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

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Fluconazole *in vitro* susceptibility test results for 256,882 isolates of *Candida* spp. were collected from 142 sites in 41 countries from June 1997 to December 2007. Data were collected for 197,619 isolates tested with voriconazole from 2001 to 2007. A total of 31 different species of *Candida* were isolated. Increased rates of isolation of the common non-*albicans* species *C. glabrata* (10.2% to 11.7%), *C. tropicalis* (5.4% to 8.0%), and *C. parapsilosis* (4.8% to 5.6%) were noted when the time periods 1997 to 2000 and 2005 to 2007 were compared. Investigators tested clinical isolates of *Candida* spp. by the CLSI M44-A disk diffusion method. Overall, 90.2% of *Candida* isolates tested were susceptible (S) to fluconazole; however, 13 of 31 species identified exhibited decreased susceptibility (<75% S), similar to that seen with the resistant (R) species *C. glabrata* and *C. krusei*. Among 197,619 isolates of *Candida* spp. tested against voriconazole, 95.0% were S and 3% were R. About 30% of fluconazole-R isolates of *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. rugosa*, *C. lipolytica*, *C. pelliculosa*, *C. apicola*, *C. haemulonii*, *C. humicola*, *C. lambica*, and *C. ciferrii* remained S to voriconazole. An increase in fluconazole resistance over time was seen with *C. parapsilosis*, *C. guilliermondii*, *C. lusitaniae*, *C. sake*, and *C. pelliculosa*. Among the emerging fluconazole-R species were *C. guilliermondii* (11.4% R), *C. inconspicua* (53.2% R), *C. rugosa* (41.8% R), and *C. norvegensis* (40.7% R). The rates of isolation of *C. rugosa*, *C. inconspicua*, and *C. norvegensis* increased by 5- to 10-fold over the 10.5-year study period. *C. guilliermondii* and *C. rugosa* were most prominent in Latin America, whereas *C. inconspicua* and *C. norvegensis* were most common in Eastern European countries. This survey identifies several less-common species of *Candida* with decreased susceptibility to azoles. These organisms may pose a future threat to optimal antifungal therapy and underscore the importance of prompt and accurate species identification and antifungal susceptibility testing.

Antifungal susceptibility testing is playing an increasing role as a means to track the development of antifungal resistance in epidemiological studies (2, 10, 12, 17, 27, 45–47, 55, 63). One of the important by-products of the standardization of antifungal susceptibility testing has been the ability to conduct surveillance for antifungal resistance using uniform methods (44). Meaningful large-scale surveys of antifungal susceptibility and resistance conducted over time would not be possible without a standardized broth microdilution (BMD) or disk diffusion (DD) method for performing the *in vitro* studies (12, 38, 60). Global surveillance programs such as the ARTEMIS antifungal surveillance program for DD testing (49, 57, 60) and MIC testing (12, 13), the European Confederation of Medical Mycology (ECMM) survey of candidemia (68), and the SENTRY Antifungal Surveillance Program (36–38) promote the use of standardized DD and BMD methods and provide useful and consistent antifungal susceptibility data from a broad international network of hospitals and laboratories.

The ARTEMIS global antifungal surveillance program is among the most comprehensive and long-running fungal surveillance programs (12, 45, 57, 58, 60). The ARTEMIS program was designed to address many of the potential limitations of resistance surveillance studies (26): (i) it is both longitudinal (1997 to present) and global (142 participating sites in 41 countries) in scope, (ii) it employs standardized DD (7) and BMD (9) antifungal susceptibility test methods, (iii) both internal quality control (QC) performed in each participating laboratory and external quality assurance measures are used to validate test results (48, 50, 61), (iv) results are recorded electronically using the Biomic image analysis plate reader (Giles Scientific, Santa Barbara, CA) and are stored in a central database, and (v) both *Candida* and non-*Candida* (60) yeast isolates obtained from consecutive clinical samples from all body sites are tested locally, thus avoiding misleading results based on biased selective testing. Thus, the ARTEMIS program generates massive amounts of data that have been externally validated and that can be used to identify temporal and geographic trends in the species distribution of *Candida* and other opportunistic yeasts, as well as the resistance profiles of

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these organisms to fluconazole and voriconazole as determined by standardized Clinical and Laboratory Standards Institute (CLSI) DD methods.

In the present study, we expand the ARTEMIS database to include the time period from June 1997 through December 2007 and a total of 256,882 isolates of *Candida* from 142 study sites in 41 countries. We provide comparative susceptibility data for fluconazole and voriconazole for more than 190,000 isolates collected from 2001 to 2007 and include an analysis of resistance rates by year, geographic location, hospital location, and specimen type for selected species.

MATERIALS AND METHODS

Organisms and test sites. A total of 256,882 isolates of *Candida* obtained from 142 different medical centers in the Asia-Pacific region (24 sites), Latin America (16 sites), Europe (18 sites), the Africa/Middle East region (11 sites), and North America (13 sites) were collected and tested against fluconazole between June 1997 and December 2007. In addition, 197,619 isolates from 133 institutions were tested against voriconazole between 2001 and 2007. Approximately 80% of the study sites participated in the survey for 3 or more 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 [NSBF], deep tissue, genital tract, gastrointestinal tract, respiratory tract, urine, 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 (i.e., not associated with an obvious pathology) were excluded, as were duplicate isolates from a given patient (same species and same susceptible or 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 molecular methods, and the remainder used the classical methods alone (19, 21).

Susceptibility test method. Disk diffusion (DD) testing of fluconazole and voriconazole was performed as described previously (20, 57) and in CLSI document M44-A (7). 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. Zone diameter endpoints were read at 80% growth inhibition by using a Biomic image analysis plate reader system (Giles Scientific) (20, 49, 57, 60).

The interpretive criteria for the fluconazole and voriconazole DD tests were those of the CLSI (8, 51, 52): 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 (8, 51, 52) are as follows; S, MICs of ≤8 μg/ml (fluconazole) and ≤1 μg/ml (voriconazole); SDD, MICs of 16 to 32 μg/ml (fluconazole) 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-S2 (8) by using *Candida albicans* ATCC 90029 and *C. parapsilosis* ATCC 22019. Totals 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 DD test results were read by electronic image analysis and interpreted and recorded with the Biomic plate reader system (Giles Scientific). 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 prior to analysis. In the present study, fluconazole and voriconazole S, SDD, and R results for each species of *Candida* were stratified by year of collection, geographic region, clinical specimen type, and hospital location. Because large numbers would predispose the study to type I error, we did not perform formal significance testing; rather, we focused on clinically and microbiologically relevant trends.

RESULTS

Isolation rates by species. A total of 256,882 isolates of *Candida* spp. were collected and tested at 142 study sites between June 1997 and December 2007 (Table 1). A total of 31 different species of *Candida* were isolated, of which *C. albicans* was the most common (overall, 65.3% 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 years (2001 to 2004, 62.9%; 2005 to 2007, 65.0% of all *Candida* spp.), although the rates of isolation over the most recent 3-year period did not show a continued declining trend. In contrast to that observed for *C. albicans*, increased rates of isolation of the common non-*albicans* species *C. glabrata* (10.2% to 11.7%), *C. tropicalis* (5.4% to 8.0%), and *C. parapsilosis* (4.8% to 5.6%) were noted when the time periods 1997 to 2000 and 2005 to 2007 were compared. The rates of isolation of *C. krusei*, *C. guilliermondii*, *C. lusitaniae*, *C. kefyr*, and *C. famata* did not vary significantly, whereas those of fluconazole-resistant species *C. rugosa*, *C. inconspicua*, and *C. norvegensis* increased by 5- to 10-fold over the 10.5-year study period. The rates of isolation of the remaining 19 species remained quite low; however, the increased detection of these species is further evidence of more vigorous efforts to identify clinical isolates of *Candida* to the species level in recent years.

Geographic variation in the frequency of *Candida* species. The five most common species of *Candida*, *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*, accounted for 92% of all isolates reported during the most recent 7 years of the study (Table 2). Although these five species were prominent in each of the five geographic regions, the frequency and rank order varied considerably across the regions. Whereas *C. albicans* accounted for 64% to 67% of all *Candida* isolates in the Asia-Pacific, European, and Africa/Middle East regions, it was less prominent in Latin America (51.8%) and North America (48.9%). An even greater disparity was seen with *C. glabrata*, which was fourth in rank order in Latin America, accounting for only 7.4% of the isolates, and was second in the rank order in North America, accounting for 21.1% of the isolates from that region. Likewise, *C. tropicalis* was considerably more prominent in the Asia-Pacific (11.7%) and Latin American (13.2%) regions than in the other regions (range, 4.9% to 7.3%). *C. parapsilosis*, a prominent cause of catheter-related infection (69), was an infrequent cause of invasive candidiasis (IC) in Europe (4.2%) compared to either Latin America (10.3%) or North America (13.6%).

Among the less common species of *Candida* isolated from clinical specimens, four stand out due to their decreased susceptibility to azoles and other antifungal agents and their gradual emergence as causes of invasive candidiasis (3, 11, 14, 53, 54, 62): *C. guilliermondii*, *C. inconspicua*, *C. rugosa*, and *C. norvegensis* (Table 2). Notably, each of these species appears to be more prominent in some geographic regions than in others: *C. guilliermondii* and *C. rugosa* in Latin America and *C. inconspicua* and *C. norvegensis* in Europe (Table 2).

Fluconazole and voriconazole susceptibilities of *Candida* spp. Table 3 summarizes the *in vitro* susceptibilities of 201,653 and 197,619 isolates of *Candida* spp. to fluconazole and voriconazole, respectively, as determined by CLSI DD testing (7).

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

Organism	Isolates tested by period:							
	1997–2000		2001–2004		2005–2007		1997–2007	
	No.	% of total	No.	% of total	No.	% of total	No.	% of total
Candida albicans	39,152	70.9	71,027	62.9	57,598	65.0	167,777	65.3
C. glabrata	5,634	10.2	12,963	11.5	10,342	11.7	28,939	11.3
C. tropicalis	2,996	5.4	8,496	7.5	7,050	8.0	18,542	7.2
C. parapsilosis	2,633	4.8	7,783	6.9	5,005	5.6	15,421	6.0
C. krusei	1,207	2.2	2,840	2.5	2,239	2.5	6,286	2.4
C. guilliermondii	367	0.7	902	0.8	508	0.6	1,777	0.7
C. lusitaniae	276	0.5	674	0.6	559	0.6	1,509	0.6
C. kefyr	182	0.3	527	0.5	517	0.6	1,226	0.5
C. inconspicua	9	0.02	276	0.2	290	0.3	575	0.2
C. famata	123	0.2	375	0.3	247	0.3	745	0.3
C. rugosa	35	0.06	469	0.4	134	0.2	638	0.2
C. dubliniensis	1	<0.01	113	0.1	197	0.2	311	0.1
C. norvegensis	11	0.02	135	0.1	113	0.1	259	0.1
C. lipolytica	7	0.01	80	0.07	50	0.06	137	0.05
C. sake			20	0.02	67	0.08	87	0.03
C. pelliculosa	1	<0.01	47	0.04	40	0.05	88	0.03
C. apicola					57	0.06	57	0.02
C. zeylanoides	4	<0.01	50	0.04	20	0.02	74	0.03
C. valida			9	<0.01	12	0.01	21	<0.01
C. intermedia			10	<0.01	14	0.01	24	<0.01
C. pulcherrima			6	<0.01	8	<0.01	14	<0.01
C. haemulonii			6	<0.01	3	<0.01	9	<0.01
C. stellatoidea					7	<0.01	7	<0.01
C. utilis					6	<0.01	6	<0.01
C. humicola			2	<0.01	4	<0.01	6	<0.01
C. lambica					5	<0.01	5	<0.01
C. ciferrii					2	<0.01	2	<0.01
C. colliculosa					2	<0.01	2	<0.01
C. holmii					1	<0.01	1	<0.01
C. marina					1	<0.01	1	<0.01
C. sphaerica					1	<0.01	1	<0.01
Candida spp. NOS[b]	2,591	4.7	6,186	5.5	3,558	4.0	12,335	4.8
Total	55,229	100.0	112,996	100.0	88,647	100.0	256,882	100.0

[a] Includes all specimen types and all locations in hospitals from 142 institutions in 41 countries.
[b] *Candida* spp. NOS, *Candida* species not otherwise identified.

These isolates were obtained from 133 institutions during the period from 2001 through 2007. The percentages of isolates in each category (S, SDD, and R) were 90.2%, 3.6%, and 6.2% and 95.0%, 2.0%, and 3.0% for fluconazole and voriconazole, respectively. Fluconazole was most active (>90% S) against *C. albicans* (98.0% S), *C. tropicalis* (91.0% S), *C. parapsilosis* (93.2% S), *C. lusitaniae* (92.1% S), *C. kefyr* (96.5% S), *C. dubliniensis* (96.1% S), *C. apicola* (98.2% S), *C. intermedia* (95.8% S), *C. pulcherrima* (100% S), *C. colliculosa* (100% S), *C. holmii* (100% S), and *C. sphaerica* (100% S). Decreased sus-

TABLE 2. Geographic variation in frequency of common and uncommon species of *Candida*: ARTEMIS, 2001 to 2007[a]

Species	Species distribution (%) by region (total no. of isolates)[b]:					
	APAC (44,674)	EU (109,643)	AF/ME (8,259)	LAM (27,395)	NAM (11,682)	Total (201,653)
C. albicans	64.4	67.9	67.1	51.8	48.9	63.8
C. glabrata	12.6	11.3	8.8	7.4	21.1	11.6
C. tropicalis	11.7	4.9	6.6	13.2	7.3	7.7
C. parapsilosis	7.4	4.2	6.0	10.3	13.6	6.3
C. krusei	1.2	3.4	1.6	1.4	3.1	2.5
C. guilliermondii	0.4	0.5	0.1	2.2	0.5	0.7
C. inconspicua	<0.1	0.5		<0.1	<0.1	0.3
C. rugosa	0.4	<0.1	<0.1	1.2	<0.1	0.3
C. norvegensis	<0.1	0.2	<0.1	<0.1	0.2	0.1

[a] Includes all specimen types and all locations in hospitals from 133 institutions.
[b] Abbreviations: APAC, Asia-Pacific; EU, Europe; AF/ME, Africa-Middle East; LAM, Latin America; NAM, North America.

TABLE 3. *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	128,625	98.0	1.4	125,965	98.5	1.2
C. glabrata	23,305	68.7	15.7	22,968	82.9	10.0
C. tropicalis	15,546	91.0	4.1	15,198	89.5	5.4
C. parapsilosis	12,788	93.2	3.6	12,453	97.0	1.8
C. krusei	5,079	8.6	78.3	5,005	83.2	7.6
C. guilliermondii	1,410	73.5	11.4	1,375	90.5	5.7
C. lusitaniae	1,233	92.1	5.4	1,215	96.7	2.0
C. kefyr	1,044	96.5	2.7	1,032	98.7	0.9
C. inconspicua	566	22.6	53.2	563	90.6	3.9
C. famata	622	79.1	10.3	606	90.3	5.0
C. rugosa	603	49.9	41.8	580	69.3	21.2
C. dubliniensis	310	96.1	2.6	308	98.4	1.0
C. norvegensis	248	41.9	40.7	247	91.5	4.0
C. lipolytica	130	66.2	28.5	128	77.3	14.1
C. sake	87	85.1	11.5	87	92.0	6.9
C. pelliculosa	87	89.7	6.9	86	94.2	4.7
C. apicola	57	98.2	1.8	57	98.2	1.8
C. zeylanoides	70	67.1	24.3	67	85.1	6.0
C. valida	21	23.8	61.9	22	81.8	13.6
C. intermedia	24	95.8	4.2	25	100.0	0.0
C. pulcherrima	14	100.0	0.0	14	100.0	0.0
C. haemulonii	9	88.9	11.1	9	88.9	11.1
C. stellatoidea	7	85.7	0.0	7	85.7	14.3
C. utilis	6	83.3	0.0	7	100.0	0.0
C. humicola	6	50.0	50.0	6	50.0	33.3
C. lambica	5	0.0	80.0	5	40.0	20
C. ciferrii	2	50.0	50.0	2	50.0	0.0
C. colliculosa	2	100.0	0.0	2	100.0	0.0
C. holmii	1	100.0	0.0	1	100.0	0.0
C. marina	1	0.0	0.0	1	100.0	0.0
C. sphaerica	1	100.0	0.0	1	100.0	0.0
Candida spp.[c]	9,744	86.2	8.9	9,577	93.6	4.1

[a] Isolates were obtained from 133 institutions, 2001 to 2007.
[b] Fluconazole and voriconazole disk diffusion testing was performed in accordance with CLSI document M44-A (7). 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 specified.

ceptibility to fluconazole (<75% S) was seen with *C. glabrata* (68.7% S), *C. krusei* (8.6% S), *C. guilliermondii* (73.5% S), *C. inconspicua* (22.6% S), *C. rugosa* (49.9% S), *C. norvegensis* (41.9% S), *C. valida* (23.8% S), *C. humicola* (50% S), *C. lambica* (0% S), *C. ciferrii* (50% S), and *C. marina* (0% S). Thus, despite the fact that overall 90% of all clinical isolates of *Candida* were susceptible to fluconazole, these data demonstrate that 13 of the 31 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 (57), voriconazole was more active than fluconazole against most species of *Candida* with the exception of *C. tropicalis* (91.0% S to fluconazole versus 89.5% S to voriconazole); *C. apicola* (98.2% S to both); *C. pulcherrima* (100% S to both); *C. haemulonii* (88.9% S to both); *C. stellatoidea* (85.7% S to both); *C. humicola* (50% S to both); *C. ciferrii* (50% S to both); and *C. colliculosa*, *C. holmii*, and *C. sphaerica* (100% S to both). *C. rugosa* (69.3% S to voriconazole), *C. lipolytica* (77.3% S), *C. humicola* (50% S), *C. lambica* (40% S), and *C. ciferrii* (50% S) were all considerably less susceptible to voriconazole than were all other species of *Candida*.

A total of 12,179 isolates encompassing 24 different species of *Candida* were found to be resistant to fluconazole (Table 4). Whereas voriconazole was active (≥75% S) against fluconazole-resistant isolates of *C. krusei* (79.6% S), *C. inconspicua* (83.8% S), *C. norvegensis* (81.0% S), and *C. intermedia* (100% S), activity was quite poor against the remaining 20 species. Notably, less than 30% of fluconazole-resistant isolates of *C. albicans* (28.1% S); *C. glabrata* (19.1% S); *C. tropicalis* (17.0% S); *C. rugosa* (28.1% S); *C. lipolytica* (29.7% S); *C. pelliculosa* (16.7% S); *C. lambica* (25% S); and *C. apicola*, *C. haemulonii*, *C. humicola*, and *C. ciferrii* (all 0% S) remained susceptible to voriconazole. Cross-resistance between fluconazole and voriconazole is clearly more pronounced in some species of *Candida* than others, although all are affected to some degree, emphasizing the importance of both species identification and antifungal susceptibility testing in settings of candidal infection with prior azole exposure (1, 32, 42, 43, 57, 65, 66).

Trends in resistance to fluconazole among *Candida* spp. over a 10.5-year period. There was no consistent trend toward increasing resistance to fluconazole detected among the common species *C. albicans*, *C. glabrata*, and *C. tropicalis* over the 10.5-year time period (Table 5). Likewise, consistently high levels of resistance were seen among *C. krusei*, *C. inconspicua*, *C. norvegensis*, and *C. valida*. Resistance was high among *C.*

TABLE 4. *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	1,782	28.1	8.4	63.6
C. glabrata	3,550	19.1	21.7	59.2
C. tropicalis	629	17.0	15.3	67.7
C. parapsilosis	431	39.2	20.4	40.4
C. krusei	3,889	79.6	11.3	9.2
C. guilliermondii	157	43.9	16.6	39.5
C. lusitaniae	63	55.6	17.5	27.0
C. kefyr	27	66.7	7.4	25.9
C. inconspicua	297	83.8	10.1	6.1
C. famata	62	37.1	24.2	38.7
C. rugosa	242	28.1	21.5	50.4
C. dubliniensis	8	62.5	0.0	37.5
C. norvegensis	100	81.0	10.0	9.0
C. lipolytica	37	29.7	27.0	43.2
C. sake	9	44.4	11.1	44.4
C. pelliculosa	6	16.7	16.7	66.7
C. apicola	1	0.0	0.0	100.0
C. zeylanoides	15	46.7	26.7	26.7
C. valida	14	71.4	7.1	21.4
C. intermedia	1	100.0	0.0	0.0
C. haemulonii	1	0.0	0.0	100.0
C. humicola	3	0.0	33.3	66.7
C. lambica	4	25.0	50.0	25.0
C. ciferrii	1	0.0	100.0	0.0
Candida spp.[b]	850	47.6	14.6	37.8

[a] Isolates obtained from 133 institutions, 2001 to 2007. The zone diameters for 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.

famata, *C. rugosa*, *C. lipolytica*, and *C. zeylanoides* for the years 2001 through 2004 but decreased for all four species during 2005 through 2007. Resistance to fluconazole also fell by 50% for *C. kefyr* during the latter 3-year period. The reasons for such decreases in resistance are unclear.

A slight increase in fluconazole resistance was noted among *C. parapsilosis* (2.5% to 3.6%), *C guilliermondii* (9.9% to 14.2%), and *C. lusitaniae* (2.9% to 6.0%) over the 10.5-year period. Although the numbers of isolates were small, *C. saki* (10.0% to 11.9%), *C. pelliculosa* (15.0%), *C. haemulonii* (33.3%) *C. humicola* (50%), *C. lambica* (80%), and *C. ciferrii* (50%) all showed elevated rates of resistance over the last 3 years (2005 to 2007).

Trends in resistance to voriconazole among *Candida* spp., 2001 to 2007. Voriconazole has been tested in the ARTEMIS program since its introduction into clinical use in 2001 (Table 6). As noted previously (Table 3), resistance to voriconazole was uncommon (<5%) during each of the study years; however, a trend toward increased resistance over the most recent 3 years (2005 to 2007) was observed for *C. famata* (1.1% to 5.7%), *C. norvegensis* (0.0% to 6.9%), *C. lipolytica* (0.0% to 11.1%), and *C. pelliculosa* (14.3% to 16.7%). Notably, there was no trend toward increased resistance to voriconazole among the fluconazole-resistant species *C. glabrata*, *C. krusei*, *C. guilliermondii*, *C. rugosa*, and *C. inconspicua*.

Geographic variation in the susceptibilities of *Candida* to fluconazole and voriconazole. Table 7 presents the *in vitro* susceptibility results for fluconazole and voriconazole tested against the five most common species of *Candida* (*C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*) and four uncommon fluconazole-resistant species (*C. guilliermondii*, *C. inconspicua*, *C. rugosa*, and *C. norvegensis*) stratified by geographic region for the time period from 2001 to 2007. Just as geographic variation was seen in the frequency of isolation of these different species (Table 2), considerable variation in the frequency of azole resistance was observed as well. Although both fluconazole and voriconazole were highly active against *C. albicans* in all geographic regions, considerably higher rates of resistance to both azoles were detected among isolates from North America than among those from the other four regions. Similarly to *C. albicans*, the highest rates of azole resistance among isolates of *C. glabrata* were seen in North America.

C. tropicalis is now recognized as the second most common species of *Candida* isolated from patients with invasive candidiasis in the Asia-Pacific region (5, 23, 28, 70–75) (Table 2). Reports from Taiwan have also highlighted the emergence of fluconazole resistance in *C. tropicalis* from a variety of different specimen types (71, 74). These findings are supported by the most recent ARTEMIS data, where the highest rates of resistance to both fluconazole and voriconazole were seen among isolates of *C. tropicalis* from the Asia-Pacific region (Table 7). The lowest rates of resistance to both azoles were seen with isolates of *C. tropicalis* from the Africa/Middle East region. As noted previously (57), *C. tropicalis* isolates from all regions, with the exception of those from the Africa/Middle East region, were slightly more resistant to voriconazole than to fluconazole.

Azole resistance among isolates of *C. parapsilosis* is generally considered to be infrequent (59, 69), and that is the case in all of the regions surveyed in the ARTEMIS program with the exception of those isolates from the Africa/Middle East region (Table 7). Whereas resistance to fluconazole and voriconazole was <5% and <3%, respectively, in Europe, Latin America, North America, and the Asia-Pacific regions, it was 15.0% and 11.1%, respectively, in the Africa/Middle East region, with the highest rates seen in isolates from South Africa (21% and 15%, respectively).

Among the five species of *Candida* that are recognized as having decreased susceptibility to fluconazole, *C. krusei* showed high-level resistance in all of the geographic regions. Interestingly, 14% of isolates of *C. krusei* from Latin America were resistant to voriconazole compared to only 4.5% to 7.7% of isolates from other regions.

Isolates of *C. guilliermondii* from the Asia-Pacific region and Europe were more resistant to both fluconazole and voriconazole than were those from other regions, whereas the highest rates of resistance to both agents among *C. rugosa* isolates were seen in Latin America. The greatest geographic variation in resistance to voriconazole was noted with *C. rugosa*, where 32.8% of Latin American isolates were resistant compared to 0% to 11.1% in the other regions.

Both *C. inconspicua* and *C. norvegensis* appear predominately in Europe, and isolates of both species from this region demonstrate a fluconazole-resistant and voriconazole-susceptible phenotype. Whereas the few isolates of *C. inconspicua* from other regions also exhibit this phenotype, isolates of *C. norvegensis* from regions other than Europe are generally susceptible to both azoles.

TABLE 5. Trends in *in vitro* resistance to fluconazole among *Candida* spp. as determined by CLSI disk diffusion testing over a 10.5-year period[a,b]

Species	1997–2000		2001–2004		2005–2007	
	No. of isolates tested	% R	No. of isolates tested	% R	No. of isolates tested	% R
C. albicans	39,152	0.9	71,027	1.4	57,598	1.4
C. glabrata	5,634	19.2	12,963	15.9	10,342	15.4
C. tropicalis	2,996	3.6	8,496	4.5	7,050	3.6
C. parapsilosis	2,633	2.5	7,783	3.5	5,005	3.6
C. krusei	1,207	65.8	2,840	77.5	2,239	79.3
C. guilliermondii	367	12.5	902	9.9	508	14.2
C. lusitaniae	276	2.9	674	4.3	559	6.6
C. kefyr	182	3.3	527	3.6	517	1.7
C. inconspicua	9	55.6	276	52.2	290	54.1
C. famata	123	17.1	375	12.5	247	6.9
C. rugosa	35	34.3	238	50.7	134	10.4
C. dubliniensis	1	0.0	113	2.7	197	2.0
C. norvegensis	11	54.5	135	36.3	113	46.0
C. lipolytica	7	0.0	80	37.5	50	14.0
C. sake			20	10.0	67	11.9
C. pelliculosa	1	0.0	47	0.0	40	15.0
C. apicola					57	1.8
C. zeylanoides	4	0.0	50	28.0	20	15.0
C. valida			9	66.7	12	58.3
C. intermedia			10	0.0	14	7.1
C. pulcherrima			6	0.0	8	0.0
C. haemulonii			6	0.0	3	33.3
C. stellatoidea					7	0.0
C. utilis					6	0.0
C. humicola			2	50.0	4	50.0
C. lambica					5	80.0
C. ciferrii					2	50.0
C. colliculosa					2	0.0
C. holmii					1	0.0
C. marina					1	0.0
C. sphaerica					1	0.0
Candida spp.[c]	2,591	10.5	6,186	8.2	3,558	10.1

[a] Includes all specimen types and all hospital locations in 141 institutions.
[b] % R, percent resistant (zone diameter, ≤14 mm).
[c] *Candida* species not otherwise identified.

Variation in the frequency of isolation and the antifungal susceptibility profile of *C. krusei*, *C. inconspicua*, and *C. norvegensis* by clinical service. *C. krusei*, *C. inconspicua*, and *C. norvegensis* are uncommon species of *Candida* that share a fluconazole-resistant, voriconazole-susceptible phenotype (3, 11, 14, 34, 62). Although *C. krusei* is well studied, little is known of the frequency of occurrence and variation in azole susceptibility of *C. inconspicua* and *C. norvegensis* according to clinical service (3, 11, 18, 58, 62). The clinical services reporting the isolation of those three species from patient specimens included the hematology-oncology service, medical and surgical services, intensive care units (ICUs; medical-surgical and neonatal), the dermatology service, the urology service, and the outpatient service (Table 8). Those strains from services with only a few isolates and those for which a clinical service was not specified were included in the category "other, not otherwise specified" (other, NOS).

C. krusei was isolated most frequently from the hematology-oncology service and the medical service. Whereas resistance to fluconazole was elevated in every service, resistance to voriconazole was <10% in all services except the neonatal ICU (13.8% [data not shown]) and the outpatient service (10.1%). Less than 80% of isolates from the hematology-oncology and dermatology services were susceptible to voriconazole.

As with *C. krusei*, *C. inconspicua* was isolated most frequently from the hematology-oncology and medical services. Previously, D'Antonio et al. (11) reported a cluster of catheter-related infections due to *C. inconspicua* in patients with hematologic malignancies. More than 50% of isolates from the hematology-oncology, surgical, ICU, and dermatology services were resistant to fluconazole, whereas less than 6% of isolates from all services except dermatology (only 4 isolates tested) were resistant to voriconazole.

C. norvegensis has been reported as a cause of invasive candidiasis among immunosuppressed patients in Denmark and Norway (62). This species was isolated most frequently from patients on the medical service, and more than 30% of isolates from all services except the surgical and dermatology services were resistant to fluconazole. By comparison, resistance to voriconazole was uncommon (0% to 4.2%) in all services except for the urology service (1 of 6 isolates [16.7%]).

Variation in the frequency of isolation and the antifungal susceptibility profiles of *C. krusei*, *C. inconspicua*, and *C. norvegensis* by clinical specimen type. The major specimen types

TABLE 6. Trends in *in vitro* resistance to voriconazole among *Candida* spp. as determined by CLSI disk diffusion testing over a 7-year period[a,b]

Species	2001–2004		2005		2006		2007	
	No. of isolates tested	% R	No. of isolates tested	% R	No. of isolates tested	% R	No. of isolates tested	% R
C. albicans	68,575	1.2	18,630	1.5	18,965	1.0	19,795	1.0
C. glabrata	12,643	10.3	3,185	9.5	3,413	10.2	3,727	9.4
C. tropicalis	8,171	6.1	2,136	4.5	2,317	3.8	2,574	5.1
C. parapsilosis	7,464	1.8	1,581	1.9	1,724	1.3	1,687	1.8
C. krusei	2,765	7.7	684	7.9	742	6.5	814	8.0
C. guilliermondii	872	4.9	184	6.5	155	9.7	164	5.5
C. lusitaniae	655	1.8	163	3.1	195	0.5	202	3.0
C. kefyr	514	0.8	173	2.9	153	0.0	192	0.0
C. inconspicua	274	5.5	77	2.6	89	2.2	123	2.4
C. famata	359	6.4	87	1.1	72	1.4	88	5.7
C. rugosa	446	26.7	33	3.0	38	0.0	63	4.8
C. dubliniensis	111	0.9	57	0.0	70	1.4	70	1.4
C. norvegensis	134	2.2	36	0.0	47	10.4	29	6.9
C. lipolytica	79	17.7	17	0.0	14	14.3	18	11.1
C. sake	20	0.0	13	7.7	27	11.1	27	7.4
C. pelliculosa	47	0.0	14	14.3	19	5.3	6	16.7
C. apicola					44	2.3	13	0.0
C. zeylanoides	48	8.3	7	0.0	2	0.0	10	0.0
C. valida	9	11.1	7	28.6	1	0.0	5	0.0
C. intermedia	10	0.0	8	0.0	3	0.0	4	0.0
C. pulcherrima	6	0.0	2	0.0	4	0.0	2	0.0
C. haemulonii	6	0.0	2	50.0	1	0.0		
C. stellatoidea							7	14.3
C. utilis			1	0.0	2	0.0	4	0.0
C. humicola	2	50.0			2	50.0	2	0.0
C. lambica					2	0.0	3	33.3
C. ciferrii					1	0.0	1	0.0
C. colliculosa					1	0.0	1	0.0
C. holmii							1	0.0
C. marina							1	0.0
C. sphaerica							1	0.0
Candida spp.[c]	6,022	4.7	1,183	4.9	1,031	2.4	1,341	2.0

[a] Isolates were obtained from 133 institutions.
[b] % R, percent resistant (zone diameter, ≤13 mm).
[c] *Candida* species not otherwise identified.

yielding *C. krusei*, *C. inconspicua*, and *C. norvegensis* as putative pathogens included blood, normally sterile body fluids (NSBF), urine, respiratory tract, skin and soft tissue, and genital specimens (Table 8). Those isolates from uncommon specimen types and those for which as specimen type was not recorded were grouped under "miscellaneous, NOS."

C. krusei accounted for 2 to 3% (each) of all *Candida* spp. isolated from blood, NSBF, urine, respiratory tract, and skin and soft tissue specimens. It was isolated infrequently from genital specimens. Fluconazole resistance was apparent in >70% of isolates from all specimen types, whereas resistance to voriconazole ranged from 4.5% of isolates from NSBF to 11.4% of isolates from urine. Isolates from blood (86.3% S) and cerebrospinal fluid (100% S) were more likely to be susceptible (S) to voriconazole than were those from urine (76.4% S).

The majority of *C. inconspicua* isolates reported in the literature are from the respiratory tract; however, wound, blood, and genital isolates have also been obtained (3, 11, 33–35). Whereas the previous reports concerning *C. inconspicua* contained no more than 50 clinical isolates, the present data set is considerably more robust and shows *C. inconspicua* isolated from numerous body sites, including blood and NSBF. Consistent with the literature, *C. inconspicua* was isolated most frequently from the respiratory tract.

Fluconazole resistance among isolates of *C. inconspicua* ranged from 26.1% for isolates from skin and soft tissue specimens to 62.9% from genital specimens. Half of all isolates from NSBF and more than a third of isolates from blood were resistant to fluconazole. Resistance (R) to voriconazole was less than 5% for isolates from all specimen types with the exception of isolates from urine (7.7% R) and miscellaneous specimen types (5.2% R).

C. norvegensis has been isolated from the oropharynx, blood, peritoneal fluid, urine, and a variety of deep tissue sites (22, 39, 40, 62, 67). As with *C. inconspicua*, *C. norvegensis* was isolated most frequently from the respiratory tract and with approximately equal frequency from the other specimen types (Table 9). Whereas isolates from most specimen types were highly resistant to fluconazole (>40% R), isolates from blood (7.7% R) and skin and soft tissue (8.7% R) were considerably less resistant. Resistance to voriconazole was quite uncommon (0 to 1.6%) among isolates from all specimen types with the exception of those from urine (8.7% R) and miscellaneous specimen types (8.0% R).

TABLE 7. Geographic variation in the *in vitro* susceptibilities of common and uncommon species of *Candida* to fluconazole and voriconazole, 2001 to 2007[a]

Species	Antifungal agent	APAC		EU		AF/ME		LAM		NAM	
		No. of isolates	% R	No. of isolates	% R	No. of isolates	% R	No. of isolates	% R	No. of isolates	% R
C. albicans	Fluconazole	28,781	0.9	74,408	1.3	5,539	0.6	14,178	2.1	5,718	5.1
	Voriconazole	27,827	0.8	72,873	1.1	5,502	0.3	13,711	1.7	5,681	3.6
C. glabrata	Fluconazole	5,629	13.0	12,439	16.3	728	16.2	2,039	15.1	2,470	19.5
	Voriconazole	5,515	8.2	12,288	9.8	705	8.1	2,000	11.3	2,460	14.6
C. tropicalis	Fluconazole	5,178	6.5	5,349	2.9	544	2.6	3,625	2.6	850	4.4
	Voriconazole	5,062	8.4	5,128	3.9	542	2.4	3,522	3.7	836	5.3
C. parapsilosis	Fluconazole	3,294	4.3	4,578	2.6	499	15.0	2,830	2.1	1,587	3.5
	Voriconazole	3,120	1.7	4,487	1.1	496	11.1	2,779	0.9	1,517	2.4
C. krusei	Fluconazole	532	73.5	3,678	80.8	134	72.4	370	66.8	361	74.0
	Voriconazole	516	5.0	3,637	7.7	134	4.5	351	14.0	363	5.5
C. guilliermondii	Fluconazole	178	13.5	567	13.8	12	8.3	590	9.0	63	7.9
	Voriconazole	175	10.9	558	6.1	12	0.0	567	3.7	63	4.8
C. inconspicua	Fluconazole	4	25.0	558	53.0			2	100.0	2	100.0
	Voriconazole	4	0.0	555	3.8			2	50.0	2	0.0
C. rugosa	Fluconazole	165	32.1	89	10.1	1	0.0	339	55.5	9	22.2
	Voriconazole	145	6.9	87	1.1	1	0.0	338	32.8	9	11.1
C. norvegensis	Fluconazole	7	14.3	204	49.0	1	0.0	13	0.0	21	0.0
	Voriconazole	7	0.0	203	4.9	1	0.0	13	0.0	21	0.0

[a] For definitions of abbreviations, see Table 2, footnote *b*.

DISCUSSION

There is no lack of data concerning the *in vitro* susceptibility of isolates of *C. albicans*, *C. glabrata*, *C. tropicalis*, and *C. parapsilosis* to both fluconazole and voriconazole (24, 55). Longitudinal surveillance studies from individual institutions, cities, countries, and broad geographic regions document the sustained activities of these agents versus *C. albicans*, *C. tropicalis*, and *C. parapsilosis* and the ongoing potential for *C. glabrata* to develop resistance to both triazoles (2, 10, 12, 17, 27, 46, 55, 63). Using the ARTEMIS database, we have confirmed and extended these observations globally over a 10.5-year period of study.

These four major yeast pathogens vary in frequency of occurrence and azole susceptibility over the four geographic regions encompassed in this survey (Tables 2 and 7). Although *C. albicans* remains quite susceptible to both azoles, the data reported herein demonstrate a lower frequency of occurrence and yet a higher rate of resistance of this species to both fluconazole and voriconazole in North America compared to the other regions (Tables 2 and 7). Likewise, *C. glabrata* remains more common in North America, and isolates from this region exhibit higher rates of azole resistance than do those from other parts of the world (Tables 2 and 7). *C. tropicalis* is a prominent cause of invasive candidiasis in both the Latin American and Asia-Pacific regions (Table 2). We have confirmed the earlier reports of increased resistance to fluconazole among isolates of *C. tropicalis* from the Asia-Pacific region (Table 7) (71, 74). *C. parapsilosis* is well known as an exogenous cause of catheter-related fungemia (59, 69). Although resistance to fluconazole remains relatively uncommon (Table 3), there appears to be a slight trend toward increasing resistance over time (Table 5). Local outbreaks of *C. parapsilosis* fungemia document its role as a nosocomial pathogen (69), and it is evident that when lapses in infection control precautions are coupled with broad use of fluconazole, an endemic, fluconazole-resistant strain of this species may emerge (6, 64).

The present study extends the list of species of *Candida* that may be isolated from clinical specimens (Table 1). Although many of these species are uncommon, their appearance in this survey underscores an increased effort by clinical laboratories worldwide to identify isolates of *Candida* to the species level. One limitation of this survey is that most laboratories employed commercial identification methods that may have problems identifying the more unusual species (25). Previously we have been able to validate the identification of many of these species (47), including cryptic species such as *C. dubliniensis*, *C. metapsilosis*, *C. orthopsilosis*, *C. nivariensis*, *C. bracarensis*, and *C. fermentati* (16, 29–31). Unfortunately, with a survey of this magnitude we have been unable to do so in every case.

Despite the fact that 90% of the more than 250,000 isolates reported herein remain susceptible to fluconazole, it is important to realize that many of the less common species of *Candida* exhibit decreased susceptibilities to both fluconazole and voriconazole compared to those of *C. albicans*, *C. tropicalis*, and *C. parapsilosis*. Furthermore, despite the very potent activity and broad spectrum of activity shown by voriconazole (Table 3), this agent is considerably less active against most

TABLE 8. Susceptibilities of *C. krusei*, *C. inconspicua*, and *C. norvegensis* to fluconazole and voriconazole by clinical service[a]

Clinical service (total no. of isolates)	Antifungal agent	*C. krusei*		*C. inconspicua*		*C. norvegensis*	
		No. of isolates tested	% R[b]	No. of isolates tested	% R	No. of isolates tested	% R
Hematology-oncology (11,930)	Fluconazole	757	83.1	113	51.3	24	50.0
	Voriconazole	741	9.6	113	5.3	24	4.2
Medical (47,024)	Fluconazole	1,128	79.9	101	42.6	68	33.8
	Voriconazole	1,106	7.8	101	4.0	68	2.9
Surgical (12,659)	Fluconazole	316	78.5	62	61.3	25	28.0
	Voriconazole	320	5.6	62	1.6	25	0.0
ICU (27,758)	Fluconazole	706	79.0	78	50.0	26	42.3
	Voriconazole	692	6.6	76	2.6	26	0.0
Dermatology (3,001)	Fluconazole	32	71.9	4	75.0	2	0.0
	Voriconazole	31	6.5	4	50.0	2	0.0
Urology (1,954)	Fluconazole	40	60.0	4	25.0	6	83.3
	Voriconazole	40	7.5	4	0.0	6	16.7
Outpatient (15,810)	Fluconazole	212	74.5	17	23.5	23	34.8
	Voriconazole	213	10.3	17	5.9	22	0.0
Other NOS (81,517)	Fluconazole	1,888	75.9	187	61.5	74	47.3
	Voriconazole	1,862	7.0	186	3.2	74	8.1

[a] Isolates were obtained from 133 institutions.
[b] % R, percent resistant (zone diameter, ≤14 mm [fluconazole] and ≤13 mm [voriconazole]).

fluconazole-resistant isolates (Table 4). Thus, with few exceptions, *Candida* spp. causing infection in patients with previous fluconazole exposure are very likely to show decreased susceptibility to voriconazole as well (1, 32, 42).

This report highlights the few species that routinely express a fluconazole-resistant, voriconazole-susceptible phenotype (Tables 4 and 7 to 9). The most common of these, *C. krusei*, is well known, and studies have demonstrated that the voriconazole activity against this species may be attributed to enhanced binding of this triazole to the target enzyme compared to that of fluconazole (15, 56, 58). Two additional species, *C. inconspicua* and *C. norvegensis*, share this fluconazole-resistant, voriconazole-susceptible phenotype (Tables 3 and 4). Although quite uncommon in most regions of the world (Table

TABLE 9. Susceptibilities of *C. krusei*, *C. inconspicua*, and *C. norvegensis* to fluconazole and voriconazole by specimen type[a]

Specimen type/site (total no. of isolates)	Antifungal agent	*C. krusei*		*C. inconspicua*		*C. norvegensis*	
		No. of isolates tested	% R[b]	No. of isolates tested	% R	No. of isolates tested	% R
Blood (20,704)	Fluconazole	459	74.5	24	37.5	13	7.7
	Voriconazole	459	8.5	24	4.2	13	0.0
NSBF (8,650)	Fluconazole	246	80.5	45	51.1	18	55.6
	Voriconazole	243	4.5	45	4.4	18	0.0
Urine (25,881)	Fluconazole	518	80.1	26	53.8	23	56.5
	Voriconazole	516	11.4	26	7.7	23	8.7
Respiratory tract (56,961)	Fluconazole	1,787	79.2	231	51.5	64	42.2
	Voriconazole	1,760	7.8	229	2.2	63	1.6
Skin/soft tissue (11,221)	Fluconazole	252	81.7	23	26.1	23	8.7
	Voriconazole	251	8.0	23	4.3	23	0.0
Genital tract (44,839)	Fluconazole	566	71.9	62	62.9	19	52.6
	Voriconazole	553	6.9	62	4.8	19	0.0
Miscellaneous NOS (33,397)	Fluconazole	1,251	79.2	155	58.7	88	43.2
	Voriconazole	1,223	5.8	154	5.2	88	8.0

[a] Isolates were obtained from 133 institutions.
[b] % R, percent resistant (zone diameter, ≤14 mm [fluconazole] and ≤13 mm [voriconazole]).

2), these two species have been recognized for some time in Europe as fluconazole-resistant causes of candidal colonization and infection (3, 11, 14, 22, 34, 35, 39, 40, 62). Among the isolates of *C. krusei*, *C. inconspicua*, and *C. norvegensis* in the present study, it is notable that they appear to be especially localized to Eastern Europe, namely, Hungary, Russia, and the Czech Republic. Whereas these three countries account for 21% of the *Candida* isolates overall, they account for 38% of all *C. krusei*, 31% of all *C. norvegensis*, and 75% of all *C. inconspicua* isolates (data not shown). European isolates of *C. inconspicua* and *C. norvegensis* appear to be more resistant to fluconazole than those from other geographic regions (Table 7). The epidemiological niche for these two species appears to be similar to that of *C. krusei*, with infection/colonization seen more frequently among patients housed in the hematology-oncology and medical services (Table 8). Whereas these species, as well as *C. krusei*, are often seen as colonizers (3, 22, 58, 62), isolates from blood and NSBF are reported in this survey (Table 9) and in other reports in the literature (3, 11, 34, 35, 39, 40, 62).

These and other relatively rare species of *Candida* are unlikely to be familiar to many clinicians and microbiologists, and there are few or no data concerning prognosis or optimal treatment strategies (13, 14, 25, 41, 43, 47, 53, 54, 65, 66). Given the ubiquitous use of azoles in prophylaxis and empirical and directed therapies (4, 43, 65, 66), it is important to know the activities of the systemically active agents, such as fluconazole and voriconazole, against these organisms (65, 66). The less common species of *Candida* often exhibit decreased susceptibility to fluconazole and, in some strains, to voriconazole (Table 3); this is important because these organisms may emerge as pathogens in immunocompromised patients who have already been receiving an azole (3, 11, 39, 41, 62, 65). Whereas most species of *Candida* that exhibit acquired resistance to fluconazole also appear to be considerably less susceptible to voriconazole than their wild-type "fluconazole-naïve" counterparts (Table 4), species such as *C. krusei*, *C. inconspicua*, and *C. norvegensis* may emerge during fluconazole therapy due to their intrinsic resistance to fluconazole and yet remain susceptible to voriconazole (Table 3 and 4).

In summary, we have used the ARTEMIS database to provide further evidence of the sustained activity of fluconazole and voriconazole against a broad range of *Candida* species. With an ever-expanding array of species causing infection in highly compromised patients, it is important to understand the activity of these "workhorse" antifungal agents against both common and uncommon species. It is comforting to know that both of these triazoles remain active against many of the more common species; however, reduced activity of fluconazole may be seen among the less common species, and resistance to voriconazole is often encountered among species with acquired fluconazole resistance (Table 4). Continued surveillance, both locally and on a regional and international basis, is clearly warranted.

Since it is a descriptive and sentinel-based study, there are certain limitations inherent in the ARTEMIS passive surveillance program that must be acknowledged. Despite a long-standing protocol for testing and reporting consecutive isolates from individual infectious episodes, there are no controls for participant compliance with the isolate submission protocol from one year to the next. This leads to the possibility that variations in the frequency of isolation of certain species may be influenced by financial, human resource, or policy changes and constraints and may under- or overestimate the true prevalence of any given species. Close monitoring of each study site's level of participation by the study coordinators using e-mail and other means of communication represents our efforts to ensure compliance with the data collection protocol. We recognize that studies of this scope are bound to have some variation in center participation, and we point out that the sheer number of submitted isolates from every region should help minimize individual center effects. Rigorous standardization of the CLSI disk diffusion method is ensured by both internal QC monitoring and external validation of both isolate identification and antifungal susceptibility results (29–31, 48, 50, 61). Despite these limitations, the overall size of this collection of *Candida* isolates does provide useful descriptive information. Such information will continue to be useful as a basis for comparison for future studies regarding the prevalence and antifungal susceptibility of both common and uncommon species of *Candida* as agents of IC throughout the world.

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A listing of the participants may be found at ARTEMIS Participating Sites (http://www.medicine.uiowa.edu/pathology/site/faculty/pfaller/artemis_participants.pdf).

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