-resistance between azoles to warrant the use of alternative agents such as amphotericin B and echinocandins in patients with prior azole use.

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Author contributions

H. Q., R. L., W. L., F. G., Q. F., D. L., X. G. and K. Y. designed the study, W. L. and R. L. contributed to manuscript writing, W. L., R. L., J. T., W. L. and Z. W. contributed to *Candida* spp. identification and antifungal susceptibility testing/assaying and J. S., Z. X., M. L., Q. Y., H. S., L. Z., W. C., B. Z., D. J., Q. F., B. Q., T. Q., W. L., F. G., D. L., X. G., K. Y. and H. Q. were involved in fungal isolate collections or patient recruitment. All authors served as study investigators at their hospital site and reviewed the final manuscript.

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