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SUPPLEMENT ARTICLE

Distribution and Antifungal Susceptibility of *Candida* Species Causing Candidemia in China: An Update From the CHIF-NET Study

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Background. Candidemia is the most common, serious fungal infection and *Candida* antifungal resistance is a challenge. We report recent surveillance of candidemia in China.

Methods. The study encompassed 77 Chinese hospitals over 3 years. Identification of *Candida* species was by mass spectrometry and DNA sequencing. Antifungal susceptibility was determined using the Clinical and Laboratory Standards Institute broth microdilution method.

Results. In total, 4010 isolates were collected from candidemia patients. Although *C. albicans* was the most common species, non-*albicans Candida* species accounted for over two-thirds of isolates, predominated *C. parapsilosis* complex (27.1%), *C. tropicalis* (18.7%), and *C. glabrata* complex (12.0%). Most *C. albicans* and *C. parapsilosis* complex isolates were susceptible to all antifungal agents (resistance rate <5%). However, there was a decrease in voriconazole susceptibility to *C. glabrata sensu stricto* over the 3 years and fluconazole resistance rate in *C. tropicalis* tripled. Amongst less common *Candida* species, over one-third of *C. pelliculosa* isolates were coresistant to fluconazole and 5-flucytocine, and >56% of *C. haemulonii* isolates were multidrug resistance.

Conclusions. Non-*albicans Candida* species are the predominant cause of candidemia in China. Azole resistance is notable amongst *C. tropicalis* and *C. glabrata*. Coresistance and multidrug resistance has emerged in less common *Candida* species.

Keywords. candidemia; species distribution; antifungal susceptibility.

It is well recognized that candidemia is a life-threatening disease that is associated with high morbidity, mortality, and extra hospital costs [1, 2]. In addition, the increasing prevalence of non-*albicans Candida* species and growing recognition of antifungal resistance among these species, including emergence of multidrug-resistant *Candida* species such as *C. auris*, has posed further clinical challenges worldwide [2–4]. Timely, appropriate antifungal therapy is essential to improve the outcomes of candidemia patients [5, 6].

However, as current culture-based laboratory techniques cannot meet the clinical demands for rapid and sensitive diagnosis of candidemia, clinicians most often need to initiate empirical antifungal therapy [7, 8]. Selection of such empirical therapy largely relies on epidemiology and antifungal susceptibility data, which varies substantially with geographic region [1, 2, 6]. Therefore, representative regional and local surveillance data are essential.

Until a decade ago, data for invasive fungal infections, including candidemia in China, were mostly limited to single-center reports; in addition, methodology of previous studies, for example the species identification and antifungal susceptibility testing assays, was not well standardized [9]. To overcome these deficiencies, in August 2009, the China Hospital Invasive Fungal Surveillance Net (CHIF-NET) was initiated [9]. In the first 5-year time period (August 2009 to July 2014), useful information on species distribution and fluconazole and voriconazole susceptibility of *Candida* species causing invasive fungal infections in China was provided [10]. Here we report the most recent 3-year (August 2015 to July 2017) surveillance results on candidemia, in comparison with data from previous surveillance years. More importantly, the antifungal agents involved in the surveillance have been expanded from only 2 azoles to 9 commonly used drugs representing 4 drug classes.

MATERIALS AND METHODS

Study Design

The CHIF-NET study is a laboratory-based, multicenter study of invasive yeast infections, including candidemia. Each

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surveillance year began on 1 August of the year and continued to 31 July of the following year [9, 10]. This report includes 3 years of data from CHIF-NET15 to CHIF-NET17. A total of 77 hospitals participated (median bed size 2800; interquartile range, 2200 to 4100); 84.4% were tertiary A teaching hospitals in China.

The study inclusion criteria were as previously described [9]. For each surveillance year, all isolates from eligible patients with invasive fungal infections, including candidemia patients, were forwarded to a central laboratory (Peking Union Medical College Hospital), for confirmatory species identification and antifungal susceptibility testing. The study was approved by the Human Research Ethics Committee of Peking Union Medical College Hospital.

Species Identification

All *Candida* isolates were identified to the species level in the central laboratory by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) using the Vitek MS system (software version V2.0, bioMérieux). For any isolate with no identification or uncertain identification (eg, low confidence value) results by MALDI-TOF MS, and for all isolates identified within *C. parapsilosis* complex (ie, *C. parapsilosis sensu stricto*, *C. metapsilosis,* and *C. orthopsilosis*), *C. glabrata* complex (ie, *C. glabrata sensu stricto*, *C. nivariensis,* and *C. bracarensis*), and *C. haemulonii* complex (ie, *C. haemulonii* and *C. auris*), sequencing of the internal transcribed spacer rDNA region was performed for definitive species identification [9, 10].

Antifungal Susceptibility Testing

Susceptibility to 9 antifungal agents, including 4 azoles (fluconazole, voriconazole, itraconazole, and posaconazole), 3 echinocandins (caspofungin, micafungin, and anidulafungin), 5-flucytosine, and amphotericin B were determined, using in-house prepared 96-well plates following Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods [11]. For 7 species, *C. albicans*, *C. parapsilosis* complex, *C. tropicalis*, *C. glabrata* complex, *C. guilliermondii*, *C. krusei,* and *C. lusitaniae*, species-specific CLSI clinical breakpoints (CBPs) [12], or epidemiological cutoff values (ECVs) where CBPs were not available [13–17], were applied (Supplementary Table 1).

Quality control was performed using *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258 [12].

Statistical Analysis

All comparisons were performed using IBM SPSS software (version 22.0; SPSS Inc.). Comparisons of continuous variables were performed by using the Mann-Whitney test, and comparisons of categorical variables were performed by using a X^2 test or Fisher exact test, as appropriate. A P value of .05 was considered significant.

RESULTS

Candida Species

A total of 4010 nonduplicate *Candida* isolates were collected from separate candidemia patients over the 3 years; 62.5% of these patients were male and 37.5% were female. Twenty-seven *Candida* species were identified (Table 1). Although *C. albicans* remained the most common species, it comprised less than one-third of all isolates (32.9%; Table 1). *C. parapsilosis* complex isolates were the second most common (27.1% isolates) of which 93.5% were *C. parapsilosis sensu stricto* and 6.5% were *C. orthopsilosis* (Table 1). *C. tropicalis* (18.7%) was the third most common species, followed by *C. glabrata* complex (12.0%), *C. guilliermondii* (3.5%), *C. pelliculosa* (2.5%), and *C. krusei* (1.0%) (Table 1). The frequency of the other 17 species was collectively <1% (Table 1). The overall agreement between initial identification results from participating hospitals and confirmative identification results from the central laboratory was 83.7% (3357/4010).

Patient Clinical Services

Isolates from patients from outpatient/emergency departments comprised 5.5% (222/4010) of the collection. Isolates from inpatient wards accounted for 94.5% (3788/4010), including 35.0% from surgical (1326/3788), 33.7% from intensive care units (1276/3788), and 23.4% from medical departments (885/3788), with the remaining from other inpatient wards (7.9%, 301/3788). *C. albicans* was the most common species in all clinical services except for medical departments, where *C. tropicalis* (37.3%, 330/885 isolates) ranked first (Table 2). In comparison, the frequency of *C. tropicalis* was lower in surgical departments (10.8%, 143/1326) and other inpatient wards (10.6%, 32/301; Table 2).

Patient Age Groups

Patient age ranged from 0 to 100 years (median, 59; interquartile range, 42 to 71), and patients ≥66 years of age accounted for 36.3% (1455/4010) of all isolates. There was variation in species with age group. *C. parapsilosis* complex was most common in patients 0–17 years of age (31.8%, 112/352), but the prevalence of uncommon *Candida* species was also high (17.9%, 63/352) in this age group (Table 2). In comparison, *C. tropicalis* was the most common species in patients aged 18–45 years (29.1%, 224/771; Table 2). In other age groups, *C. albicans* dominated but the frequency of *C. glabrata* complex was slightly higher in older patients (aged 66–79 years, 14.0%, 137/976; and >80 years, 15.7%, 75/479) compared to the overall average (11.9%, 497/4010; $P > .05$; Table 2).

In Vitro Susceptibility to Azoles

Generally, *C. albicans* and *C. parapsilosis* complex isolates were susceptible or had wild-type (WT) minimum inhibitory concentrations (MICs) to all 4 azoles (resistance or

Table 1. Distribution of *Candida* Species Causing Candidemia From CHIF-NET15 to CHIF-NET17

Species	No. of Isolates (%)			
	Total CHIF-NET15-17	CHIF-NET15	CHIF-NET16	CHIF-NET17
Total	4010 (100)	1449 (100)	1270 (100)	1291 (100)
C. albicans	1318 (32.9)	488 (33.7)	438 (34.5)	392 (30.4)
C. parapsilosis complex	1085 (27.1)	354 (24.4)	381 (30.0)	350 (27.1)
C. parapsilosis sensu stricto	1015 (25.3)	347 (23.9)	352 (27.7)	316 (24.5)
C. orthopsilosis	70 (1.8)	7 (0.5)	29 (2.3)	34 (2.6)
C. tropicalis	750 (18.7)	313 (21.6)	203 (16.0)	234 (18.1)
C. glabrata complex	479 (12.0)	177 (12.2)	138 (10.9)	164 (12.7)
C. glabrata sensu stricto	474 (11.8)	175 (12.1)	137 (10.8)	162 (12.5)
C. nivariensis	3 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
C. bracarensis	2 (0.1)	1 (0.1)	0	1 (0.1)
C. guilliermondii	142 (3.5)	23 (1.6)	25 (2.0)	94 (7.3)
C. pelliculosa	102 (2.5)	48 (3.3)	40 (3.1)	14 (1.1)
C. krusei	39 (1.0)	16 (1.1)	7 (0.6)	16 (1.2)
C. lusitaniae	37 (0.9)	12 (0.8)	13 (1.0)	12 (0.9)
C. haemulonii	32 (0.8)	9 (0.6)	12 (0.9)	11 (0.9)
C. norvegensis	5 (0.1)	2 (0.1)	1 (0.1)	2 (0.2)
C. lipolytica	3 (0.1)	1 (0.1)	2 (0.2)	0 (0)
C. catenulata	2 (0.1)	0 (0)	2 (0.2)	0 (0)
C. fabianii	2 (0.1)	0 (0)	2 (0.2)	0 (0)
C. boidinii	2 (0.1)	2 (0.1)	0 (0)	0 (0)
C. famata	2 (0.1)	1 (0.1)	1 (0.1)	0 (0)
C. aaseri	2 (0.1)	0 (0)	2 (0.2)	0 (0)
C. intermedia	1 (<0.1)	1 (0.1)	0 (0)	0 (0)
C. quercitrusa	1 (<0.1)	0 (0)	1 (0.1)	0 (0)
C. ciferrii	1 (<0.1)	0 (0)	1 (0.1)	0 (0)
C. kefyr	1 (<0.1)	1 (0.1)	0 (0)	0 (0)
C. rugosa	1 (<0.1)	0 (0)	0 (0)	1 (0.1)
C. fermentati	1 (<0.1)	0 (0)	1 (0.1)	0 (0)
C. utilis	1 (<0.1)	1 (0.1)	0 (0)	0 (0)
C. infanticola	1 (<0.1)	0 (0)	0 (0)	1 (0.1)

Abbreviation: CHIF-NET, China Hospital Invasive Fungal Surveillance Net.

Table 2. Species Distribution of Candidemia Isolates by Clinical Service and Age Group From CHIF-NET15-17

Characteristic	No. of Isolates (%)				
	C. albicans	*C. parapsilosis* complex	*C. tropicalis*	*C. glabrata* complex	Other *Candida* spp.
Clinical services					
Outpatient/emergency	78 (35.1)	45 (20.3)	45 (20.3)	36 (16.2)	18 (8.1)
Inpatient wards	1240 (32.7)	1040 (27.5)	705 (18.6)	443 (11.7)	360 (9.5)
Intensive care units	472 (37.0)	344 (27.0)	200 (15.7)	174 (13.6)	86 (6.7)
Medical departments	236 (26.7)	178 (20.1)	330 (37.3)	93 (10.5)	48 (5.4)
Surgical departments	432 (32.6)	420 (31.7)	143 (10.8)	147 (11.1)	184 (13.9)
Other wards	100 (33.2)	98 (32.6)	32 (10.6)	29 (9.6)	42 (14.0)
Age group, y					
0–17	109 (31.0)	112 (31.8)	47 (13.4)	21 (6.0)	63 (17.9)
18–45	209 (27.1)	198 (25.7)	224 (29.1)	75 (9.7)	65 (8.4)
46–65	437 (30.5)	397 (27.7)	288 (20.1)	171 (11.9)	139 (9.7)
66–79	385 (39.4)	256 (26.2)	125 (12.8)	137 (14.0)	73 (7.5)
>80	178 (37.2)	122 (25.5)	66 (13.8)	75 (15.7)	38 (7.9)

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nonwild-type [NWT] rates <6%; Table 3). However, compared with *C. parapsilosis sensu stricto*, *C. orthopsilosis* had a significantly higher resistance rate to fluconazole (21.4% vs 3.7%) and voriconazole (10.0% vs 0.7%) ($P < .01$), and exhibited over 3-fold higher 90% minimum inhibitory concentration (MIC_{90}) values (fluconazole 16 mg/L vs 2 mg/L, and voriconazole 0.95 mg/L vs 0.03 mg/L; Table 3). The 15 fluconazole-resistant *C. orthopsilosis* isolates were recovered from 13 hospitals and there was no epidemiological link. Azole susceptibility of *C. tropicalis* was also low, with only 63.5% (476/750) of isolates susceptible to fluconazole and 49.2% (369/750) susceptible to voriconazole (Table 3); furthermore, 26.5% (199/750) of isolates were cross-resistant to fluconazole and voriconazole, and 70.7% (530/750) of *C. tropicalis* isolates had NWT MICs to posaconazole (Table 3). For *C. glabrata* complex, the overall fluconazole resistance rate was 10.2% (49/479) with all fluconazole-resistant strains being *C. glabrata sensu stricto* (10.3%, 49/474; Table 3). Amongst *C. krusei*, >94% of isolates remained susceptible or were of the WT phenotype to voriconazole, itraconazole, and posaconazole (Table 3). *C. lusitaniae* had similar MIC distribution to *C. albicans* (Table 3). However, the remaining non-*albicans Candida* species (those with >5% prevalence), including *C. guilliermondii*, *C. pelliculosa,* and *C. haemulonii*, exhibited reduced azole susceptibility, and their 50% minimum

Table 3. Categorical[a] and MIC[b] Characteristics of Antifungal Susceptibility Data for *Candida* Species Prevalence >5% From CHIF-NET15-17

Species (No. of Isolates)	Characteristic	FLC	VRC	ITC	POS	CAS	MCF	ANF	5FC	AMB
C. albicans (n = 1318)	%S/WT	95.9	95.5	95.3	94.4	99.5	99.3	99.1	98.5	100
	MIC_{50}	0.5	0.004	0.06	0.03	0.03	0.015	0.008	0.03	0.5
	MIC_{90}	1	0.03	0.12	0.06	0.06	0.015	0.12	0.12	1
	GM	0.431	0.007	0.049	0.03	0.035	0.009	0.02	0.046	0.498
C. parapsilosis sensu stricto (n = 1015)	%S/WT	94.8	97.0	99.4	98.6	99.7	99.3	99.8	93.1	99.9
	MIC_{50}	0.5	0.015	0.06	0.03	0.5	1	1	0.03	0.5
	MIC_{90}	2	0.03	0.12	0.06	1	2	2	0.25	1
	GM	0.625	0.01	0.04	0.026	0.402	0.824	0.765	0.078	0.447
C. orthopsilosis (n = 70)	%S/WT	77.1	78.6	98.6	94.3	98.6	98.6	98.6	95.7	98.6
	MIC_{50}	1	0.03	0.12	0.12	0.5	0.5	1	0.03	0.5
	MIC_{90}	16	1	0.25	0.25	0.5	1	1	0.12	1
	GM	1.443	0.052	0.134	0.106	0.393	0.536	0.796	0.058	0.476
C. tropicalis (n = 750)	%S/WT	63.5	49.2	81.9	29.3	98.8	98.8	98.3	99.6	99.9
	MIC_{50}	2	0.25	0.25	0.25	0.03	0.03	0.12	0.03	1
	MIC_{90}	512	16	1	1	0.12	0.06	0.12	0.12	1
	GM	5.766	0.354	0.305	0.299	0.042	0.032	0.068	0.037	0.791
C. glabrata sensu stricto (n = 474)	%S/WT	NA	58.4	96.6	71.7	93.5	96.0	96.8	98.9	99.8
	MIC_{50}	8	0.25	0.5	1	0.06	0.015	0.03	0.03	1
	MIC_{90}	64	1.5	1	2	0.12	0.03	0.12	0.03	1
	GM	9.813	0.302	0.552	0.928	0.06	0.017	0.031	0.033	0.734
C. guilliermondii (n = 142)	%S/WT	81.0	92.3	97.2	88.0	95.8	98.6	93.0	98.6	100
	MIC_{50}	8	0.12	0.5	0.25	1	1	2	0.03	0.5
	MIC_{90}	16	0.5	1	1	2	1	2	0.12	1
	GM	6.298	0.14	0.35	0.284	0.722	0.637	1.379	0.041	0.562
C. pelliculosa (n = 102)	MIC_{50}	4	0.185	0.25	0.5	0.06	0.03	0.008	0.5	0.5
	MIC_{90}	64	1	0.5	2	0.12	0.06	0.03	128	1
	GM	5.279	0.136	0.147	0.321	0.048	0.03	0.011	1.116	0.426
C. krusei (n = 39)	%S/WT	0	94.9	100	94.9	87.2	97.4	100	97.4	100
	MIC_{50}	64	0.25	0.25	0.25	0.25	0.12	0.03	8	0.5
	MIC_{90}	128	0.5	0.5	0.5	0.5	0.25	0.12	16	1
	GM	54.54	0.285	0.207	0.28	0.21	0.118	0.038	6.697	0.689
C. lusitaniae (n = 37)	%S/WT	94.6	100	89.2	100	100	100	100	100	94.6
	MIC_{50}	0.5	0.004	0.06	0.03	0.25	0.06	0.12	0.03	0.5
	MIC_{90}	2	0.03	0.146	0.12	0.5	0.12	0.25	0.048	0.5
	GM	0.625	0.007	0.061	0.026	0.146	0.064	0.119	0.034	0.337
C. haemulonii (n = 32)	MIC_{50}	512	8	1	0.5	0.12	0.12	0.12	128	4
	MIC_{90}	512	16	32	16	0.5	0.5	1	128	8
	GM	94.396	1.786	1.998	0.815	0.104	0.106	0.103	6.208	2.372

Abbreviations: 5FC, 5-flucytosine; AMB, amphotericin B; ANF, anidulafungin; CAS, caspofungin; CHIF-NET, China Hospital Invasive Fungal Surveillance Net; FLC, fluconazole; GM, geometric mean; ITC, itraconazole; MCF, micafungin; NA, not applicable; POS, posaconazole, S, susceptible; VRC, voriconazole; WT, wild type.

[a]For available clinical break points and/or epidemiological cutoff values see Supplementary Table 1.

[b]MIC unit, mg/L.

inhibitory concentration (MIC_{50}), MIC_{90}, and geometric mean MIC, except for itraconazole of *C. pelliculosa*, were 3-fold to 11-fold higher than those of *C. albicans* (Table 3).

Across 7 administrative regions in China, variations in fluconazole resistance were noted amongst the 4 most common *Candida* species (Table 4), but the discrepancies were not significant for *C. albicans* (0.6% to 3.8%, average 2.5%), *C. tropicalis* (23.1% to 37.5%, average 29.7%), and *C. glabrata sensu stricto* (3.1% to 11.4%, average 10.3%) (all $P > .05$). However, geographic variation in fluconazole resistance was significant in *C. parapsilosis sensu stricto*, with the highest observed in the North China region (9.8%) and lowest observed in the South and Southwest region (0%), compared to the average of 3.7% ($P < .01$).

In Vitro Susceptibility to Echinocandins, Amphotericin B, and 5-Flucytosine

All 3 echinocandin agents tested showed good in vitro activity against common *Candida* species, with resistant or NWT rates of <4% (Table 3). *C. parapsilosis sensu stricto* and *C. guilliermondii* isolates had over 3-fold to 8-fold higher MICs than *C. albicans* (Table 3).

Amphotericin B also had good overall activity against common *Candida* species, with NWT rates <2% (Table 3). However, although no CBP or ECV has been established for *C. haemulonii*, 56.2% (18/32) of *C. haemulonii* isolates had amphotericin B MICs of ≥4 mg/L (Table 3), which are considered NWT for other *Candida* species (Supplementary Table 1).

Less than 7% of common *Candida* species were of NWT phenotype to 5-flucytosine (Table 3), whilst, in general, 5-flucytosine MICs of *C. pelliculosa*, *C. krusei,* and *C. haemulonii* were more than 4-fold higher than other species (Table 3).

Coresistance and Multidrug Resistance

We chose fluconazole and micafungin as representative antifungal agents in the azole and echinocandin class, respectively, to analyze antifungal coresistance or multidrug resistance (ie, isolates that were resistant or NWT to at least 2 classes of antifungal agents tested). For species with established ECVs and CBPs, only 20 isolates were coresistant to 2 classes of antifungal agent (<5% for each species; Table 5). No isolate was multidrug resistant.

However, 2 species (*C. haemulonii* and *C. pelliculosa*) currently do not have CPBs or ECVs established, and these 2 species exhibited coresistance and multidrug resistance. For MIC distributions, *C. pelliculosa* isolates had elevated MICs to azoles (fluconazole MIC_{50} 4 mg/L and MIC_{90} 64 mg/L) and 5-flucytosine (MIC_{50} 0.5 mg/L and MIC_{90} 128 mg/L), whilst *C. haemulonii* isolates had even higher MICs to azoles (fluconazole MIC_{50} 128 mg/L and MIC_{90} 128 mg/L), 5-flucytosine (MIC_{50} 128 mg/L and MIC_{90} 128 mg/L), and amphotericin B (MIC_{50} 4 mg/L and MIC_{90} 8 mg/L; Table 3). If CPBs or ECVs of *C. albicans* were used as interpretative criteria, 34.3% (35/102) of *C. pelliculosa* isolates had a coresistant phenotype, with 71.9% (23/32) of *C. haemulonii* isolates resistant to ≥2 classes of antifungal agents, including 56.5% (13/23) that were multidrug resistant (Table 5).

Trends in Fluconazole and Voriconazole Resistance over Time

Trends in fluconazole and voriconazole resistance/NWT rates for common *Candida* species over time are shown in Figure 1. Generally, fluconazole resistance in *C. albicans* slightly increased from CHIF-NET10-14 (0.5%–1.3%) to CHIF-NET15-17 (1.6%–3.4%) but this increase was not statistically significant ($P > .05$; Figure 1). Significant increases in resistance rates were observed in *C. tropicalis* to both fluconazole and voriconazole (frequency of resistance tripled from <10% to >30%), and *C. glabrata* complex to voriconazole (NWT phenotype increased from <20% to approximately 50%; Figure 1). There were no trends in resistance for other species (Figure 1).

DISCUSSION

To date, there have been a number of excellent surveillance programs for clinical pathogenic *Candida* species worldwide, for example the global SENTRY [4, 18] and ARTEMIS DISK study [19], PATH-Alliance surveillance in the United States [20], European Confederation of Medical Mycology-initiated

Table 4. Geographic Variation in Fluconazole Resistance in the 4 Most Common *Candida* Species

	C. albicans		*C. parapsilosis sensu stricto*		*C. tropicalis*		*C. glabrata sensu stricto*	
Geographic Region	No.[a]	% R[b]	No.	% R	No.	% R	No.	% R
East	454	2.6	354	5.4	283	25.4	165	13.3
Middle	167	1.8	132	2.3	124	32.3	58	8.6
North	174	0.6	122	9.8	96	37.5	64	10.9
Northeast	157	3.8	245	1.2	65	23.1	64	3.1
Northwest	83	3.6	22	0.5	33	30.3	27	11.1
South	79	2.5	41	0	57	36.8	35	11.4
Southwest	204	2.9	99	0	92	31.5	61	9.8
Total	1318	2.5	1015	3.7	750	29.7	474	10.3

[a]Number of isolates tested.

[b]Percent of isolates resistant.

Table 5. Number of *Candida* Isolates in Each Species Resistant to 2 Classes of Antifungal Agents Tested

Species	No. Resistant Isolates									Total, No. (%)
	FLC and MCF	FLC and 5FC	FLC and AMB	MCF and AMB	5FC and AMB	FLC, MCF, and 5FC	FLC, MCF, and AMB	FLC, 5FC, and AMB	FLC, MCF, 5FC, and AMB	
Species with available CPBs or ECVs										
C. albicans	1	0	0	0	0	0	0	0	0	1 (0.1)
C. glabrata sensu stricto	2	3	1	0	1	0	0	0	0	7 (1.5)
C. guilliermondii	1	1	0	0	0	0	0	0	0	2 (1.4)
C. orthopsilosis	1	0	1	1	0	0	0	0	0	3 (4.3)
C. parapsilosis sensu stricto	0	3	0	0	0	0	0	0	0	3 (0.3)
C. tropicalis	3	0	0	0	0	0	0	0	0	3 (0.4)
C. krusei	0	1	0	0	0	0	0	0	0	1 (2.6)
Species without available CPBs or ECVs[a]										
C. haemulonii	0	5	5	0	0	1	0	11	1	23 (71.9)
C. pelliculosa	0	33	0	0	0	1	1	0	0	35 (34.3)

Abbreviations: 5FC, 5-flucytosine; AMB, amphotericin B; CPB, clinical break point; ECV, epidemiological cutoff value; FLC, fluconazole; MCF, micafungin.

[a]For *C. haemulonii* and *C. pelliculosa*, we referred to CPBs and ECVs of *C. albicans* (fluconazole ≥8 mg/L, micafungin ≥1 mg/L, 5-flucytosine ≥2 mg/L, and fluconazole ≥4 mg/L) for evaluation of multidrug resistance.

study in Europe [21], and Australian and New Zealand Mycoses Interest Group-initiated surveillance in Australia [22]. Data from China are incorporated into the SENTRY and ARTEMIS studies, but with participation from only a few hospitals [18, 19] the local representativeness of data from this vast country was limited. To extend surveillance, the CHIF-NET study not only covered most administrative regions (30/33 provinces) in mainland China, but also has provided a much-needed longitudinal view in trends of epidemiology and antifungal susceptibility since 2009.

While no significant changes were observed in distribution of the most common *Candida* species in this study, increasing prevalence of non-*albicans Candida* species over time has been noted in other studies, which is generally considered to be associated with reduced antifungal susceptibilities [1, 2, 19, 23]. Non-*albicans Candida* species accounted for >67% of the present collection. As expected, variation in species distribution was noted amongst different clinical services and age groups; for example *C. tropicalis* was predominant in medical departments and young adults. This may be due to differences in virulence of *Candida* species or host susceptibility factors [1]. Nonetheless, in-depth stratified analysis of surveillance data is essential for assisting clinicians in different services to choose empiric antifungal therapy.

Since the first surveillance year (August 2009 to July 2010), the CHIF-NET study has employed DNA sequencing and MALDI-TOF MS methods for identification of all isolates to species level to ensure data accuracy, including for genetically closely related species, for example in *C. parapsilosis* and *C. glabrata* complexes [9, 10]. *C. parapsilosis sensu stricto* was found to be the second most common species (>25%). In addition, large nosocomial outbreaks due to *C. parapsilosis sensu stricto* have been reported in China [24]. This species was well recognized to be association of catheter-related candidemia, and its prevalence has decreased in the United States, which may be the result of good infection control practices [4, 25]. In comparison, *C. orthopsilosis*, although less common (prevalence 1.8%) than *C. parapsilosis sensu stricto*, exhibited higher fluconazole MIC values, in accordance with previous results found globally [26].

C. tropicalis and *C. glabrata sensu stricto* are considered to exhibit moderate to high-level intrinsic azole resistance, with the prevalence and resistance rates varying with geographic region [1, 2, 27]. In the United States, Australia, and several European countries, *C. glabrata* was the most common non-*albicans Candida* species (prevalence >25%), and there were increasing trends in prevalence of the species over time in these regions, with 6%–15% of isolates resistant to fluconazole [4, 22, 23]. Whilst fluconazole resistance of *C. tropicalis* has been rare in the United States (<3%), with 1 study in US hematologic malignancy patients even observing a decrease in incidence of *C. tropicalis* [28], the prevalence of *C. tropicalis* is much higher in Latin America and the Asia-Pacific region (13%–20%) [4, 9, 10]. In these regions, there has been high fluconazole and azole cross-resistance rates (>10%) in, for example, Australia, Brazil, China, and India [4, 22, 27]. Of note, here the CHIF-NET15-17 study identified a sharp increase in fluconazole resistance rates of *C. tropicalis* (from <6% to >20%) in CHIF-NET10-14 [10, 27], with resistance now reaching >30% (this study, in CHIF-NET17). Investigation has shown that the *ERG11* mutation A395T was the major resistance mechanism, which was responsible for >83% of azole resistance in China [29].

Echinocandins are the latest class of antifungal agents introduced for treatment of invasive fungal infections, and these drugs showed good activity against the majority of *Candida* species, including those resistant to azoles and polyenes [2, 4, 6]. As fluconazole resistance has become a major concern worldwide,

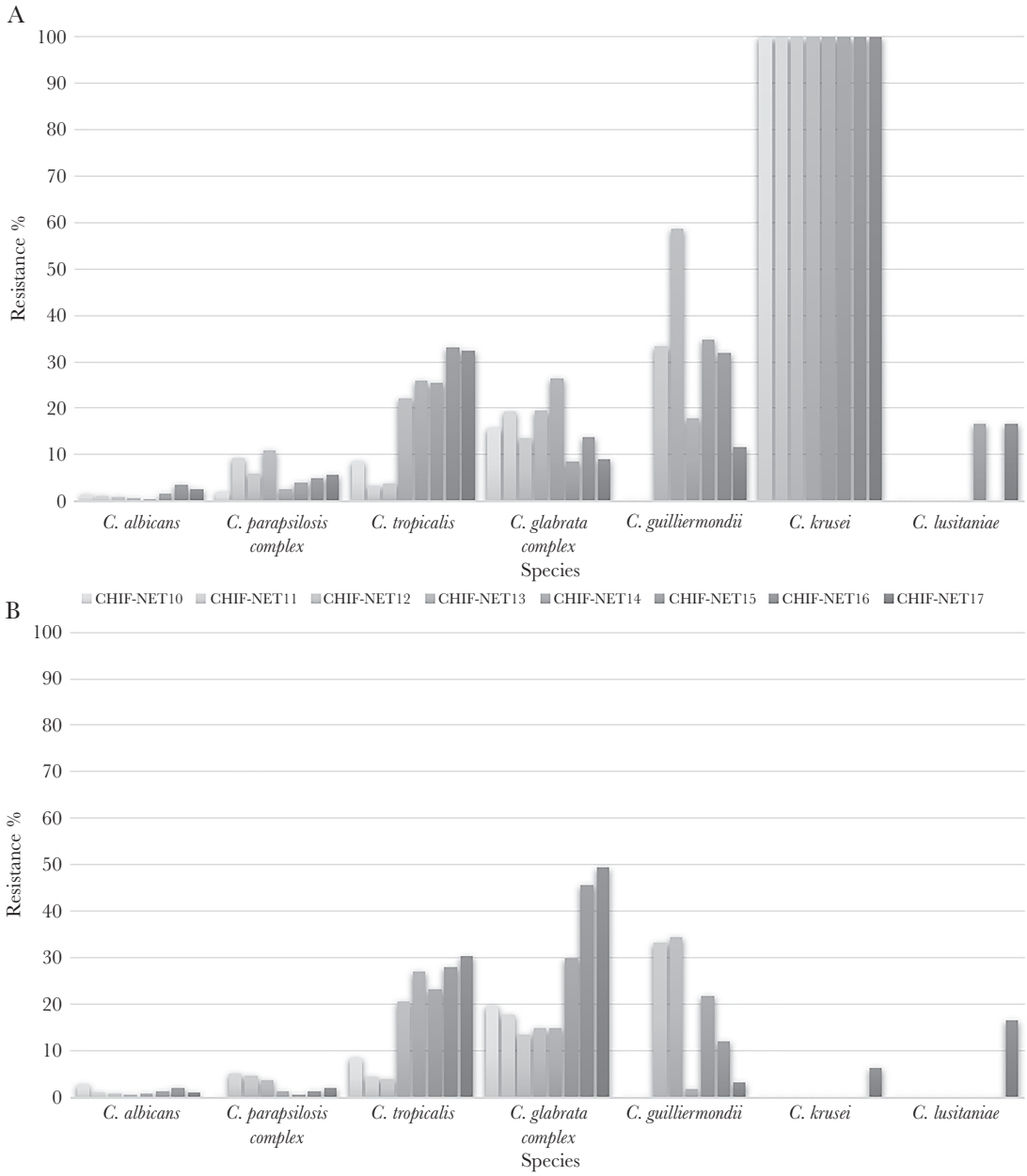

Figure 1. Trends in *Candida* species of fluconazole (*A*) and voriconazole (*B*) resistance or nonwild-type phenotype rates over 8 surveillance years. Abbreviation: CHIF-NET, China Hospital Invasive Fungal Surveillance Net.

echinocandins have been recommended as first-line therapy for invasive candidiasis, including candidemia, by Infectious Diseases Society of America and European Society of Clinical Microbiology and Infectious Diseases guidelines [6, 30]. With expanded using of echinocandins, not surprisingly, rapid emergence of echinocandin resistance has been observed, and up to >10% of echinocandin resistance has been reported amongst *C. glabrata* isolates in the United States [2, 31]. We previously reported the first cases with echinocandin-resistant *C. tropicalis* and *C. glabrata sensu stricto*, including 1 case without a previous echinocandin-exposure history [32]. Until now, the overall echinocandin resistance rates have remained low (1.4% and approximately 2.5% in these 2 species, respectively). In comparison, all *C. parapsilosis* complex and *C. guilliermondii* isolates was intrinsically less susceptible to echinocandin agents with significant elevated MICs, due to the natural presence of *FKS* mutations in these species [2]. However, there have been no clinical failures associated with these relatively high echinocandin MICs [6].

Given the relative few choices of antifungal agents for candidemia, any coresistance or multidrug resistance introduces huge clinical management dilemmas. Recently, the emergence of a novel *Candida* species globally with reduced

susceptibility to azoles, 5-flucytosine, and amphotericin B caused numerous nosocomial transmissions [3]. In China, 18 cases of *C. auris* have been reported and these strains were only resistant to fluconazole [33–35]. However, as noted in the present study, multidrug resistance was observed in a significant proportion (>56%) of *C. haemulonii* isolates, a species that is closely related to *C. auris* [3, 34], including 1 isolate that was pandrug resistant. In addition, *C. pelliculosa* isolates accounted for 1%–3% of candidemia cases in each surveillance year, and over one-third of the isolates coresistant to azoles and 5-flucytocine.

One limitation of the study was that, as CHIF-NET was a laboratory-based study, more detailed demographic and clinical characteristics were not collected, but it is the intention to include the collection of such data prospectively from this time forward. The average turn-around time from isolate collection to data analysis in the central laboratory was approximately 8 to 10 months, with a general report accessible to all participating hospitals. In addition, the central laboratory's testing results for each hospital will be reported back to the corresponding participants annually. We are also testing a web-based CHIF-NET data collection, presentation, and feedback system (http://chifnet.com) to improve data exchange and connectivity and reduce report turn-around time. The primary immediate and short-term goal for the CHIF-NET program is to further adapt the surveillance system to more effectively guide antifungal treatment and enhance national- to hospital-level antifungal stewardship efforts.

In conclusion, our study has provided important updated information at national level in China on species distribution and antifungal susceptibility of *Candida* species causing candidemia. Non-*albicans Candida* species have become predominant cause of candidemia, and azole resistance is notable amongst *C. tropicalis* and *C. glabrata sensu stricto* isolates. While overall resistance to echinocandins, 5-flucytocine, and amphotericin B remains rare, coresistance and multidrug resistance have emerged in some less common species such as *C. pelliculosa* and *C. haemulonii*. Continued surveillance, especially of national antifungal susceptibility trends, are warranted.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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