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Results from the ARTEMIS DISK Global Antifungal Surveillance Study, 1997 to 2007: 10.5-Year Analysis of Susceptibilities of Noncandidal Yeast Species to Fluconazole and Voriconazole Determined by CLSI Standardized Disk Diffusion Testing▽

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Fluconazole in vitro susceptibility test results determined by the CLSI M44-A disk diffusion method for 11,240 isolates of noncandidal yeasts were collected from 134 study sites in 40 countries from June 1997 through December 2007. Data were collected for 8,717 yeast isolates tested with voriconazole from 2001 through 2007. A total of 22 different species/organism groups were isolated, of which *Cryptococcus neoformans* was the most common (31.2% of all isolates). Overall, *Cryptococcus* (32.9%), *Saccharomyces* (11.7%), *Trichosporon* (10.6%), and *Rhodotorula* (4.1%) were the most commonly identified genera. The overall percentages of isolates in each category (susceptible, susceptible dose dependent, and resistant) were 78.0%, 9.5%, and 12.5% and 92.7%, 2.3%, and 5.0% for fluconazole and voriconazole, respectively. Less than 30% of fluconazole-resistant isolates of *Cryptococcus* spp., *Cryptococcus albidus*, *Cryptococcus laurentii*, *Trichosporon beigelii*/*Trichosporon cutaneum*, *Rhodotorula* spp., *Rhodotorula rubra*/*Rhodotorula mucilaginosa*, and *Rhodotorula glutinis* remained susceptible to voriconazole. Emerging resistance to fluconazole was documented among isolates of *C. neoformans* from the Asia-Pacific, Africa/Middle East, and Latin American regions but not among isolates from Europe or North America. This survey documents the continuing broad spectrum of activity of voriconazole against opportunistic yeast pathogens but identifies several of the less common species with decreased azole susceptibility. These organisms may pose a future threat to optimal antifungal therapy and emphasize the importance of prompt and accurate species identification.

Although the majority of infections caused by yeasts are due to *Candida* (46, 54, 55, 57), there are other yeast genera that may be considered to be "true pathogens" (i.e., *Cryptococcus neoformans*) or opportunists (e.g., *Saccharomyces*, *Trichosporon*, and *Rhodotorula*) that have taken advantage of immunocompromising conditions, indwelling devices, and broad-spectrum antimicrobial use to colonize and infect at-risk patients (6, 7, 20, 26, 33, 39, 46, 55–57, 61, 62). Life-threatening infections caused by these less common fungi pose difficult management issues (1, 7, 55, 61, 62).

Our knowledge of the epidemiology and antifungal susceptibilities of both *Candida* and *C. neoformans* has been enhanced through national, regional, and global surveillance (4, 7, 8, 10, 26, 27, 40, 54, 56, 57, 66); however, the same cannot be said for the other opportunistic yeast pathogens (46, 55). Among the few surveillance programs that have monitored infection and resistance associated with noncandidal yeasts (15, 21, 56–58), only the ARTEMIS Global Antifungal Surveillance Program has tracked this disparate group of organisms in a program that is both longitudinal and global in scope (29, 51, 56).

The ARTEMIS program employs standardized Clinical Laboratory Standards Institute (CLSI) methods used for "routine" testing of fluconazole and voriconazole in participating laboratories (disk diffusion), uses electronic data capture and storage in a central database, and conducts external validation of the data generated by the participating laboratories (29, 37, 48, 49, 56). Although there is no standardized method for testing most of these fungi, the vast majority grow well on the supplemented Mueller-Hinton agar plates used in the study, and the zone diameters are easily determined (47, 56). For the purposes of the study, we utilized the interpretive breakpoints for fluconazole and voriconazole that have been established for *Candida* (52, 53), and we recognize that they may need to be adjusted for noncandidal yeasts in the future.

MATERIALS AND METHODS

Organisms and test sites. A total of 11,240 isolates of noncandidal yeasts obtained from 134 different medical centers in the Asia-Pacific region (28 sites), Latin America (16 sites), Europe (66 sites), the Africa/Middle East region (11

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TABLE 1. Species distribution of non-*Candida* yeast isolates over 10.5 years[a]

Organism	1997–2000		2001–2004		2005–2007		1997–2007	
	No. of isolates tested	% of total isolates tested	No. of isolates tested	% of total isolates tested	No. of isolates tested	% of total isolates tested	No. of isolates tested	% of total isolates tested
C. neoformans	688	28.1	1,812	35.1	1,012	27.8	3,512	31.2
C. gattii			26	0.5	6	0.2	32	0.3
C. laurentii	1	<0.1	31	0.6	24	0.7	56	0.5
C. albidus	2	<0.1	15	0.3	8	0.2	25	0.2
Cryptococcus spp.			33	0.6	35	1.0	68	0.6
Saccharomyces spp.	189	7.7	33	0.6	19	0.5	241	2.1
S. cerevisiae	58	2.4	552	10.7	470	12.9	1,080	9.6
Trichosporon spp.	211	8.6	375	7.3	169	4.6	755	6.7
T. asahii	13	0.5	15	0.3	149	4.1	177	1.6
T. beigelii/*T. cutaneum*	25	1.0	101	2.0	45	1.2	171	1.5
T. mucoides	1	<0.1	37	0.7	31	0.9	69	0.6
T. inkin	2	<0.1	7	0.1	10	0.3	19	0.2
T. ovoides			2	<0.1	3	<0.1	5	<0.1
Rhodotorula spp.	78	3.2	166	3.2	116	3.2	360	3.2
R. rubra/*R. mucilaginosa*	3	0.1	44	0.9	17	0.5	64	0.6
R. glutinis			20	0.4	17	0.5	37	0.3
R. minuta					1	<0.1	1	<0.1
Blastoschizomyces capitatus	1	<0.1	70	1.4	38	1.0	109	1.0
Pichia spp.	7	0.3	81	1.6	46	1.2	134	1.2
Hansenula spp.	10	0.4	14	0.3	4	0.1	28	0.2
Debaromyces spp.			1	<0.1	2	<0.1	3	<0.1
Other yeast	1,157	47.3	1,723	33.4	1,414	38.9	4,294	38.2
Total	2,446	100.0	5,158	100.0	3,636	100.0	11,240	100.0

[a] Includes all specimen types and all locations in hospitals from 134 institutions, 1997 to 2007.

sites), and North America (13 sites) were collected and tested against fluconazole between June 1997 and December 2007. In addition, a total of 8,717 isolates (133 institutions in 39 countries) were tested against voriconazole between 2001 and 2007. Approximately 80% of the study sites participated in the survey for at least 3 years (average duration of participation, 4.5 years; range, 1 to 10.5 years).

All yeasts considered pathogens from all body sites (e.g., blood, normally sterile body fluids, deep tissue, genital tract, gastrointestinal tract, respiratory tract, and skin and soft tissue) and isolates from patients in all in-hospital and outpatient locations during the study period were tested. Yeasts considered by the local site investigator to be colonizers, that is, not associated with an obvious pathology, were excluded, as were duplicate isolates from a given patient (the same species and the same susceptible-resistant biotype profile within any 7-day period). The identification of isolates was performed locally in accordance with each sites' routine methods. The majority (76%) of the study sites employed one or more commercially available yeast identification systems (API, Vitek, and/or MicroScan) supplemented by classical biochemical and morphological methods, and the remainder used the classical methods alone (28, 30).

Susceptibility test method. Disk diffusion testing of fluconazole and voriconazole was performed as described by Pfaller et al. (51, 56) and in CLSI document M44-A (14). Agar plates (90-, 100-, or 150-mm diameter) containing Mueller-Hinton agar (obtained locally at all sites) supplemented with 2% glucose and 0.5 μg of methylene blue per ml at a depth of 4.0 mm were used. The agar surface was inoculated by using a swab dipped in a cell suspension adjusted to the turbidity of 0.5 McFarland standard. Fluconazole (25 μg) and voriconazole (1 μg) disks (Becton Dickinson, Sparks, MD) were placed onto the surfaces of the inoculated plates, and the plates were incubated in air at 35 to 37°C and read at 18 to 24 h. Slowly growing isolates, primarily members of the genus *Cryptococcus*, were read after 48 h of incubation. Zone diameter endpoints were read at 80% growth inhibition by using a Biomic image analysis plate reader system (Giles Scientific, Santa Barbara, CA) (29, 51, 56).

The interpretive criteria for the fluconazole and voriconazole disk diffusion tests were those described by Pfaller et al. (52, 53) and published in CLSI document M44-S2 (14a): susceptible (S), zone diameters of ≥19 mm (fluconazole) and ≥17 mm (voriconazole); susceptible dose dependent (SDD), zone diameters of 15 to 18 mm (fluconazole) and 14 to 16 mm (voriconazole); and resistant (R), zone diameters of ≤14 mm (fluconazole) and ≤13 mm (voriconazole).

QC. Quality control (QC) was performed with each test run in accordance with CLSI document M44-A (14) by using *Candida albicans* ATCC 90029 and *Candida parapsilosis* ATCC 22019. A total of 15,413 and 14,987 QC results were obtained for fluconazole and voriconazole, respectively, more than 94% of which were within the acceptable limits.

Analysis of results. All yeast disk test results were read by electronic image analysis and interpreted and recorded with the Biomic plate reader system (Giles Scientific, Inc.). Test results were sent by e-mail to Giles Scientific for analysis. The zone diameter, susceptibility category (S, SDD, or R), and QC test results were all recorded electronically. Patient and doctor names, duplicate test results (same patient, same species, and same biotype results), and uncontrolled results were automatically eliminated by the Biomic system prior to analysis.

RESULTS

Isolation rates by species. A total of 11,240 noncandidal yeast isolates were collected and tested at 134 study sites between June 1997 and December 2007 (Table 1). A total of 22 different species/organism groups were isolated, of which *C. neoformans* was the most common (31.2%). Although the proportion of isolates representing *C. neoformans* increased from 28.1% (1997 to 2000) to 35.1% (2001 to 2004), it decreased to 27.8% during the last 3 years of the study (2005 to 2007). Overall, *Cryptococcus* (32.9% of 11,240 isolates), *Saccharomyces* (11.7%), *Trichosporon* (10.6%), and *Rhodotorula* (4.1%) were the most commonly identified genera.

Fluconazole and voriconazole susceptibilities of noncandidal yeasts and yeast-like fungi. Table 2 summarizes the in vitro susceptibilities of 8,794 and 8,717 isolates of noncandidal yeasts to fluconazole and voriconazole, respectively, as determined by CLSI disk diffusion testing (14). These isolates were obtained from 133 institutions in 39 countries during the pe-

TABLE 2. In vitro susceptibilities of non-*Candida* yeasts to fluconazole and voriconazole as determined by CLSI disk diffusion testing[a]

Species	Fluconazole[b]			Voriconazole[b]		
	No. of isolates tested	% S	% R	No. of isolates tested	% S	% R
C. neoformans	2,824	77.1	11.2	2,804	97.0	1.7
C. gattii	32	62.5	9.4	32	96.9	3.1
C. laurentii	55	70.9	16.4	54	87.0	9.3
C. albidus	23	47.8	43.5	24	62.5	25.0
Cryptococcus spp.	68	80.9	11.8	68	91.2	8.8
Saccharomyces spp.	52	92.3	1.9	48	97.9	2.1
S. cerevisiae	1,022	89.9	6.0	1,010	95.8	2.7
Trichosporon spp.	544	85.1	8.6	523	95.6	2.3
T. asahii	164	76.2	14.0	164	92.1	5.5
T. beigelii/*T. cutaneum*	146	78.8	11.6	144	85.4	11.1
T. mucoides	68	94.1	0.0	68	98.5	0.0
T. inkin	17	94.1	5.9	17	100.0	0.0
T. ovoides	5	100.0	0.0	5	100.0	0.0
Rhodotorula spp.	283	44.0	50.4	282	54.1	39.5
R. rubra/*R. mucilaginosa*	61	14.8	82.0	61	23.0	68.9
R. glutinis	37	35.1	62.2	37	54.1	45.9
Blastoschizomyces capitatus	108	81.5	12.0	108	92.6	2.8
Pichia spp.	127	81.1	14.2	125	99.2	0.0
Hansenula spp.	18	76.5	5.9	18	94.1	5.9
Debaromyces spp.	3	100.0	0.0	3	100.0	0.0
Other yeasts NOS[c]	3,137	83.9	10.2	3,122	94.4	3.9

[a] The isolates were obtained from 133 institutions from 2001 to 2007.
[b] Fluconazole and voriconazole disk diffusion testing was performed in accordance with CLSI document M44-A (14). The interpretive breakpoints (zone diameters) were as follows: S, >19 mm (fluconazole) and >17 mm (voriconazole); R, <14 mm (fluconazole) and <13 mm (voriconazole).
[c] Yeast species, not otherwise specified (NOS).

riod from 2001 through 2007. The overall percentages of isolates in each category (S, SDD, and R) were 78.0%, 9.5%, and 12.5% and 92.7%, 2.3%, and 5.0% for fluconazole and voriconazole, respectively. By comparison, the overall results for *Candida* spp. tested during the same period were 90.2%, 3.6%, and 6.2% and 95.0%, 2.0%, and 3.0% for fluconazole and voriconazole, respectively (data not shown), emphasizing the decreased coverage of the noncandidal yeasts by fluconazole and the very broad spectrum of voriconazole activity for both *Candida* and noncandidal yeasts.

Fluconazole was most active (>90% S) against *Saccharomyces* spp. (92.3%), *Trichosporon mucoides* (94.1%), *Trichosporon inkin* (94.1%), *Trichosporon ovoides* (100.0%), and *Debaromyces* spp. (100.0%). Decreased susceptibility to fluconazole (<80% S) was seen with *C. neoformans* (77.1%), *Cryptococcus gattii* (62.5%), *Cryptococcus laurentii* (70.9%), *Cryptococcus albidus* (47.8%), *Rhodotorula* spp. (44.0%), *Rhodotorula rubra*/*Rhodotorula mucilaginosa* (14.8%), *Rhodotorula glutinis* (35.1%), *Trichosporon asahii* (76.2%), *Trichosporon beigelii*/*Trichosporon cutaneum* (78.8%), and *Hansenula* spp. (76.5%). Overall, with the exception of species of *Trichosporon* that typically cause more superficial infections (*T. inkin*, *T. mucoides*, and *T. ovoides*), the noncandidal yeasts identified in this survey exhibited decreased susceptibility to fluconazole on the order of that typically encountered with fluconazole-resistant species of *Candida*, such as *Candida glabrata* and *Candida krusei*.

Voriconazole was considerably more active than fluconazole against all of the noncandidal yeasts, although it was not particularly active against *C. albidus* (62.5%) or any of the species of *Rhodotorula* (23.0 to 54.1% S). The apparent innate resistance of *Rhodotorula* spp. to the triazole antifungal agents has been noted previously (18, 23, 65).

A total of 728 isolates comprising 17 different species/genera of noncandidal yeasts were found to be resistant to fluconazole. Whereas voriconazole was active (>90% S) against the rare fluconazole-resistant isolates of *T. inkin* (100.0%), *Pichia* spp. (94.1%), and *Hansenula* sp. (100.0%), activity was quite poor against the remaining species. Although almost 80% of fluconazole-resistant isolates of *C. neoformans* were susceptible to voriconazole, this level of activity was considerably lower than that observed with the fluconazole-susceptible isolates (Table 2). Notably, fewer than 30% of fluconazole-resistant isolates of *C. laurentii* (22.2%), *C. albidus* (27.3%), *Cryptococcus* spp. (28.6%), *T. beigelii*/*T. cutaneum* (17.6%), *Rhodotorula* spp. (17.6%), *R. rubra*/*R. mucilaginosa* (14.3%), and *R. glutinis* (26.1%) remained susceptible to voriconazole. Thus, cross-resistance between fluconazole and voriconazole is even more prominent for the noncandidal yeasts than for *Candida* spp. (56).

Trends in resistance to fluconazole and voriconazole among noncandidal yeasts. A progressive increase in resistance to fluconazole was observed among isolates of *C. neoformans* when results from the time periods 1997 to 2000 (7.3%), 2001 to 2004 (10.9%), and 2005 to 2007 (11.7%) were compared. Resistance to voriconazole remained low (1.7% to 1.8%) among *C. neoformans* isolates over the 7-year period. Overall, the rates of resistance to voriconazole were 5.3% for the years 2001 to 2004 and 4.5% for the years 2005 to 2007 (Table 3).

Geographic variation in the susceptibilities of *C. neoformans*, *S. cerevisiae*, *Trichosporon* spp., and *Rhodotorula* spp. to fluconazole and voriconazole. Table 4 presents the in vitro

TABLE 3. Trends in in vitro resistance to fluconazole and voriconazole among selected non-*Candida* yeast species as determined by CLSI disk diffusion testing over a 10.5-year period[a]

Species	Antifungal agent	1997–2000		2001–2004		2005–2007	
		No. of isolates tested	% R	No. of isolates tested	% R	No. of isolates tested	% R
C. neoformans	Fluconazole	688	7.3	1,812	10.9	1,012	11.7
	Voriconazole			1,795	1.7	1,009	1.8
S. cerevisiae	Fluconazole	58	5.2	552	6.3	470	5.5
	Voriconazole			540	2.8	470	2.6
Trichosporon spp.	Fluconazole	211	5.2	375	9.9	169	5.9
	Voriconazole			354	2.3	169	2.4
T. asahii	Fluconazole	13	0.0	15	13.3	149	14.1
	Voriconazole			15	13.3	92	7.6
T. beigelii/*T. cutaneum*	Fluconazole	25	40.0	101	13.9	45	6.6
	Voriconazole			99	14.1	45	4.4
Rhodotorula spp.	Fluconazole	78	92.3	166	52.4	116	47.4
	Voriconazole			164	42.1	117	35.9
Blastoschizomyces capitatus	Fluconazole	1	0.0	70	14.3	38	7.9
	Voriconazole			70	4.3	38	0.0
Pichia spp.	Fluconazole	7	14.3	81	7.4	46	26.1
	Voriconazole			79	0.0	46	0.0
Total (all non-*Candida* yeasts)	Fluconazole	2,446	14.2	5,158	12.2	3,636	11.9
	Voriconazole			5,084	5.3	3,576	4.5

[a] Includes all specimen types and all hospital locations in 134 institutions. Zone diameters: R, <14 mm for fluconazole, <13 mm for voriconazole. Data for voriconazole are available for 2001 to 2007 only.

susceptibility results for fluconazole and voriconazole tested against the four most common species/genera, *C. neoformans*, *S. cerevisiae*, *Trichosporon* spp., and *Rhodotorula* spp., stratified by geographic region for the period 2001 to 2007. Low rates of resistance to both fluconazole and voriconazole were detected among isolates of *C. neoformans* from Europe and North America. Although voriconazole resistance remained low for *C. neoformans* isolates from the Asia-Pacific, Africa/Middle East, and Latin American regions, resistance to fluconazole exceeded 10% in each of the regions. Notably, fluconazole resistance among *C. neoformans* isolates increased from 5.1% to 22.6% in the Asia-Pacific region, from 4.2% to 7.1% in Europe, and from 7.0% to 33.3% in Africa/Middle East over the 7-year period. Resistance to fluconazole among North American isolates of *C. neoformans* increased from 3.7% in 2001 to 15.4% in 2004 but decreased to 0.0% for the years 2005 to 2007.

DISCUSSION

This report constitutes the largest survey of noncandidal yeasts in the literature to date. The value of such a large database is that now even for these uncommon opportunistic pathogens we can assess trends in resistance to the "workhorse" azoles, fluconazole and voriconazole, over time and by geographic region. Aside from *C. neoformans*, these relatively rare pathogens are unlikely to be familiar to both clinicians and microbiologists, and there are few or no data regarding prognosis or optimal treatment strategies (39, 46, 55, 61, 62). Given how commonly azoles are used (5, 13, 41, 59, 61, 63), it is important to know the activities of the systemically active agents, such as fluconazole and voriconazole, against these organisms (55, 61). Indeed, the overall decreased susceptibility of most of these organisms to azoles may increase the likelihood that they will emerge as pathogens in immunocompro-

TABLE 4. Geographic variation in azole resistance among selected non-*Candida* yeasts[a]

Region	Antifungal agent	*C. neoformans*		*S. cerevisiae*		*Trichosporon* spp.		*Rhodotorula* spp.	
		n	% R	*n*	% R	*n*	% R	*n*	% R
Asia-Pacific	Fluconazole	530	10.8	25	24.0	175	8.6	149	21.5
	Voriconazole	502	3.0	24	12.5	175	4.0	147	15.0
Europe	Fluconazole	470	6.6	902	5.1	415	12.3	103	71.8
	Voriconazole	456	1.5	893	2.4	401	3.5	103	62.1
Africa/Middle East	Fluconazole	869	12.4	16	0.0	37	0.0	16	87.5
	Voriconazole	868	1.8	16	0.0	37	0.0	16	75.0
Latin America	Fluconazole	595	13.6	29	24.1	254	7.1	55	81.2
	Voriconazole	580	2.4	28	10.7	245	5.3	56	62.5
North America	Fluconazole	255	8.1	49	2.0	63	6.3	58	87.9
	Voriconazole	255	1.2	49	0.0	63	4.8	58	63.8

[a] Isolates were obtained from 133 institutions. The interpretive breakpoints (zone diameters) for resistance (R) were as follows: fluconazole, <14 mm; voriconazole, <13 mm.

mised patients who have already been receiving an azole (46, 55, 62). Unfortunately, as with *Candida*, fluconazole-resistant isolates of these noncandidal yeasts also exhibit decreased susceptibility to voriconazole This is further complicated by the fact that the most common genera, *Cryptococcus*, *Trichosporon*, and *Rhodotorula*, are intrinsically resistant to the echinocandins (55), thus limiting the role of this class of agents in treating yeast infections that break through azole coverage.

There are several aspects of this survey that bear emphasis. First of all, although rare, infections due to species of *Cryptococcus*, *Saccharomyces*, *Trichosporon*, and *Rhodotorula* may have increased over the past 10 years. This could be due in part to an increased awareness of the need to isolate and characterize fungi other than the common *Candida* species (28, 46); however, increasingly there are reports of breakthrough infections with these organisms (20, 24, 36, 61).

Perhaps of greatest concern in this survey is the trend of increasing resistance of *C. neoformans* to fluconazole (Table 3). Although it has been suggested that the susceptibility of *C. neoformans* has actually improved (2) or at least remained stable (10, 11, 17, 50, 64) since the introduction of antiretroviral therapy (ART), a number of recent reports suggest that resistance may be a problem in certain geographic regions (3, 6–9, 12, 16, 34, 42, 43, 60). Broad surveys in the United Kingdom (17), United States (10), and globally (50) support the notion that resistance to fluconazole among *C. neoformans* isolates is uncommon and does not appear to be increasing; however, the majority of isolates in those studies came from countries where ART is common and cryptococcal disease is declining (e.g., the United Kingdom and the United States) or include few isolates beyond the year 2000. In contrast, reports from Cambodia (12), Africa (6–9), and Spain (43) indicate that more recent isolates from those areas exhibit decreased susceptibility to fluconazole and other azoles. In one report from Africa (7), 75% of isolates from patients with a clinical relapse following treatment with fluconazole as first-line therapy had reduced susceptibility to fluconazole. Factors underlying this emerging resistance include increased use of fluconazole in low doses as a primary therapy or prophylaxis and the lack of access to amphotericin B, flucytosine, and ART in some areas (5–8, 34). These findings are supported by our data. Resistance to fluconazole among *C. neoformans* isolates is less prominent in Europe and North America than that seen in the Asia-Pacific, Africa/Middle East, and Latin American regions (Table 4). Furthermore, the rates of resistance in those regions have increased steadily from 2001 to 2007. Thus, as mentioned by Lortholary (34) and by Bicanic et al. (6), there is a need for attention to azole resistance and optimal therapy of cryptococcosis that is much more imperative in some parts of the world than in others.

The isolation of *S. cerevisiae* from clinical specimens may reflect the practice of using the organism (subtype *boulardii*) as a probiotic in the treatment of antibiotic-associated diarrhea (19, 38). This practice has been associated with catheter-related fungemia and dissemination of the probiotic strain within a given hospital unit (31). Treatment of *S. cerevisiae* infection should rely on withdrawal of the probiotic regimen, if given; administration of an antifungal with activity against the organism; and removal of indwelling vascular catheters (38).

Although the vast majority of *Trichosporon* infections reported in the literature have been ascribed to *T. beigelii*, molecular taxonomic approaches have demonstrated the existence of numerous species of *Trichosporon* (25, 58). Three species, *T. asahii*, *T. inkin*, and *T. mucoides*, are regularly isolated from clinical specimens (58). Although these three species plus *T. beigelii*/*T. cutaneum* were isolated and identified in this survey, it is notable that sequencing of the intergenic spacer 1 region of the rRNA gene is necessary to confirm species identification of *Trichosporon* (58). Unfortunately this technique is not widely available and was not performed in this study. Although the commercial yeast identification systems Vitek and API 20C AUX (bioMérieux), have been shown to be capable of identifying *T. asahii* and *T. inkin*, they are of little value in identifying other species (58). Correct identification of the various species of *Trichosporon* may be important at the therapeutic level in view of their distinct antifungal susceptibility profiles (Table 2), particularly those of *T. asahii*, which is highly resistant to amphotericin B, in addition to fluconazole and the echinocandins (55, 58). It may be more practical to perform antifungal susceptibility testing on clinical isolates of *Trichosporon*, as opposed to species identification, as an aid in selecting an antifungal agent that exhibits activity against the infecting strain (58).

All of the species encompassed by the genus *Rhodotorula* must be considered to be intrinsically resistant to both the azole and the echinocandin classes of antifungal agents (18, 65). Recently, prophylaxis or treatment with fluconazole has been found to be a risk factor for *Rhodotorula* fungemia, in addition to the presence of a central venous catheter, hyperalimentation, broad-spectrum antibacterials, neutropenia, and surgery (22, 35, 44, 45). *Rhodotorula* fungemia has been associated with a crude mortality of up to 20% (35) and can cause sepsis syndrome and other life-threatening complications (32). Amphotericin B, coupled with catheter removal, is an optimal approach to the management of infections due to *Rhodotorula* spp. (35, 63, 65). Neither fluconazole nor the echinocandins should be used to treat infections due to *Rhodotorula*, and patients receiving these agents are susceptible to developing breakthrough *Rhodotorula* fungemia (35).

As the population of immunocompromised patients has continued to expand, infections due to yeast species that were previously considered to be unusual and/or nonpathogenic are likely to become increasingly common. As can be seen from the listings of noncandidal yeasts in Table 1, the diversity of organisms is considerable and will pose significant challenges. We have highlighted both emerging (e.g., *C. neoformans*) and intrinsic (e.g., *Rhodotorula* sp.) resistance to fluconazole and voriconazole. The fact that such resistance may be more prominent in some regions than others should prompt increased surveillance at the local or national level.

Treatment recommendations for infections with these less common organisms are not standardized, given the relative rarity of their occurrence; however, as such infections become more frequent, additional reports will help clarify the optimal therapeutic regimens. Until that time, identification of the noncandidal yeasts, at least to the genus, if not the species, level, coupled with survey data, such as that of ARTEMIS, will help guide the selection of initial antifungal therapy. Specific antifungal susceptibility testing may help optimize therapy in instances where a suboptimal response is observed to what

would ordinarily be considered adequate therapy. In such cases, the flexibility of the CLSI disk diffusion method may well be an advantage in assessing the antifungal susceptibilities of these "emerging" pathogens.

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