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ORIGINAL RESEARCH

Five-year China Hospital Invasive Fungal Surveillance Net (CHIF-NET) study of invasive fungal infections caused by noncandidal yeasts: species distribution and azole susceptibility

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Purpose: In this study, we report results from a 5-year surveillance for noncandidal yeast species causing invasive infections from 65 hospitals in China.

Materials and methods: Species identification was carried out by matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) supplemented by rDNA sequencing, and fluconazole and voriconazole susceptibilities of yeasts were determined by Clinical and Laboratory Standards Institute (CLSI) disk diffusion methods.

Results: Overall, 884 noncandidal isolates belonging to 38 species were collected. *Cryptococcus neoformans* was the most common (75.6%), which also comprised 96.5% of the isolates from cerebrospinal fluid (CSF) and 62.6% from blood, followed by *Trichosporon asahii* (6.9%) and *Rhodotorula mucilaginosa* (5.1%). Fluconazole susceptibility and resistant rates were 74.1% and 9.7% for *C. neoformans* and 81.0% and 5.2% for *T. asahii*. Voriconazole exhibited good activity in comparison to these two species (99.5% and 98.3% of the isolates, were susceptible). However, 100% of the *R. mucilaginosa* isolates were resistant to both azoles. Other noncandidal yeast species showed reduced susceptibility to fluconazole (53.3%) but most were susceptible to voriconazole (94.3%). Over the 5 years, a decrease in the proportion of fluconazole-susceptible isolates was observed for *C. neoformans* (90%–67%, $P<0.001$) and other noncandidal yeast species (91%–66%, $P<0.001$). Moreover, the prevalence of azole-resistant *R. mucilaginosa* increased from 1% to 7% ($P<0.001$).

Conclusion: The shift in azole susceptibilities in mainland China calls for continued surveillance for noncandidal yeasts.

Keywords: invasive fungal infections, noncandidal yeasts, epidemiology, azole susceptibility, China

Introduction

Invasive yeast infections are a major threat to patients, particularly the immunocompromised and critically ill, with high morbidity and mortality.[1–5] Although *Candida* species remain the major cause of such infections, noncandidal yeast species are increasingly encountered as pathogens.[1,5–8] However, knowledge of the clinical characteristics and epidemiology of these pathogens remains relatively limited.[1,6,9] Moreover, data on antifungal susceptibility profiles of noncandidal yeasts are relatively few. Even where antifungal susceptibility was performed, there are no clinical breakpoints (CBPs) established using standard broth microdilution methods to guide interpretation.[10,11] These limitations result in uncertainty in clinical management and best practice use of antifungal drugs.[1,6]

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China, as one of the most fast developing countries, also suffers from the challenges of relative lack of epidemiology and drug resistance data for invasive yeast infections.[7,12] To close this knowledge gap and to assist clinical management, the China Hospital Invasive Fungal Surveillance Net (CHIF-NET) study was initiated in 2009, focusing on both invasive candidiasis (IC) and noncandidal infections.[7] Up to the fifth surveillance year (2014), 65 hospitals from 27 of the 34 provinces in China participated, enabling over 8,000 yeast isolates being collected.

In this study, we summarize the overall comparative species distribution of noncandidal yeast isolates and their antifungal susceptibility to fluconazole and voriconazole as determined by the Clinical and Laboratory Standards Institute (CLSI) disk diffusion methodology.[10,13]

Materials and methods

Study design and isolates

The CHIF-NET study is a prospective, laboratory-based, multicenter study of invasive yeast infections.[7] This study comprised data from August 1, 2009, to July 31, 2014, and study inclusion criteria have been described previously.[7] Each surveillance year, all non-repetitive yeast isolates from eligible patients with invasive infections were forwarded to the central laboratory, the Department of Clinical Laboratory, Peking Union Medical College Hospital, for species confirmative identification and antifungal susceptibility testing. The study was approved by the Human Research Ethics Committee of Peking Union Medical College Hospital (S-263). The quality control strains for identification and antifungal susceptibility testing were *Candida parapsilosis* ATCC 22019 and *Candida krusei* ATCC 6258.

Species identification

All yeast isolates were identified to the species level in the central laboratory by sequencing of the fungal rDNA internal transcribed spacer (ITS) regions in year 1[7] or by an algorithm of matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS, Vitek MS system; bioMérieux, Marcy-l'Étoile, France) supplemented by ITS sequencing.[14]

Antifungal susceptibility testing

Susceptibility to fluconazole and voriconazole was determined using the CLSI disk diffusion method,[6,10] and the results were interpreted as per the CLSI M44-S3 document (for fluconazole, susceptible, ≥19 mm; susceptible dose-dependent [SDD], 15–18 mm; resistant, ≤14 mm; for voriconazole, susceptible, ≥17 mm; SDD, 14–16 mm; resistant, ≤13 mm).[13]

Statistical analyses

All comparisons were performed using SPSS software version 12.0 (SPSS Inc., Chicago, IL, USA). Comparisons of continuous variables were performed by using the Mann–Whitney test, and comparisons of categorical variables were performed by using a chi-squared test or Fisher's exact test, as appropriate. A *P*-value of 0.05 was significant.

Results

Isolates and patients

Fifty-five of 65 participating hospitals submitted a total of 884 non-repetitive noncandidal yeast isolates from separate patients (the remaining 10 hospitals identified no episodes of noncandidal yeast infection cases during the study period) (Figure 1). Of the isolates, 300 (35.5%) were cultured from female patients and 544 (64.5%) from male patients. Patient age ranged from 0 to 91 years (median 58, IQR 30–44).

A total of 38 noncandidal yeast species were identified (Table 1). By genera, *Cryptococcus* species was most common (77.5% or 654/844 isolates), followed by *Trichosporon* species (74/844, 8.8%), *Rhodotorula* species (44/844, 5.2%), and other uncommon genera (<4%). At the species level, *Cryptococcus neoformans* was predominant, accounting for over 75.6% of the isolates (638/844), but *Cryptococcus gattii* was rare (7/844, 0.8%). *Trichosporon asahii* was the second commonest species (58/844, 6.9%), followed by *Rhodotorula mucilaginosa* (43/844, 5.1%), *Kodamaea ohmeri* (26/844, 3.1%), and *Saccharomyces cerevisiae* (16/844, 1.9%) (Table 1).

Although *Cryptococcus* spp. was predominant in all seven geographic regions, its frequency varied from 56.3% in northeast China to 89.4% in southwest China (Table 2). *Trichosporon* spp. was more prevalent in northwest and south China regions (frequency 21.7% and 20.9%, respectively), *Rhodotorula* spp. was more commonly seen in north and northeast regions (12.5% and 11.3%, respectively), whereas other noncandidal yeast species had a frequency of 16.3% and 15%, respectively, in the south and north China regions (Table 2).

Species distribution by hospital service

Overall, only 7.1% (60/844) and 6.8% (57/844) of the noncandidal yeast isolates were collected from emergency departments and outpatient clinics, respectively, and the majority of isolates (727/844, 86.1%) were cultured from patients in inpatient wards.

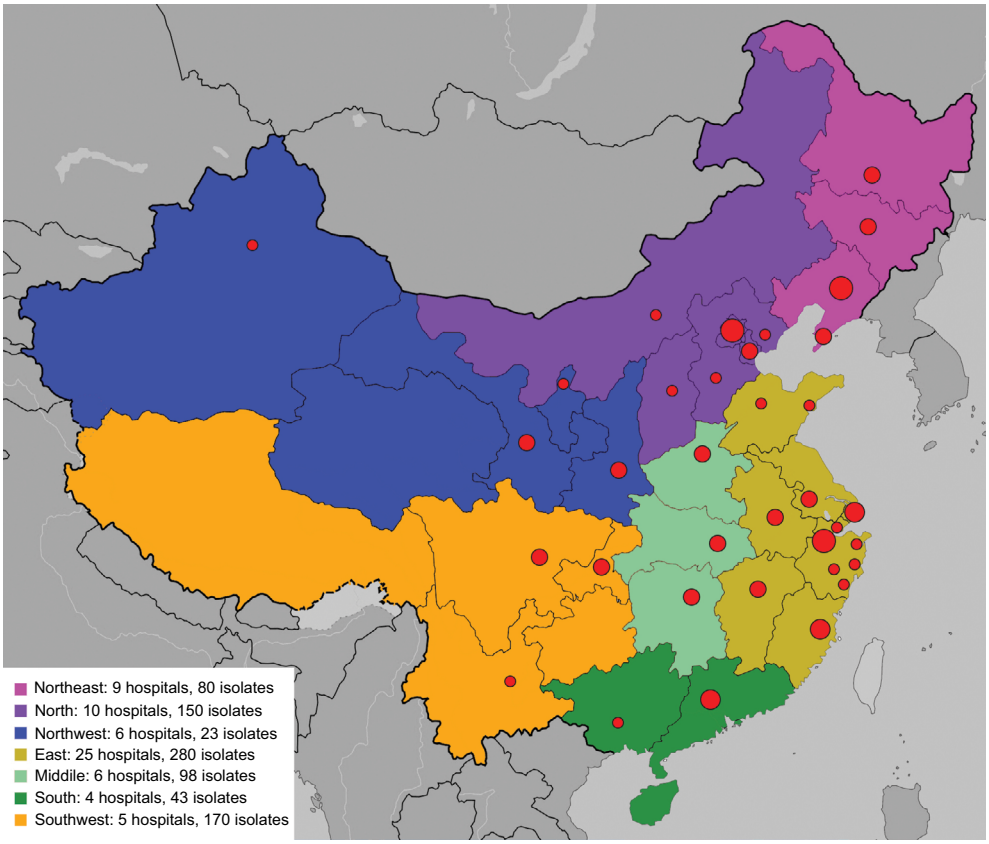

Figure 1 Noncandidal invasive yeast isolates collected in the five-year China Hospital Invasive Fungal Surveillance Net study.
Note: Seven geographic regions in China were labeled by different colors in the map, and locations of participant hospitals were labeled by red dots.

Of these 727 isolates, 487 (67.0%) were from inpatients in medical wards, 95 (13.1%) from surgical wards, 92 (12.7%) from patients in intensive care units (ICUs), and 53 (7.3%) from other ward types. Of note, the variation in specimen distribution among different inpatient departments largely stemmed from the proportions of the most common organism, *C. neoformans*, 67.2% (429/638) of which were isolated from medical wards. In comparison, isolate rates of other species from medical, surgical wards, and ICUs exhibited less variation (28%–32.9%).

Species distribution by specimen types

In this study, over 50% of the isolates (433/844) were cultured from cerebrospinal fluid (CSF), followed by blood (31.4%), ascitic fluid (4.1%), pus (3.7%), tissue (3%), venous catheter (2.5%), and pleural fluid (1.9%) (Table 3). The specimen distribution in noncandidal yeast infections was notably different to that in IC, among which blood samples predominated (3,858/8,829 isolates, 43.7% during the same period of time in CHIF-NET), and CSF samples only accounted for <2% (162/8,829) of the collection (Xiao M et al, unpublished data).

There was a high frequency of *Cryptococcus* spp. in CSF samples (428/433 isolates, 98.8%) (Table 3), whereas other species were rarely recovered from CSF (four isolates of *T. asahii* and one isolate of *Sporidiobolus* spp.) (Table 3). *Cryptococcus* spp. were also the most common pathogens identified in blood, pus, tissue, and pleural fluid samples (Table 3). However, non-CSF clinical samples comprised a broader range of noncandidal pathogens, with a total of 19 species identified from blood and 16 and 12 species from ascitic fluid and pus samples, respectively.

Antifungal susceptibilities

Overall, 576/844 (68.2%) isolates were susceptible to fluconazole, and 15.6% of the isolates (132/844) were fluconazole-resistant (Table 1). In comparison, voriconazole exhibited superior activity, with 93.7% (791/844) of the isolates being susceptible to the agent and resistance only occurred in 5.7% (48/844) of the cases (Table 1).

The azole susceptibilities varied between different species and for both the azoles tested. For the most common species, *C. neoformans* and *T. asahii*, 74.1% and 81.0% of the isolates were susceptible to fluconazole, respectively, while

Table 1 Species distribution of noncandidal yeast isolates causing invasive infections and azole susceptibility of each species

Species	Total	%	Antifungal susceptibility (%)					
			Fluconazole			Voriconazole		
			S	SDD	R	S	SDD	R
Cryptococcus spp.	**654**	**77.5**	**73.7**	**16.4**	**9.9**	**99.4**	**0.5**	**0.2**
Cryptococcus neoformans	638	76.4	74.1	16.1	9.7	99.5	0.5	
Cryptococcus gattii	7	0.8	57.1	28.6	14.3	100		
Cryptococcus laurentii	4	0.5	50.0	25.0	25.0	100		
Cryptococcus curvatus	3	0.4	66.7	33.3		100		
Cryptococcus arboriformis	1	0.1	100			100		
Cryptococcus humicola	1	0.1			100			100
Trichosporon spp.	**74**	**8.8**	**77.0**	**16.2**	**6.8**	**97.3**		**2.7**
Trichosporon asahii	58	6.9	81.0	13.8	5.2	98.3		1.7
Trichosporon mucoides	3	0.4	66.7	33.3		100		
Trichosporon japonicum	3	0.4	33.3	33.3	33.3	66.7		33.3
Trichosporon asteroides	3	0.4	100			100		
Trichosporon inkin	3	0.4	33.3	33.3	33.3	100		
Trichosporon dermatis	1	0.1	100			100		
Trichophyton interdigitale	1	0.1		100		100		
Trichosporon jirovecii	1	0.1	100			100		
Trichosporon montevideense	1	0.1	100			100		
Rhodotorula spp.	**44**	**5.2**			**100**			**100**
Rhodotorula mucilaginosa	43	5.1			100			100
Rhodotorula diobovatum	1	0.1			100			100
Other yeast spp.	**72**	**8.5**	**51.4**	**23.6**	**25.0**	**95.8**	**2.8**	**1.4**
Kodamaea ohmeri	26	3.1	38.5	42.3	19.2	100		
Saccharomyces cerevisiae	16	1.9	87.5		12.5	93.8	6.3	
Dipodascus capitatus	7	0.8	71.4	28.6		100		
Pichia caribbica	5	0.6	20.0	60.0	20.0	80.0	20.0	
Arthrographis kalrae	2	0.2			100	100		
Aureobasidium pullulans	1	0.1			100	100		
Cyberlindnera rhodanensis	1	0.1			100	100		
Debaryomyces nepalensis	1	0.1		100		100		
Trichomonascus ciferrii	1	0.1			100	100		
Hanseniaspora opuntiae	1	0.1	100			100		
Kazachstania telluris	1	0.1			100	100		
Pichia fabianii	1	0.1	100			100		
Pichia jadinii	1	0.1	100			100		
Pichia kluyveri	1	0.1			100	100		
Pichia manshurica	1	0.1			100	100		
Pichia sydowiorum	1	0.1	100			100		
Pseudozyma antarctica	1	0.1	100			100		
Pseudozyma spp.	1	0.1	100			100		
Quambalaria cyanescens	1	0.1	100			100		
Rhodosporidiobolus fluvialis	1	0.1			100			100
Sporidiobolus spp.	1	0.1			100	100		
Total	**844**	**100**	**68.2**	**16.1**	**15.6**	**93.7**	**0.6**	**5.7**

Note: Bold data represented as summarized data.
Abbreviations: R, resistant; S, susceptible; SDD, susceptible dose-dependent.

both species had susceptibility rates of >98% to voriconazole (Table 1). However, all isolates of *R. mucilaginosa* were cross-resistant to fluconazole and voriconazole (Table 1). Only around half of the other uncommon noncandidal yeast isolates (37/72, 51.4%) were susceptible to fluconazole, and one-fourth (18/72, 25.0%) were fluconazole resistant. However, these species were susceptible to voriconazole (69/72, 95.8%).

Five-year trends

Over 5 years, the frequency of isolation of *Cryptococcus* spp., *Trichosporon* spp., and other noncandidal yeast spp. varied between 73.6%–82.1%, 5.8%–11.3%, and 6.6%–10.5%, respectively, with no significant trend. However, *Rhodotorula* spp. increased significantly from 1.3% in year 1 to 7.0% in year 5 ($P<0.001$).

Table 2 Geographic distribution of noncandidal yeast genera in mainland China

Geographic region	Number of isolates (%)			
	Cryptococcus spp.	*Trichosporon* spp.	*Rhodotorula* spp.	Other yeast spp.
East	230 (82.1)	15 (5.4)	13 (4.6)	22 (0.1)
Middle	80 (81.6)	8 (8.2)	1 (1.0)	9 (0.1)
North	106 (70.7)	19 (12.7)	17 (11.3)	8 (0.1)
Northeast	45 (56.3)	13 (16.3)	10 (12.5)	12 (0.2)
Northwest	16 (69.6)	5 (21.7)	0 (0)	2 (0.1)
South	25 (58.1)	9 (20.9)	2 (4.7)	7 (0.2)
Southwest	152 (89.4)	5 (2.9)	1 (0.6)	12 (0.1)

Table 3 Species distribution by specimen types

Specimen type	Number of isolates (%)				
	Total	*Cryptococcus* spp.	*Trichosporon* spp.	*Rhodotorula* spp.	Other yeast spp.
Cerebrospinal fluid	433 (51.3)	428 (98.8)	4 (0.9)		1 (0.2)
Blood	265 (31.4)	169 (63.8)	28 (10.6)	34 (12.8)	34 (12.8)
Ascitic fluid	35 (4.1)	9 (25.7)	13 (37.1)	2 (5.7)	11 (31.4)
Pus	31 (3.7)	11 (35.5)	10 (32.3)	2 (6.5)	8 (25.8)
Tissue	25 (3.0)	21 (84.0)		1 (4.0)	3 (12.0)
Venous catheter	21 (2.5)	3 (14.3)	11 (52.4)	2 (9.5)	5 (23.8)
Pleural fluid	16 (1.9)	8 (50.0)	3 (18.8)		5 (31.3)
Bronchoalveolar lavage fluid	5 (0.6)	2 (40.0)	2 (40.0)		1 (20.0)
Hydrarthrosis	5 (0.6)		3 (60.0)		2 (40.0)
Peritoneal dialysate	4 (0.5)			2 (50.0)	2 (50.0)
Bone marrow	3 (0.4)	2 (66.7)		1 (33.3)	
Bile	1 (0.1)	1 (100)			

Cryptococcus spp. exhibited a significantly decreased fluconazole susceptibility from 90.5% in year 1 to 66.0% in year 5 ($P<0.001$) (Figure 2). In addition, there were no fluconazole-resistant *Trichosporon* species strains in years 1–3, but 21.4% of the strains were resistant in year 4, and 6.3% in year 5 ($P<0.001$) (Figure 2). Other noncandidal species also exhibited decreased susceptibility from 90.5% in year 1 to 66.0% in year 5 ($P<0.001$) (Figure 2).

Discussion

The growing population of immunosuppressed patients and increase in medical interventions have resulted in the rise of invasive fungal infections and emergence of novel opportunistic pathogen species.[1,4,5,15] Although epidemiology and antifungal susceptibility data on IC, which account for a large proportion of invasive fungal infections, are well established, knowledge of infections caused by noncandidal yeasts remain limited in China.

Of note, the significance of antifungal resistance is well acknowledged in non-*Candida albicans* species and increasing trend in species distribution from *C. albicans* to non-*C. albicans* species.[1,16,17] However, similar issues in noncandidal yeast species have been relatively understudied, despite the fact that noncandidal yeast species may be less susceptible to antifungal drugs.[1,8,18,19] One difficulty in assigning susceptibility is the absence of CBPs for noncandidal yeast species based on broth microdilution methods,[10,11] with epidemiologic cutoff values (ECVs) only developed for *C. neoformans*.[20] In the CHIF-NET study, CLSI disk diffusion methods were employed, as interpretative criteria have been well studied and verified in the ARTEMIS global surveillance program and provide a less expensive and more flexible antifungal susceptibility testing alternative.[6,10,17] Disk diffusion assays have exhibited good correlation with broth microdilution methods.[21,22]

Of the 844 isolates collected, *C. neoformans* was the most common organism (>75%), predominating in both CNS (>98%) and bloodstream infections (~63%). In comparison, non-*C. neoformans* species, including *C. gattii*, were sporadically discovered (<1%). Although globally *Cryptococcus* spp. cause infections mainly in HIV/AIDS patients,[5] a large proportion of cryptococcal infections occur in non-HIV infected patients in China[23] and are predominantly caused by *C. neoformans* ST5/VNI/α genotype.[24] Although as shown in our previous reports, *Cryptococcus* spp. remained highly susceptible to amphotericin B and 5-flucytosine (>98% of the isolates had wild-type phenotype to these two agents),[24] as azoles are still the mainstay of treatment for

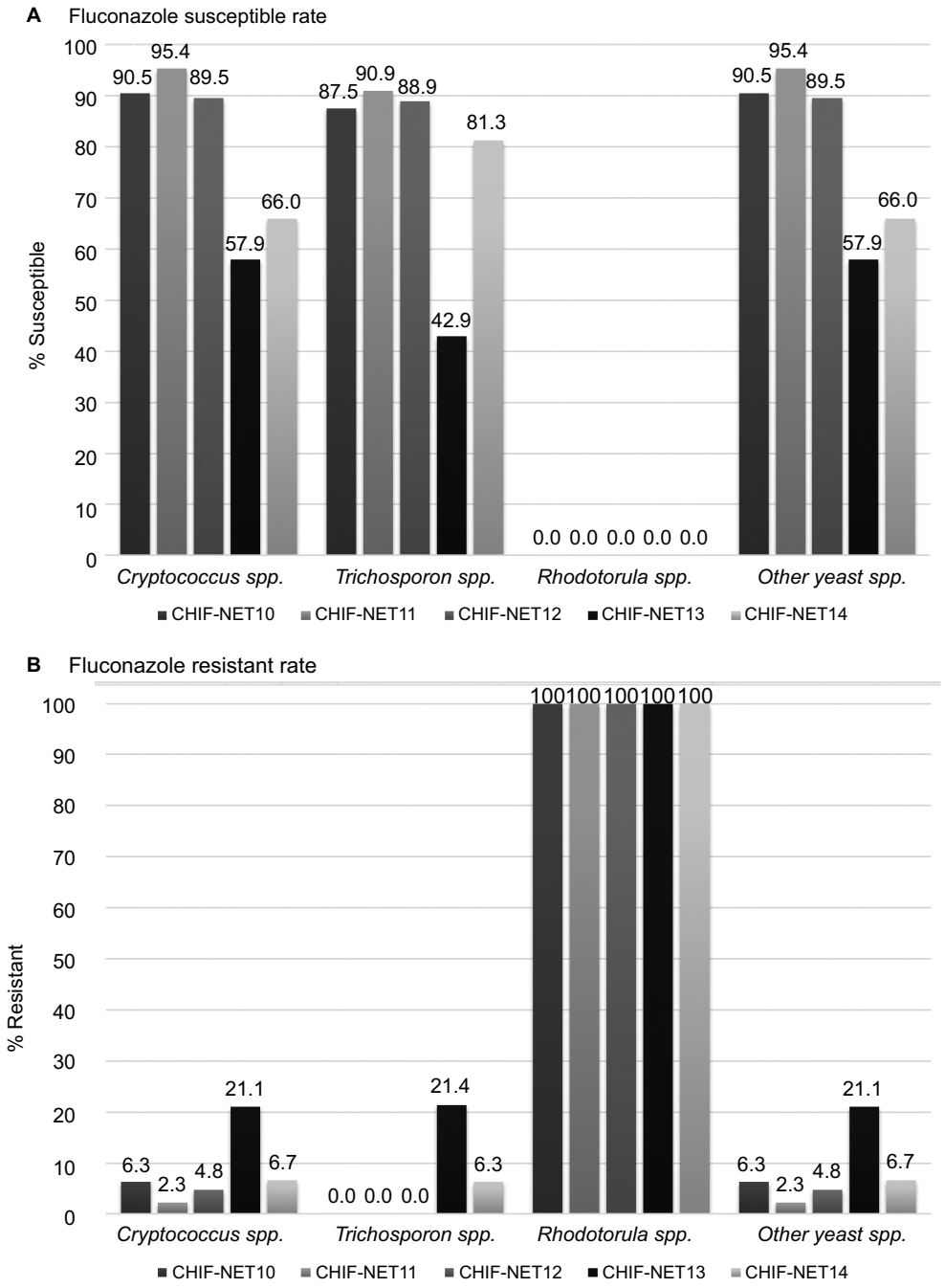

Figure 2 Trends of fluconazole susceptibility over 5 years.
Notes: (**A**) Trends of fluconazole susceptible rate. (**B**) Trends of fluconazole resistant rate.
Abbreviation: CHIF-NET, China Hospital Invasive Fungal Surveillance Net.

cryptococcosis,[25,26] the decreasing trend of susceptibility to fluconazole observed in this study is clinically relevant.

Trichosporon spp. was the third most common noncandidal yeast genus reported in the ARTEMIS global study,[6] and in this study, the second most common. The genus can been found in the environment and is associated with summer-type hypersensitivity pneumonitis mostly reported in Japan.[1,27] Invasive fungal infections caused by *Trichosporon* spp., particularly fungemia, most commonly affect patients with hematological diseases.[1,19] Although the *Trichosporon* spp. was all formerly classified as *Trichosporon beigelii*, molecular assays had reclassified the genus, and *T. asahii* remained most common human pathogenic species.[19,27]

Rhodotorula species are also emerging opportunistic pathogens, with a higher prevalence in the Asia-pacific regions (17%) than in other regions (5%–14%).[6] As found in this study, fungemia is typically the predominant clinical manifestation for *Rhodotorula* infection,[28] although the

species can also cause central nervous system infection.[29] The major risk factors for *Rhodotorula* infection include patient immunosuppression and the presence of a central venous catheter.[28,29] In addition, the genus is notable because of its intrinsic resistance to both echinocandins, fluconazole, and often to other azoles.[1,8,29] Although susceptibility to voriconazole may be variable,[1] in this study, all *Rhodotorula* isolates were cross-resistant to voriconazole. The frequency of *Rhodotorula* spp., over 95% of which were *R. mucilaginosa*, significantly increased over 5 years.

Other noncandidal yeast species, although accounting for less than 4% of the collection, also exhibited decreased fluconazole susceptibility (susceptible rate of around 50% overall), but remaining susceptible to voriconazole. There are no robust guidelines to inform antifungal therapy for these infections. Better diagnostics coupled with surveillance data such as that from the CHIF-NET study could benefit selection of initial antifungal therapy.

As a limitation of this study, CBPs used for CLSI disk diffusion testing were not species-specific adjusted for noncandidal yeast species, as previously noted.[6] In addition, only two azole agents were studied, as the CLSI disk diffusion methodology was only established for fluconazole and voriconazole when the CHIF-NET study was initiated.[6,17] Although many noncandidal yeast species, eg, *Cryptococcus*, *Trichosporon*, and *Rhodotorula* species, are echinocandin-resistant, data on susceptibility profiles to a broad range of antifungal agents remain a guide to antifungal therapy testing for such susceptibility, including the newer azoles, echinocandins, amphotericin, and flucytosine, will be undertaken in the next stage of the CHIF-NET study.

Conclusion

Our surveillance provided accurate epidemiology and robust antifungal susceptibility data on noncandidal yeast causing invasive infections in China, which was useful for guiding the selection of adequate antifungal therapy. In addition, the notable trends of decreased fluconazole susceptibility in noncandidal yeast species warranted further continued surveillance and essential stewardship interventions.

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Author contributions

All authors contributed toward data analysis, drafting, and revising the study and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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