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Results from the ARTEMIS DISK Global Antifungal Surveillance Study, 1997 to 2005: an 8.5-Year Analysis of Susceptibilities of *Candida* Species and Other Yeast Species to Fluconazole and Voriconazole Determined by CLSI Standardized Disk Diffusion Testing▽

M. A. Pfaller,[1]* D. J. Diekema,[1,2] D. L. Gibbs,[3] V. A. Newell,[3] J. F. Meis,[4] I. M. Gould,[5] W. Fu,[6] A. L. Colombo,[7] E. Rodriguez-Noriega,[8] and the Global Antifungal Surveillance Group

Departments of Pathology[1] and Medicine[2], Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City, Iowa; Giles Scientific, Inc., Santa Barbara, California[3]; Department of Medical Microbiology and Infectious Diseases, Canisius Wilhemina Hospital, Nijmegen, The Netherlands[4]; Department of Medical Microbiology, Aberdeen Royal Hospital, Aberdeen, Scotland[5]; Hua Shan Hospital, Shanghai, China[6]; Division of Infectious Diseases, Federal University of Sao Paulo, Sao Paulo, Brazil[7]; and Instituto de Patologia Infecciosa y Experimental, Universidad de Guadalajara, Guadalajara, Mexico[8]

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Fluconazole in vitro susceptibility test results for 205,329 yeasts were collected from 134 study sites in 40 countries from June 1997 through December 2005. Data were collected for 147,776 yeast isolates tested with voriconazole from 2001 through 2005. All investigators tested clinical yeast isolates by the CLSI M44-A disk diffusion method. Test plates were automatically read and results recorded with a BIOMIC image analysis system. Species, drug, zone diameter, susceptibility category, and quality control results were collected quarterly. Duplicate (same patient, same species, and same susceptible-resistant biotype profile during any 7-day period) and uncontrolled test results were not analyzed. Overall, 90.1% of all *Candida* isolates tested were susceptible (S) to fluconazole; however, 10 of the 22 species identified exhibited decreased susceptibility (<75% S) on the order of that seen with the resistant (R) species *C. glabrata* and *C. krusei*. Among 137,487 isolates of *Candida* spp. tested against voriconazole, 94.8% were S and 3.1% were R. Less than 30% of fluconazole-resistant isolates of *C. albicans*, *C. glabrata*, *C. tropicalis*, and *C. rugosa* remained S to voriconazole. The non-*Candida* yeasts (8,821 isolates) were generally less susceptible to fluconazole than *Candida* spp. but, aside from *Rhodotorula* spp., remained susceptible to voriconazole. This survey demonstrates the broad spectrum of these azoles against the most common opportunistic yeast pathogens but identifies several less common yeast species with decreased susceptibility to antifungal agents. These organisms may pose a future threat to optimal antifungal therapy and emphasize the importance of prompt and accurate species identification.

Although the list of opportunistic fungi causing serious, life-threatening infection increases every year (1, 6, 17, 24, 30, 44), without question the single most important cause of opportunistic mycoses worldwide remains *Candida* species (34). Despite fewer infections, the opportunistic yeasts other than *Candida* species, led by *Cryptococcus neoformans*, also cause disastrous infections in the most fragile immunocompromised patients (3, 24, 44).

More than 20 different species of *Candida* have been reported as etiologic agents of invasive candidiasis in humans (8, 24). Although more than 90% of invasive infections due to *Candida* spp. can be attributed to five species, *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*, the list of reported species continues to grow as laboratories are pushed to provide an identification to the species level as an aid in optimizing therapy of candidal infections (20, 31, 32, 34, 41). Likewise, the diverse array of opportunistic yeasts and yeast-like fungi and their variable susceptibilities to both new and established antifungal agents has made the need for prompt identification of noncandidal yeasts from clinical material much more compelling (24, 40, 44). Our understanding of the frequency of occurrence and the antifungal susceptibility of both *Candida* and non-*Candida* yeasts has been enhanced in recent years through the efforts of several large surveillance programs conducted throughout the world (2, 7, 9, 13, 19, 23, 26, 34, 37, 45).

Among the fungal surveillance programs, the ARTEMIS Global Antifungal Surveillance Program is the largest and most comprehensive in that it includes both *Candida* and non-*Candida* yeasts, is both longitudinal (>8 years in duration, 1997-present) and global (134 institutions in 40 countries) in scope, employs standardized in vitro susceptibility testing methods used for "routine" testing in participating laboratories and for "reference" testing in a central reference laboratory, uses electronic data capture and storage in a central database, and conducts external validation of the data generated by the participating laboratories (9, 13, 25–27, 31, 32). In 2005, we reported the results from the ARTEMIS DISK Global Anti-

* Corresponding author. Mailing address: Medical Microbiology Division, C606 GH, Department of Pathology, University of Iowa College of Medicine, Iowa City, IA 52242. Phone: (319) 356-8615. Fax: (319) 356-4916. E-mail: michael-pfaller@uiowa.edu.

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fungal Surveillance Program in which species identification and the fluconazole and voriconazole antifungal susceptibility profiles were determined for 134,715 consecutive clinical isolates of *Candida* and 6,052 isolates of noncandidal yeasts collected from cases of mucosal and invasive fungal infections in 127 medical centers in 39 countries over a 6.5-year period (1997 through 2003) (26). In the present study, we expand the ARTEMIS database to include the time period from June 1997 through December 2005 and a total of 205,329 yeast isolates (196,508 isolates of *Candida* and 8,821 isolates of noncandidal yeasts) from 134 study sites in 40 countries. We provide comparative susceptibility data for fluconazole and voriconazole for 147,766 isolates collected from 2001 to 2005 and include an analysis of resistance rates by year, geographic region, hospital location, and clinical specimen type for selected species.

MATERIALS AND METHODS

Organisms and test sites. A total of 196,508 isolates of *Candida* spp. and 8,821 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 sites), and North America (13 sites) were collected and tested against fluconazole between June 1997 and December 2005. In addition, a total of 147,766 isolates (141,229 isolates of *Candida* spp. and 6,379 other yeasts) from 124 study sites in 35 countries were tested against voriconazole between 2001 and 2005. Approximately 80% of the study sites participated in the survey for 3 or more years (average duration of participation, 4.2 years; range, 1 to 8 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 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 (same species and same susceptible-resistant biotype profile within any 7-day period). The identification of isolates was performed locally in accordance with each site's 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 (8, 9).

Susceptibility test method. Disk diffusion testing of fluconazole and voriconazole was performed as described by Hazen et al. (9) and in CLSI (formerly NCCLS) document M44-A (16). 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 a 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) (9, 25–27).

The interpretive criteria for the fluconazole and voriconazole disk diffusion tests were those of the CLSI (16, 28, 29): 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). The corresponding MIC breakpoints (16, 28, 29) are as follows: S, MICs of ≤8 μg/ml (fluconazole) and ≤1 μg/ml (voriconazole); SDD, MICs of 16 to 32 μg/ml and 2 μg/ml (voriconazole); and R, MICs of ≥64 μg/ml (fluconazole) and ≥4 μg/ml (voriconazole).

QC. Quality control (QC) was performed in accordance with CLSI document M44-A (16) by using *Candida albicans* ATCC 90029 and *C. parapsilosis* ATCC 22019. A total of 14,484 and 10,146 QC results were obtained for fluconazole and voriconazole, respectively, of which more than 99% 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. In the present study, fluconazole and voriconazole S, SDD, and R results for each yeast species were stratified by year of collection, geographic region, clinical specimen type, and hospital location.

RESULTS

Isolation rates by species. A total of 205,329 yeast isolates were collected and tested at 134 study sites between June 1997 and December 2005 (Table 1). *Candida* species accounted for 95.2 to 96.3% of all isolates in each study year (overall, 95.7%). A total of 22 different species of *Candida* were isolated, of which *C. albicans* was the most common (overall, 65.6% of all *Candida* spp.). A decreased rate of isolation of *C. albicans* was noted when the first 3 years of the study (1997 to 2000, 70.9% of all *Candida* spp.) were compared with the subsequent 5-year time period (2001 to 2005, 63.5%), although the rates of isolation over the latter time period did not show a continued declining trend. In contrast, slightly increased rates of isolation of *C. glabrata* (10.2% to 11.4%), *C. tropicalis* (5.4% to 7.5%), and *C. parapsilosis* (4.8% to 6.6%) were noted when the time periods 1997 to 2000 and 2001 to 2005 were compared. Similar to that seen with *C. albicans*, the annual isolation rates for each of these species were relatively stable for the years 2001 to 2005. The rates of isolation of *C. krusei*, *C. guilliermondii*, *C. lusitaniae*, *C. kefyr*, *C. rugosa*, and *C. famata* did not vary significantly over the 8.5-year study period. The rates of isolation of the remaining 12 species remained quite low; however, the increased detection of these species, especially in the last 3 years of the study, is evidence of increased efforts to identify clinical isolates of *Candida* to the species level in recent years.

Among the noncandidal yeasts, *Cryptococcus neoformans* (33% of 8,821 isolates), *Saccharomyces* spp. (11.3%), *Trichosporon* spp. (10.7%), and *Rhodotorula* spp. (4.2%) were the most commonly identified species (Table 1). Unfortunately, 33% of the noncandidal yeast isolates were reported as "other" unidentified yeast species. This indicates a relative shortcoming in the commercial yeast identification systems and/or financial or policy constraints in the clinical laboratories that may need attention in the future.

Fluconazole and voriconazole susceptibilities of *Candida* spp. Table 2 summarizes the in vitro susceptibilities of 141,282 and 137,487 isolates of *Candida* spp. to fluconazole and voriconazole, respectively, as determined by CLSI disk diffusion testing (16). These isolates were obtained from 124 institutions in 35 countries during the period from 2001 through 2005. The percentages of isolates in each category (S, SDD, and R) were 90.1%, 3.6%, and 6.2% and 94.8%, 2.1%, and 3.1% for fluconazole and voriconazole, respectively. Fluconazole was most active (>90% S) against *C. albicans* (97.9% S), *C. tropicalis* (90.4% S), *C. parapsilosis* (93.3% S), *C. lusitaniae* (92.6% S), *C. kefyr* (95.6% S), *C. dubliniensis* (97.6% S), *C. pelliculosa* (90.3% S), *C. pulcherrima* (93.8% S), and *C. intermedia* (100% S). Decreased susceptibility to fluconazole (<75% S) was seen with *C. glabrata* (68.9% S), *C. krusei* (9.2% S), *C. guilliermondii* (73.9% S), *C. rugosa* (43.8% S), *C. inconspicua* (23.4% S), *C.*

TABLE 1. Species distribution of *Candida* and other yeast isolates by year[a]

Organism	1997–2000		2001		2002		2003		2004		2005	
	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	No. of isolates tested	% of total isolates tested	No. of isolates tested	% of total isolates tested
Candida spp.	55,229	95.8	21,804	96.3	24,680	95.3	33,002	95.2	33,406	95.6	28,387	95.9
C. albicans	39,152	67.9	14,268	63.0	15,147	58.5	20,624	59.5	20,988	60.0	18,723	63.2
C. glabrata	5,634	9.8	2,431	10.7	2,635	10.2	3,993	11.5	3,904	11.2	3,189	10.8
C. tropicalis	2,996	5.2	1,634	7.2	1,838	7.1	2,504	7.2	2,520	7.2	2,151	7.3
C. parapsilosis	2,633	4.6	1,501	6.6	1,632	6.3	2,416	7.0	2,234	6.4	1,588	5.4
C. krusei	1,207	2.1	544	2.4	639	2.5	884	2.6	773	2.2	678	2.3
C. guilliermondii	367	0.6	163	0.7	239	0.9	263	0.8	237	0.7	186	0.6
C. lusitaniae	276	0.5	122	0.5	131	0.5	212	0.6	209	0.6	161	0.5
C. kefyr	182	0.3	86	0.4	87	0.3	171	0.5	183	0.5	171	0.6
C. rugosa	35	0.1	151	0.7	150	0.6	117	0.3	51	0.2	33	0.1
C. famata	123	0.2	54	0.2	110	0.4	90	0.3	121	0.4	87	0.3
C. inconspicua	9	0.02	30	0.1	44	0.2	113	0.3	89	0.3	78	0.3
C. norvegensis	11	0.02	32	0.1	18	0.1	42	0.1	43	0.1	36	0.1
C. dubliniensis	1	<0.01	19	0.1	26	0.1	18	0.1	50	0.1	56	0.2
C. lipolytica	7	0.01	14	0.1	14	0.1	25	0.1	27	0.1	17	0.1
C. zeylanoides	4	0.01	19	0.1	5	0.02	13	0.04	13	0.04	7	0.02
C. pelliculosa	1	<0.01	14	0.1	12	0.1	12	0.03	9	0.03	15	0.1
C. sake			1		9	0.03	2	0.01	8	0.02	13	0.04
C. pulcherrima							4	0.01	5	0.01	7	0.02
C. valida							7	0.02	2	0.01	6	0.02
C. intermedia					7	0.03					2	0.01
C. haemulonii					2	0.01	2	0.01	2	0.01	2	0.01
C. humicola							1	<0.01	1	<0.01		
Candida spp. NOS	2,591	4.5	721	3.2	1,935	7.5	1,593	4.6	1,937	5.5	1,181	4.0
Other yeasts	2,442	4.2	849	3.7	1,210	4.7	1,547	4.5	1,548	4.4	1,225	4.1
Cryptococcus neoformans	688	1.2	312	1.4	575	2.2	463	1.3	464	1.3	420	1.4
Trichosporon spp.	252	0.4	134	0.6	118	0.5	139	0.4	147	0.4	151	0.5
Saccharomyces spp.	247	0.4	101	0.4	141	0.5	200	0.6	143	0.4	165	0.6
Rhodotorula spp.	81	0.1	17	0.1	42	0.2	80	0.2	91	0.3	56	0.2
Blastoschizomyes capitatus	1	<0.01	17	0.1	22	0.1	16	0.04	14	0.04	16	0.1
Cryptococcus spp.	3	0.01	17	0.1	12	0.1	43	0.1	28	0.1	29	0.1
Pichia spp.	7	0.01	5	0.02	7	0.03	15	0.04	53	0.2	13	0.04
Hansenula spp.	10	0.02	2	0.01	9	0.03	2	0.01	1	<0.01	1	<0.01
Debaryomyces spp.									1	<0.01	1	<0.01
Other yeasts NOS	1,157	2.0	244	1.1	284	1.1	589	1.7	606	1.7	373	1.3
Total	57,675		22,653		25,890		34,657		34,954		29,612	

[a] Includes all specimen types and all locations in hospitals from 134 institutions in 40 countries.

norvegensis (48.5% S), *C. lipolytica* (64.9% S), *C. zeylanoides* (66.7% S), *C. valida* (20.0% S), and *C. humicola* (50.0% S). Thus, despite the fact that ~90% of all clinical isolates of *Candida* were susceptible to fluconazole, these data demonstrate that 10 of the 22 species identified in this survey exhibit decreased susceptibility on the order of that seen with the well-known resistant species *C. glabrata* and *C. krusei.*

As noted previously (26), voriconazole was more active than fluconazole against most species of *Candida* with the exception of *C. tropicalis* (90.4% S to fluconazole versus 88.5% S to voriconazole), *C. intermedia* (100% S to both), *C. haemulonii* (87.5% S to both), and *C. humicola* (50% S to both). Although voriconazole was more active than fluconazole against *C. rugosa* (64.1% S versus 43.8% S, respectively), *C. lipolytica* (75.0% S versus 64.9% S, respectively), and *C. valida* (75.0% S versus 20.0% S, respectively), these species were considerably less susceptible and more resistant (14.6% to 25.1%) to voriconazole than all other species of *Candida.*

A total of 8,545 isolates encompassing 21 different species of *Candida* were found to be resistant to fluconazole (Table 3). Whereas voriconazole was active (≥75% S) against fluconazole-resistant isolates of *C. krusei* (79.1% S), *C. inconspicua* (83.9% S), *C. norvegensis* (85.7% S), *C. dubliniensis* (75.0% S), *C. sake* (100% S), and *C. pulcherrima* (100% S), activity was quite poor against the remaining 15 species. Notably, less than 30% of fluconazole-resistant isolates of *C. albicans* (28.8% S),

TABLE 2. In vitro susceptibilities of *Candida* spp. 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. albicans	89,750	97.9	1.5	87,191	98.4	1.2
C. glabrata	16,152	68.9	15.8	15,824	82.2	10.1
C. tropicalis	10,647	90.4	4.4	10,306	88.5	5.8
C. parapsilosis	9,371	93.3	3.6	9,041	96.8	1.9
C. krusei	3,518	9.2	77.8	3,448	82.9	7.7
C. guilliermondii	1,088	73.9	10.7	1,056	91.3	5.2
C. lusitaniae	835	92.6	4.7	818	96.6	2.1
C. kefyr	698	95.6	3.4	686	98.3	1.3
C. rugosa	502	43.8	47.8	479	64.1	25.1
C. famata	462	80.1	10.6	446	89.5	5.4
C. inconspicua	354	23.4	53.4	351	90.9	4.8
C. norvegensis	171	48.5	36.8	170	94.1	1.8
C. dubliniensis	169	97.6	2.4	168	99.4	0.6
C. lipolytica	97	64.9	30.9	96	75.0	14.6
C. pelliculosa	62	90.3	4.8	61	96.7	3.3
C. zeylanoides	57	66.7	24.6	55	81.8	7.3
C. sake	33	84.8	9.1	33	97.0	3.0
C. pulcherrima	16	93.8	6.3	17	100.0	0.0
C. valida	15	20.0	66.7	16	75.0	18.8
C. intermedia	9	100.0	0.0	9	100.0	0.0
C. haemulonii	8	87.5	12.5	8	87.5	12.5
C. humicola	2	50.0	50.0	2	50.0	50.0
Candida spp.[c]	7,367	86.8	8.2	7,205	92.9	4.7

[a] Isolates were obtained from 124 institutions.
[b] Fluconazole and voriconazole disk diffusion testing was performed in accordance with CLSI document M44-A (16). 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] *Candida* species not otherwise identified.

TABLE 3. In vitro susceptibilities of fluconazole-resistant isolates of *Candida* spp. to voriconazole as determined by CLSI disk diffusion testing[a]

Species	No. of isolates tested	% S	% SDD	% R
C. albicans	1,289	28.8	8.3	62.9
C. glabrata	2,456	17.3	23.2	59.5
C. tropicalis	457	17.7	13.6	68.7
C. parapsilosis	319	36.7	20.7	42.6
C. krusei	2,674	79.1	11.4	9.4
C. guilliermondii	113	47.8	17.7	34.5
C. lusitaniae	36	52.8	16.7	30.6
C. kefyr	23	65.2	4.3	30.4
C. rugosa	230	26.5	21.7	51.7
C. famata	47	31.9	27.7	40.4
C. inconspicua	186	83.9	8.1	8.1
C. norvegensis	63	85.7	9.5	4.8
C. dubliniensis	4	75.0		25.0
C. lipolytica	30	30.0	30.0	40.0
C. pelliculosa	3	33.3		66.7
C. zeylanoides	13	38.5	30.8	30.8
C. sake	3	100.0		
C. pulcherrima	1	100.0		
C. valida	11	63.6	9.1	27.3
C. haemulonii	1			100.0
C. humicola	1			100.0
Candida spp.[b]	585	36.4	16.1	47.5

[a] Isolates were obtained from 124 institutions. The zone diameters for the voriconazole disk diffusion susceptibility categories were as follows: S, ≥17 mm; SDD, 14 to 16 mm; R, ≤13 mm.
[b] *Candida* species not otherwise identified.

C. glabrata (17.3% S), *C. tropicalis* (17.7% S), and *C. rugosa* (26.5% S) remained susceptible to voriconazole. Cross-resistance between fluconazole and voriconazole is clearly more pronounced for some species of *Candida* than for others, although all are affected to some degree, emphasizing the importance of both species identification and antifungal susceptibility testing in the settings of candidal infection with prior azole exposure (11, 18, 20, 40, 41).

Trends in resistance to fluconazole among *Candida* spp. over an 8.5-year period. There was no consistent trend towards increasing resistance to fluconazole detected among the common species *C. albicans*, *C. glabrata*, or *C. tropicalis* over the 8.5-year time period (Table 4). Likewise, consistently high levels of resistance were seen among *C. glabrata*, *C. krusei*, *C. guilliermondii*, *C. inconspicua*, and *C. norvegensis.* Resistance remained high among *C. rugosa*, *C. famata*, *C. lipolytica*, and *C. zeylanoides* for the years 2001 through 2004 but was ≤6% for all four species in 2005. The reasons for such a decrease in resistance are unclear, and the results are likely spurious due to relatively few isolates of these species being tested in 2005.

A slight increase in resistance was noted among *C. parapsilosis* and *C. lusitaniae* when the time periods 1997 to 2000 and 2001 to 2005 were compared (2.5% versus 3.7% for *C. parapsilosis* and 2.9% versus 4.7% for *C. lusitaniae*). Although the number of isolates was small, both *C. pulcherrima* (25 to 50% R) and *C. valida* (50 to 71.4% R) appear to be newly recognized fluconazole-resistant species over the last 3 years (2003 to 2005).

Trends in resistance to voriconazole among *Candida* spp., 2001 to 2005. Voriconazole has been tested in the ARTEMIS Global Surveillance Program since its introduction into clinical use in 2001 (Table 5). Overall, the rates of resistance by year were 2.6%, 3.1%, 3.5%, 3.3%, and 3.0% for the years 2001 to 2005, respectively. Although increases in resistance to voriconazole were observed for several species between 2001 and 2003 (26), this was not sustained for any species over the next 2 years (Table 5). Thus, resistance to voriconazole among *Candida* spp. is not negligible but no significant trend towards increasing resistance can be identified over the first 5 years of clinical use.

Geographic variation in the susceptibilities of *C. albicans*, *C. glabrata*, and *C. tropicalis* to fluconazole and voriconazole. Table 6 presents the in vitro susceptibility results for fluconazole and voriconazole tested against the three most common species of *Candida*, *C. albicans*, *C. glabrata*, and *C. tropicalis*, stratified by geographic region for the time period from 2001 to 2005. Low rates of resistance to both fluconazole and voriconazole were detected among isolates of *C. albicans* from all regions, although isolates from North America were more resistant than those from other regions.

As noted previously (26), the resistance rates for both fluconazole and voriconazole among isolates of *C. glabrata* varied considerably among the various geographic regions. The lowest rates of resistance to both agents were seen in the Asia-Pacific region and the highest in North America. Although voriconazole was more active than fluconazole against isolates

TABLE 4. Trends in in vitro resistance to fluconazole among *Candida* spp. as determined by CLSI disk diffusion testing over an 8.5-year period[a]

Species	1997–2000		2001		2002		2003		2004		2005	
	No. of isolates tested	% R	No. of isolates tested	% R	No. of isolates tested	% R	No. of isolates tested	% R	No. of isolates tested	% R	No. of isolates tested	% R
C. albicans	39,152	0.9	14,268	1.0	15,147	1.5	20,576	1.4	20,988	1.6	18,723	1.6
C. glabrata	5,634	19.2	2,431	18.3	2,635	14.7	3,993	16.9	3,904	14.3	3,189	15.2
C. tropicalis	2,996	3.6	1,634	3.0	1,838	6.6	2,504	5.0	2,520	3.5	2,151	3.8
C. parapsilosis	2,633	2.5	1,501	4.2	1,632	3.9	2,416	3.1	2,234	3.3	1,588	4.2
C. krusei	1,207	65.8	544	70.4	639	78.9	884	80.2	773	78.1	678	79.2
C. guilliermondii	367	12.5	163	11.7	239	10.5	263	8.0	237	10.1	186	14.5
C. lusitaniae	276	2.9	122	6.6	131	4.6	212	2.4	209	4.8	161	6.2
C. kefyr	182	3.3	86	2.3	87	5.7	171	2.9	183	3.8	171	2.9
C. rugosa	35	34.3	151	30.5	150	66.0	117	61.5	51	41.2	33	6.1
C. famata	123	17.1	54	14.8	110	10.9	90	11.1	121	14.0	87	2.3
C. inconspicua	9	55.6	30	60.0	44	47.7	113	46.9	89	58.4	78	57.7
C. norvegensis	11	54.5	32	43.8	18	55.6	42	26.2	43	32.6	36	38.9
C. dubliniensis	1	0.0	19	0.0	26	0.0	18	11.1	50	2.0	56	1.8
C. lipolytica	7	0.0	14	28.6	14	35.7	25	48.0	27	33.3	17	0.0
C. pelliculosa	1	0.0	14	0.0	12	0.0	12	0.0	9	0.0	15	20.0
C. zeylanoides	4	0.0	19	52.6	5	20.0	13	23.1	13	0.0	7	0.0
C. sake			1	0.0	9	11.1	2	0.0	8	12.5	13	7.7
C. pulcherrima			3	33.3			8	25.0	4	50.0	4	50.0
C. valida							7	71.4	2	50.0	6	66.7
C. intermedia					7	0.0					2	0.0
C. haemulonii					2	0.0	2	0.0	2	0.0	2	50.0
C. humicola							1	100.0	1	0.0		
Candida spp.[b]	2,591	10.5	721	9.6	1,935	5.2	1,593	11.2	1,937	8.3	1,181	7.9

[a] Includes all specimen types and all hospital locations in 134 institutions. Zone diameter, ≤14 mm. Fluconazole disk diffusion testing was performed in accordance with CLSI document M44-A (16).
[b] *Candida* species not otherwise defined.

of *C. glabrata* from all five regions, as resistance to fluconazole increased so did resistance to voriconazole.

The lowest rates of resistance to both azoles among *C. tropicalis* isolates were seen in the Africa/Middle East region. Although the rates of resistance in North America were higher than those in the Africa/Middle East region, the highest rates of resistance to both azoles were seen in the Asia-Pacific region. In contrast to that seen with virtually all other species of *Candida*, *C. tropicalis* isolates were generally more resistant to voriconazole than to fluconazole. This was true in all geographic regions with the exception of the Asia-Pacific and Africa/Middle East regions. At present, we have no mechanistic explanation for this phenomenon, although the differences in resistance rates were generally only 1 to 1.5% in favor of fluconazole.

Variation in the frequency of isolation and the antifungal susceptibility profile of *C. albicans*, *C. glabrata*, and *C. tropicalis* by clinical service. The clinical services reporting the isolation of *C. albicans*, *C. glabrata*, and *C. tropicalis* from patient specimens included the hematology-oncology service, medical and surgical services, intensive care units (ICUs) (medical, surgical, and neonatal), and dermatology, urology, and outpatient services (Table 7). Those isolates from services with only a few isolates and those for which a clinical service was not specified were included in the category "other NOS" (not otherwise specified).

C. albicans was isolated most frequently from hospitalized patients from the medical and ICU services and from outpatients and was the least common from the dermatology and urology services. Resistance to both fluconazole and voriconazole was low across all services, with the lowest resistance rates seen among isolates from the outpatient service.

C. glabrata was isolated most frequently from the medical and ICU services, although the highest proportion of *Candida* isolates that were *C. glabrata* was seen with the urology service (16% of all *Candida* isolates). The lowest total number of *C. glabrata* isolates and the lowest proportion of *Candida* isolates that were *C. glabrata* (4%) were seen with the dermatology service. The rates of resistance to both fluconazole and voriconazole were highest among *C. glabrata* isolates obtained from the hematology-oncology service and lowest among isolates obtained from the urology service.

The largest number of *C. tropicalis* isolates originated from patients hospitalized in the medical and ICU services. This species accounted for a greater proportion of the *Candida* isolates obtained from the ICU (10.5%) than from other services (8%; range, 3.4 to 9.8%). *C. tropicalis* accounted for only 3.4% of all *Candida* isolates from the dermatology service and 4.8% of all isolates from the outpatient service. The lowest rates of resistance to fluconazole and voriconazole were seen among *C. tropicalis* isolates obtained from the outpatient service, followed by those obtained from the hematology-oncology and surgical services. The most resistant isolates came from the urology service.

Variation in the frequency of isolation and the antifungal susceptibility profile of *C. albicans*, *C. glabrata*, and *C. tropicalis* by clinical specimen type. The major specimen types yielding *C. albicans*, *C. glabrata*, and *C. tropicalis* as putative pathogens included blood, normally sterile body fluid (NSBF), urine, respiratory tract, skin and soft tissue, and genital specimens

TABLE 5. Trends in in vitro resistance to voriconazole among *Candida* spp. as determined by CLSI disk diffusion testing over a 5-year period[a]

Species	2001		2002		2003		2004		2005	
	No. of isolates tested	% R	No. of isolates tested	% R	No. of isolates tested	% R	No. of isolates tested	% R	No. of isolates tested	% R
C. albicans	11,980	0.8	15,086	1.1	20,570	1.1	20,939	1.5	18,616	1.5
C. glabrata	2,123	9.8	2,625	8.5	3,991	11.5	3,904	10.4	3,181	9.6
C. tropicalis	1,350	4.7	1,820	8.1	2,490	6.7	2,511	4.9	2,135	4.5
C. parapsilosis	1,205	1.9	1,627	2.3	2,411	1.5	2,221	1.9	1,577	1.9
C. krusei	474	8.0	635	6.1	887	8.1	769	8.3	683	7.9
C. guilliermondii	142	4.2	235	5.5	259	4.6	236	5.1	184	6.5
C. lusitaniae	106	2.8	129	1.6	211	1.9	209	1.4	163	3.1
C. kefyr	75	1.3	85	1.2	171	0.0	183	1.1	172	2.9
C. rugosa	129	3.1	149	37.6	117	37.6	51	29.4	33	3.0
C. famata	39	10.3	110	1.8	90	7.8	120	8.3	87	1.1
C. inconspicua	30	6.7	43	4.7	113	5.3	88	5.7	77	2.6
C. norvegensis	31	0.0	18	0.0	42	2.4	43	4.7	36	0.0
C. dubliniensis	19	0.0	26	0.0	18	0.0	48	2.1	51	0.0
C. lipolytica	13	7.7	14	42.9	25	12.0	27	14.8	17	0.0
C. pelliculosa	14	0.0	12	0.0	12	0.0	9	0.0	14	14.3
C. zeylanoides	17	11.8	5	20.0	13	7.7	13	0.0	7	0.0
C. sake	1	0.0	9	0.0	2	0.0	8	0.0	13	7.7
C. pulcherrima					4	0.0	5	0.0	8	0.0
C. valida					7	0.0	2	50.0	7	28.6
C. intermedia			7	0.0					2	0.0
C. haemulonii			2	0.0	2	0.0	2	0.0	2	50.0
C. humicola					1	100.0	1	0.0		
Candida spp.[b]	572	4.0	1,935	2.9	1,591	7.3	1,924	4.5	1,183	4.9

[a] Isolates were obtained from 124 institutions. Zone diameter, ≤13 mm. Voriconazole disk diffusion testing was performed in accordance with CLSI document M44-A (16).
[b] *Candida* species not otherwise defined.

(Table 8). Those isolates from uncommon specimen types and those for which a specimen type was not recorded were grouped under "miscellaneous NOS."

C. albicans constituted more than 70% of the *Candida* spp. isolated from respiratory (71%) and genital (79%) tract specimens but accounted for only 43% of *Candida* sp. isolates obtained from blood cultures. There was very little variation in the rates of resistance of *C. albicans* to either fluconazole or voriconazole among the different specimen types. Isolates from genital specimens had the lowest frequency of resistance to both agents.

C. glabrata accounted for 14% of all *Candida* spp. isolated from blood and NSBF and for 19% of those isolated from urine but for less than 10% of isolates from other sites of infection. The resistance rates to fluconazole and voriconazole were highest for isolates from skin and soft tissue specimens and did not vary appreciably across the other specimen types.

C. tropicalis accounted for 12% of all bloodstream isolates of

TABLE 6. Geographic variation in the in vitro susceptibilities of *C. albicans, C. glabrata*, and *C. tropicalis* to fluconazole and voriconazole[a]

Region	Antifungal agent	*C. albicans*		*C. glabrata*		*C. tropicalis*	
		No. of isolates tested	% R	No. of isolates tested	% R	No. of isolates tested	% R
Asia-Pacific	Fluconazole	18,125	0.9	3,368	13.5	3,120	8.1
	Voriconazole	17,298	0.9	3,259	7.7	2,989	4.7
Europe	Fluconazole	52,127	1.2	8,642	16.0	3,930	2.6
	Voriconazole	50,926	1.1	8,492	9.9	3,817	3.5
Africa/Middle East	Fluconazole	4,566	0.6	564	19.1	350	2.9
	Voriconazole	4,529	0.3	541	9.1	348	2.6
Latin America	Fluconazole	10,288	2.4	1,472	14.0	2,525	3.0
	Voriconazole	9,830	1.9	1,434	9.6	2,423	4.4
North America	Fluconazole	4,644	5.1	2,106	20.5	740	3.6
	Voriconazole	4,608	3.7	2,098	15.3	729	4.7

[a] Isolates were obtained from 124 institutions. Fluconazole and voriconazole disk diffusion testing was performed in accordance with CLSI document M44-A (16). The interpretive breakpoints (zone diameters) for resistance were as follows: fluconazole, ≤14 mm; voriconazole, ≤13 mm.

TABLE 7. Susceptibilities of *C. albicans, C. glabrata*, and *C. tropicalis* to fluconazole and voriconazole by clinical service[a]

Clinical service (total no. of isolates)	Antifungal agent	*C. albicans*		*C. glabrata*		*C. tropicalis*	
		No. of isolates tested	% R	No. of isolates tested	% R	No. of isolates tested	% R
Hematology-oncology (8,432)	Fluconazole	5,154	2.2	1,089	22.0	718	3.5
	Voriconazole	5,062	2.0	1,069	15.7	693	4.5
Medical (33,681)	Fluconazole	20,958	1.4	3,637	15.2	3,193	4.2
	Voriconazole	20,409	1.3	3,574	9.8	3,098	6.0
Surgical (8,869)	Fluconazole	5,359	1.5	1,189	12.4	868	3.5
	Voriconazole	5,235	1.4	1,170	7.9	831	4.5
ICU (18,691)	Fluconazole	11,340	1.4	2,389	15.2	1,962	3.7
	Voriconazole	11,054	1.2	2,330	10.4	1,919	7.0
Dermatology (2,519)	Fluconazole	1,334	2.4	109	16.5	86	3.5
	Voriconazole	1,313	1.6	106	8.5	79	5.1
Urology (1,293)	Fluconazole	775	1.9	212	13.2	124	6.5
	Voriconazole	759	2.0	210	4.8	122	7.4
Outpatient (11,621)	Fluconazole	7,690	1.2	901	19.2	559	2.5
	Voriconazole	7,592	0.8	894	12.2	550	2.4
Other NOS (38,649)	Fluconazole	22,710	2.0	5,048	15.8	2,807	5.8
	Voriconazole	21,812	1.4	4,947	10.2	2,696	7.2

[a] Isolates were obtained from 124 institutions. Disk diffusion testing was performed in accordance with CLSI document M44-A (16). The interpretive breakpoints (zone diameters) for resistance were as follows: fluconazole, ≤14 mm; voriconazole, ≤13 mm.

Candida and for 14% of all urinary tract isolates but was less common (<10%) as an agent of candidiasis among other specimen types. The rates of resistance were highest for urinary tract isolates and lowest for respiratory tract isolates.

Activities of fluconazole and voriconazole against other opportunistic yeasts and yeast-like fungi. Although uncommon, the number and types of noncandidal yeasts isolated from clinical specimens have continued to increase over the duration of this study (Tables 1 and 9). *Cryptococcus neoformans* continues to predominate, but the numbers of isolates of *Saccharomyces*, *Trichosporon*, and *Rhodotorula* species are also substantial. In general, these yeast-like fungi are considerably less susceptible to fluconazole than are *Candida* spp.

Among the species of *Cryptococcus*, it is important to note

TABLE 8. Susceptibilities of *C. albicans, C. glabrata*, and *C. tropicalis* to fluconazole and voriconazole by specimen type[a]

Specimen type/site (total no. of isolates)	Antifungal agent	*C. albicans*		*C. glabrata*		*C. tropicalis*	
		No. of isolates tested	% R	No. of isolates tested	% R	No. of isolates tested	% R
Blood (14,887)	Fluconazole	6,443	1.4	2,078	16.7	1,816	4.0
	Voriconazole	6,337	1.2	2,030	11.8	1,771	5.5
NSBF (6,055)	Fluconazole	3,608	1.4	809	14.3	552	4.5
	Voriconazole	3,535	1.4	795	8.3	542	5.2
Urine (18,168)	Fluconazole	9,296	1.4	3,381	16.2	2,585	5.5
	Voriconazole	9,059	1.2	3,330	11.2	2,479	7.9
Respiratory (39,523)	Fluconazole	28,114	1.9	3,719	15.7	2,972	3.1
	Voriconazole	27,421	1.5	3,650	9.9	2,897	4.2
Skin/soft tissue (8,290)	Fluconazole	4,107	1.6	627	19.0	608	4.9
	Voriconazole	4,007	1.2	621	12.7	586	5.3
Genital (31,157)	Fluconazole	24,574	0.8	2,785	16.6	507	4.9
	Voriconazole	23,658	0.7	2,691	8.7	484	6.6
Miscellaneous NOS (23,303)	Fluconazole	13,608	2.0	2,753	13.5	1,607	4.9
	Voriconazole	13,174	1.6	2,707	8.9	1,547	5.1

[a] Isolates were obtained from 124 institutions. Disk diffusion testing was performed in accordance with CLSI document M44-A (16). The interpretive breakpoints (zone diameters) for resistance were as follows: fluconazole, ≤14 mm; voriconazole, ≤13 mm.

TABLE 9. 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	2,230	78.0	10.4	2,209	97.1	1.7
C. gattii	28	57.1	10.7	28	96.4	3.6
Cryptococcus spp.[c]	108	71.3	16.7	108	86.1	9.3
Saccharomyces spp.[d]	41	90.2	2.4	37	97.3	2.7
S. cerevisiae	709	88.6	6.3	697	95.1	3.0
Trichosporon spp.[e]	443	84.7	9.0	422	95.0	2.4
T. beigelii/T. cutaneum	125	77.6	12.0	123	83.7	12.2
T. mucoides	51	94.1	0.0	51	100.0	0.0
T. asahii	53	79.2	15.1	53	92.5	7.5
T. inkin	13	92.3	7.7	13	100.0	0.0
T. ovoides	3	100.0	0.0	3	100.0	0.0
Rhodotorula spp.[f]	210	45.2	49.0	209	56.9	37.3
R. rubra/mucilaginosa	52	17.3	78.8	52	25.0	67.3
R. glutinis	24	41.7	54.2	24	58.3	41.7
Blastoschizomyces capitatus	86	81.4	11.6	86	91.9	3.5
Pichia spp.[g]	94	86.2	9.6	92	97.8	0.0
Hansenula spp.[h]	15	71.4	7.1	15	93.3	6.7
Debaryomyces spp.[i]	2	100.0	0.0	2	100.0	0.0

[a] Isolates were obtained from 124 institutions.
[b] Fluconazole and voriconazole disk diffusion testing was performed in accordance with CLSI document M44-A (16). 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] *Cryptococcus* species other than *C. neoformans* and *C. gattii.*
[d] *Saccharomyces* species not otherwise identified.
[e] *Trichosporon* species not otherwise identified.
[f] *Rhodotorula* species not otherwise identified.
[g] *Pichia* species not otherwise identified.
[h] *Hansenula* species not otherwise identified.
[i] *Debaryomyces* species not otherwise identified.

TABLE 10. In vitro susceptibilities of fluconazole-resistant isolates of non-*Candida* yeasts to voriconazole as determined by CLSI disk diffusion testing[a]

Species	No. of isolates tested	% S	% SDD	% R
C. neoformans	228	79.8	6.6	13.6
C. gattii	3	66.7	0.0	33.3
Cryptococcus spp.[b]	18	27.8	22.2	50.0
Saccharomyces spp.[c]	1	0.0	0.0	100.0
S. cerevisiae	43	34.9	25.6	39.5
Trichosporon spp.[d]	38	55.3	21.1	23.7
T. beigelii/T. cutaneum	15	13.3	6.7	80.0
T. asahii	8	50.0	0.0	50.0
T. inkin	1	100.0	0.0	0.0
Rhodotorula spp.[e]	104	19.2	8.7	72.1
R. rubra/mucilaginosa	41	14.6	7.3	78.0
R. glutinis	13	23.1	0.0	76.9
Blastoschizomyces capitatus	10	60.0	10.0	30.0
Pichia spp.[f]	8	87.5	12.5	0.0
Hansenula spp.[g]	1	100.0	0.0	0.0

[a] Isolates were obtained from 124 institutions. The zone diameters for the voriconazole disk diffusion susceptibility categories were as follows: S, ≥17 mm; SDD, 14 to 16 mm; R, ≤13 mm.
[b] *Cryptococcus* species other than *C. neoformans* and *C. gattii.*
[c] *Saccharomyces* species not otherwise identified.
[d] *Trichosporon* species not otherwise identified.
[e] *Rhodotorula* species not otherwise identified.
[f] *Pichia* species not otherwise identified.
[g] *Hansenula* species not otherwise identified.

the rather poor activity of fluconazole against isolates of *C. gattii* (Table 9). This species has long been noted to be an important opportunistic pathogen in tropical and subtropical climates and has recently gained importance due to an outbreak of *C. gattii* on Vancouver Island, BC, Canada (10, 15, 39). The decreased susceptibility of this species of *Cryptococcus* to fluconazole is similar to that observed by other investigators (14, 42, 43), although a recent report from Africa found low MICs to fluconazole and other azoles (15). Both *C. gattii* and *C. neoformans* were very susceptible to voriconazole in the present study (Table 9).

Both *Saccharomyces cerevisiae* and various species of *Trichosporon* appear to be moderately susceptible to fluconazole. It is interesting that *T. mucoides*, *T. inkin*, and *T. ovoides* appear to be considerably more susceptible to fluconazole than *T. asahii* and *T. beigelii/T. cutaneum*. Voriconazole exhibited very good activity against both *Saccharomyces* and *Trichosporon* species with the exception of *T. beigelii/T. cutaneum*.

Rhodotorula spp., including *R. rubra/mucilaginosa* and *R. glutinis*, are often resistant to both fluconazole and voriconazole. Amphotericin B continues to be the antifungal agent of choice for the treatment of infections due to this opportunistic yeast (5).

Fluconazole has only modest activity against isolates of *Blastoschizomyces capitatus* and *Pichia (Hansenula*) spp. Voriconazole appears to be active against these yeasts, although clinical experience in treating infections due to these rare yeasts is lacking (24, 44).

Similar to that seen with the *Candida* species, isolates of non-*Candida* yeasts that are resistant to fluconazole also show increased resistance to voriconazole (Table 10). These organisms could be quite problematic when encountered in an immunocompromised host given the fact that, in addition to the acquired azole resistance, they also exhibit intrinsic resistance to the echinocandin class of antifungal agents (24, 40).

DISCUSSION

In this most recent summary of the data from the ARTEMIS DISK Global Surveillance Program, we report fluconazole and voriconazole susceptibility results for more than 200,000 clinical isolates of *Candida* and other opportunistic yeast pathogens from throughout the world. The value of such a large database is that for the more common species of *Candida*, we can assess trends in resistance over time (Tables 4 and 5), by geographic region (Table 6), by clinical service (Table 7), and by specimen type (Table 8). Of greater potential value is the data pertaining to the less common species of *Candida* and other yeasts (Tables 1 to 3, 9, and 10). These relatively rare pathogens are unlikely to be familiar to both clinicians and microbiologists, and there is little or no data regarding prognosis or optimal treatment strategies (17, 24, 31, 32, 40, 44). Given the ubiquitous use of azoles in prophylaxis, empirical, and directed therapies (4, 20, 40, 41), it is important to know the activities of the systemically active agents, such as fluconazole and voriconazole, against these organisms (40, 41, 44). The fact that the less common species of *Candida* exhibit decreased susceptibility to fluconazole, and in some instances to voriconazole (Table 2), is important, as these organisms

could emerge as pathogens in immunocompromised patients who have already been receiving an azole (24, 31, 32). In this regard, it is also important to understand what to expect with regard to susceptibility to voriconazole among *Candida* species found to break through fluconazole therapy (Table 3) (21). Species such as *C. krusei*, *C. inconspicua*, and *C. norvegensis* may emerge during fluconazole therapy due to their intrinsic resistance to fluconazole yet remain susceptible to voriconazole (Table 3). Unfortunately, most other species of *Candida* that exhibit acquired resistance to fluconazole also appear to be significantly less susceptible to voriconazole than their "fluconazole-naïve" counterparts (Table 3) and are less likely to respond optimally to treatment with this agent (11, 18, 20, 40, 41).

Among the non-*Candida* yeasts, there is even less information to guide antifungal therapy (24, 26, 44). These organisms generally appear to be less susceptible to fluconazole than *Candida* spp. (Table 9) but, aside from *Rhodotorula* spp., remain susceptible to voriconazole (Table 9). Unfortunately, as with *Candida*, fluconazole-resistant isolates of these noncandidal yeasts also exhibit decreased susceptibility to voriconazole (Table 10). Given their intrinsic resistance to the echinocandins and their variable response to amphotericin B, these yeasts may pose considerable problems in the future (5, 12, 24, 44).

Overall, the ARTEMIS database can serve as a look into the future of clinical mycology. At present, the azoles fluconazole and voriconazole appear to be adequate in their coverage of the most common species of *Candida* (Table 2). However, the weaknesses of both of these agents, as well as posaconazole and the echinocandins (34), can be seen as we look at the less common species of *Candida* and the other opportunistic yeasts (24). Although any one of these unusual pathogens may never truly "emerge" to become a major threat in and of itself, in aggregate these organisms could pose problems among patients with prior azole exposure. Furthermore, the lack of any meaningful activity of the echinocandin class against the non-*Candida* yeasts and the increasing use of this class of antifungal agents suggest that these organisms may be prime candidates to "emerge" as new mycotic threats (12).

The potential value of large antifungal surveillance databases such as that of ARTEMIS is considerable; however, the value of such information for clinical purposes is weakened substantially without knowledge of the species identification of the infecting organism. Thus, it is imperative that clinical laboratories strive to provide rapid and accurate identification of *Candida* and other opportunistic yeasts. Although antifungal susceptibility testing of fluconazole and voriconazole is becoming more accessible (22, 25, 27, 33, 35, 36), in most instances the species identification alone, coupled with survey data such as that of ARTEMIS, is sufficient to guide the selection of initial antifungal therapy. Specific antifungal susceptibility testing may help to optimize therapy in instances where a suboptimal response is observed to what would ordinarily be considered adequate therapy (20, 38, 41).

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London, Nigel Weightman, Friarage Hospital, Northallerton, Ian M. Gould, Aberdeen Royal Hospital, Aberdeen, Claire Rennison, Royal Victoria Hospital, Newcastle, Richard Barton, General Infirmary, P.H.L.S, Leeds, and Rosemary Barnes, University of Wales College of Medicine, Cardiff, United Kingdom; Jose Vazquez, Henry Ford Hospital, Detroit, MI; Davise Larone, Cornell Medical Center NYPH, New York, NY; Mike Rinaldi, University of Texas Health Science Center, San Antonio, TX; and Heidi Reyes, Gen del Este Domingo Luciani, and Axel Santiago, Universitario de Caracas, Caracas, Venezuela.

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