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In Vitro Activities of Ravuconazole and Voriconazole Compared with Those of Four Approved Systemic Antifungal Agents against 6,970 Clinical Isolates of *Candida* spp.

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The in vitro activities of ravuconazole and voriconazole were compared with those of amphotericin B, flucytosine (5FC), itraconazole, and fluconazole against 6,970 isolates of *Candida* spp. obtained from over 200 medical centers worldwide. Both ravuconazole and voriconazole were very active against all *Candida* spp. (MIC at which 90% of the isolates tested are inhibited [MIC_{90}], 0.25 μg/ml; 98% of MICs were ≤1 μg/ml); however, a decrease in the activities of both of these agents was noted among isolates that were susceptible-dose dependent (fluconazole MIC, 16 to 32 μg/ml) and resistant (MIC, ≥ 64 μg/ml) to fluconazole. *Candida albicans* was the most susceptible species (MIC_{90} of both ravuconazole and voriconazole, 0.03 μg/ml), and *C. glabrata* was the least susceptible species (MIC_{90}, 1 to 2 μg/ml). Ravuconazole and voriconazole were each more active in vitro than amphotericin B, 5FC, itraconazole, and fluconazole against all *Candida* spp. and were the only agents with good in vitro activity against *C. krusei*. These results provide further evidence for the spectrum and potency of ravuconazole and voriconazole against a large and geographically diverse collection of *Candida* spp.

Although fluconazole has been a major advance in the systemic treatment of invasive candidiasis, concerns about potential selection of species with intrinsic or acquired resistance have resulted in the continued search for new agents with increased potency against *Candida* (19, 21, 22, 25). Among the newly developed systemic antifungal agents are three triazoles: posaconazole, ravuconazole, and voriconazole (25). We have recently reported on the activity of posaconazole against more than 3,000 clinical isolates of *Candida* spp. (19). We and others have also conducted in vitro studies of voriconazole (1, 5, 10, 13, 18). The published experience with ravuconazole has been more limited (4, 7, 13, 18).

One of the advantages cited for the new triazoles is increased activity against fluconazole-resistant (R) *Candida* (3, 6, 23, 25). However, the published data are limited to a small number of R (MIC, ≥64 μg/ml) and susceptible-dose-dependent (S-DD; MIC, 16 to 32 μg/ml) isolates and have focused primarily on *C. albicans* (12).

In the course of our sentinel surveillance studies (4, 13–16, 18), we compared the in vitro activities of antifungal agents against almost 7,000 invasive isolates of *Candida* spp. from more than 200 medical centers worldwide. We report our accumulated experience and highlight the activity of ravuconazole and voriconazole stratified according to susceptibility (S) to fluconazole and itraconazole. This report represents the largest experience with these agents tested by National Committee for Clinical Laboratory Standards (NCCLS) reference methods.

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MATERIALS AND METHODS

Organisms. A total of 6,970 clinical isolates of *Candida* spp. obtained from more than 200 medical centers worldwide were tested. The collection included the following numbers of isolates: 4,195 *C. albicans*, 949 *C. glabrata*, 814 *C. parapsilosis*, 597 *C. tropicalis*, 131 *C. krusei*, 88 *C. dubliniensis*, 85 *C. guilliermondii*, 58 *C. lusitaniae*, 15 *C. famata*, 13 *C. kefyr*, 8 *C. lipolytica*, 6 *C. rugosa,* 3 *C. pelliculosa*, 2 *C. lambica*, 1 *C. humicola*, 1 *C. zeylandoides*, and 4 *Candida* spp. not further identified. These were all clinical isolates collected between 1993 and 2001, and more than 80% were obtained from blood or normally sterile body fluids. The *C. dubliniensis* isolates were from mucosal sites. Isolates were identified by standard methods (28) and stored as water suspensions until they were used. Prior to testing, each isolate was passaged at least twice on potato dextrose agar (Remel, Lenexa, Kans.) to ensure optimal growth characteristics.

Antifungal agents. Standard antifungal powders of ravuconazole (Bristol-Myers Squibb, Wallingford, Conn.), voriconazole (Pfizer, Inc., New York, N.Y.), fluconazole (Pfizer), itraconazole (Janssen, Beerse, Belgium), amphotericin B, and flucytosine (5FC) (Sigma, St. Louis, Mo.) were obtained from their respective manufacturers. Stock solutions were prepared in dimethyl sulfoxide (DMSO; ravuconazole, voriconazole, and amphotericin B), polyethylene glycol (itraconazole), or water (5FC). Serial twofold dilutions were prepared exactly as outlined in NCCLS document M27-A (11). Final dilutions were made in RPMI 1640 medium (Sigma) buffered to pH 7.0 with 0.165 M morpholinepropanesulfonic acid (MOPS) buffer (Sigma). The final concentration of solvent did not exceed 1% in any well. Aliquots (100 μl) of each antifungal agent at a 2× final concentration were dispensed into the wells of plastic microdilution trays by using a Quick Spense II System (Dynatech Laboratories, Chantilly, Va.). The trays were sealed and frozen at −70°C until they were used.

Antifungal susceptibility studies. Broth microdilution (BMD) testing was performed in accordance with the guidelines in NCCLS document M27-A (11). The inoculum suspension was prepared by the spectrophotometric method of inoculum preparation and with a final inoculum of $(1.5 \pm 1.0) \times 10^3$ cells per ml. A 100-μl yeast inoculum was added to each well of the microdilution trays. The final concentrations of the antifungal agents were 0.007 to 8.0 μg/ml for amphotericin B, itraconazole, ravuconazole, and voriconazole and 0.12 to 128 μg/ml for fluconazole and 5FC. The trays were incubated at 35°C, and MIC endpoints were read after 48 h of incubation. Drug-free and yeast-free controls were included. Susceptibility of *Candida* isolates to amphotericin B was also determined by using Etest (AB BIODISK, Solna, Sweden) and RPMI 1640 agar with 2% glucose (Remel) as described previously (17).

Following incubation, the MICs of fluconazole, itraconazole, ravuconazole, voriconazole, and 5FC were read as the lowest concentration at which a prominent decrease (approximately 50%) in turbidity relative to the growth control

TABLE 1. In vitro activity of azole antifungal agents against 6,970 clinical isolates of *Candida* species stratified by fluconazole susceptibility

Antifungal agent	Fluconazole susceptibility category[a]	No. tested	Cumulative % inhibited at MIC (μg/ml) of:										
			0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Fluconazole	All	6,970	15	54	68	75	80	85	90	95	97	98	100
	S	6,268	17	60	75	84	89	95	100	100	100	100	100
	S-DD	463	0	0	0	0	0	0	0	73	100	100	100
	R	239	0	0	0	0	0	0	0	0	0	44	100
Itraconazole	All	6,970	69	81	90	97	98	99	99				
	S	6,268	77	89	96	99	99	100	100				
	S-DD	463	2	12	33	77	95	98	99				
	R	239	0	5	29	49	56	62	70				
Voriconazole	All	6,970	87	93	96	98	99	99	99				
	S	6,268	96	99	99	100	100	100	100				
	S-DD	463	8	44	77	96	99	100	100				
	R	239	0	10	36	52	71	80	86				
Ravuconazole	All	6,970	85	91	96	98	99	99	99				
	S	6,268	93	98	99	99	99	100	100				
	S-DD	463	10	35	63	88	97	99	99				
	R	239	12	27	49	58	69	80	86				

[a] S MIC, ≤8 μg/ml; S-DD MIC, 16 to 32 μg/ml; R MIC, ≥64 μg/ml.

well was observed (11). Amphotericin B MICs determined by Etest were read after 48 h of incubation at 35°C and were determined to be at 100% inhibition of growth, where the border of the elliptical inhibition zone intercepted the scale on the strip edge (17, 27). Quality control was ensured by testing the NCCLS-recommended strains *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019 (2, 11).

The interpretive criteria for susceptibility to fluconazole, itraconazole, and 5FC were those published by Rex et al. (20) and the NCCLS (11). The investigational triazoles ravuconazole and voriconazole have not been assigned interpretive breakpoints. For purposes of comparison, and because preliminary pharmacokinetic data indicate that achievable levels for these agents in serum may range from 2 to 6 μg/ml, depending on the dosing regimen (24, 26; D. M. Grasela, S. J. Olsen, V. Mummaenni, P. Rolan, L. Christopher, J. Norton, O. H. Hadjilabris, and M. R. Marino, Abstr. 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 839, p. 22, 2000), we have employed a susceptible breakpoint of ≤1 μg/ml for both agents. Interpretive criteria have not yet been defined for amphotericin B; however, for purposes of comparison, we have determined the percentage of isolates inhibited by ≤1 μg of amphotericin B per ml to be susceptible in this study.

Statistical methods. The chi-square test was used to compare selected categorical variables. Alpha was set at 0.05, and all reported *P* values are two tailed.

RESULTS AND DISCUSSION

Table 1 summarizes the in vitro susceptibility of 6,970 isolates of *Candida* spp. to ravuconazole, voriconazole, and itraconazole stratified by fluconazole susceptibility category. Overall, both ravuconazole and voriconazole were active in vitro (MIC at which 90% of the isolates tested are inhibited [MIC_{90}], 0.25 μg/ml; 98% of isolates were inhibited by ≤1 μg/ml); however, a decrease in the activity of both of these agents was noted among isolates that were S-DD and R to fluconazole.

The in vitro activities of all tested agents, stratified by species and fluconazole susceptibility, are outlined in Table 2. Fluconazole, ravuconazole, voriconazole, and 5FC were all highly active against *C. albicans*, *C. parapsilosis*, *C. tropicalis*, and *C. lusitaniae*. Fluconazole was less active against *C. krusei* (5% S), *C. dubliniensis* (89% S), and *C. guilliermondii* (81% S), whereas 98 to 100% of these isolates were susceptible to ravuconazole and voriconazole. Likewise, 60% of *C. glabrata* isolates were susceptible to fluconazole, and 89 and 92%, respectively, were inhibited by ≤1 μg of ravuconazole and voriconazole per ml. With the exception of *C. krusei*, species of *Candida* became less susceptible to ravuconazole and voriconazole as they showed increasing resistance to fluconazole. Notably, 98 to 100% of *C. krusei* isolates were susceptible to ravuconazole and voriconazole (MIC, ≤1 μg/ml), irrespective of their level of resistance to fluconazole. Among the six antifungal agents tested, only ravuconazole and voriconazole were reliably active against *C. krusei*.

A more detailed analysis of cross-resistance among the licensed and investigational triazoles is shown in Table 3. Only *C. albicans*, *C. glabrata*, and *C. krusei* yielded sufficient numbers of fluconazole-resistant isolates to warrant analysis. Significant differences in the activities of both ravuconazole and voriconazole were observed when tested against isolates of *C. albicans* that were resistant to both fluconazole and itraconazole (RR phenotype) versus those that were resistant to fluconazole only (RS phenotype). Both ravuconazole and voriconazole were significantly less active against the RR phenotype of *C. albicans*, whereas their activities against the RS phenotype were comparable to those observed against fluconazole-susceptible *C. albicans* isolates. Among the fluconazole-resistant *C. glabrata* isolates, all but one were also resistant to itraconazole. Similar to the findings observed with *C. albicans*, the RR phenotype of *C. glabrata* was significantly less susceptible to both ravuconazole and voriconazole than the RS phenotype or the fluconazole S and S-DD strains (Table 2). In contrast to the pattern observed with *C. albicans* and *C. glabrata*, both ravuconazole and voriconazole were highly active against both RR and RS phenotypes of *C. krusei.*

These findings confirm and extend those reported previously regarding the antifungal activity of ravuconazole (4, 7, 13, 18) and voriconazole (1, 5, 6, 10, 13, 18). Both triazoles were more active in vitro than fluconazole and itraconazole against virtu-

TABLE 2. Antifungal susceptibility of *Candida* isolates stratified by species and fluconazole susceptibility

Species (*n*)	Antifungal agent	Fluconazole susceptibility[a]											
		S			S-DD			R			All		
		n	MIC_{50}/MIC_{90}	%S	*n*	MIC_{50}/MIC_{90}	%S	*n*	MIC_{50}/MIC_{90}	%S	*n*	MIC_{50}/MIC_{90}	%S
C. albicans (4,195)	Fluconazole	4,054	0.25/0.5	100	56	16/32	0	85	>128/>128	0	4,195	0.25/0.5	97
	Itraconazole		0.03/012	96		0.5/1	11		1/>8	0		0.03/0.12	93
	Voriconazole		0.007/0.015	99		0.25/1	93		1/>8	57		0.007/0.03	99
	Ravuconazole		0.007/0.015	99		0.25/2	89		0.25/>8	73		0.007/0.03	99
	Amphotericin B[b]		0.5/1	96		1/2	85		1/2	79		0.5/1	95
	5FC		0.5/1	97		0.25/1	96		0.25/1	98		0.25/1	97
C. glabrata (949)	Fluconazole	567	4/8	100	303	16/32	0	78	>64/>64	0	949	8/32	60
	Itraconazole		0.5/1	6		1/2	0		8/>8	0		1/2	4
	Voriconazole		0.12/0.25	100		0.5/1	97		2/8	13		0.25/1	92
	Ravuconazole		0.12/0.5	99		0.5/2	87		4/8	11		0.25/2	89
	Amphotericin B		2/4	46		2/4	46		1/4	57		2/4	47[c]
	5FC		0.12/0.12	99		0.12/0.12	98		0.12/0.12	97		0.12/0.12	99
C. parapsilosis (814)	Fluconazole	803	0.5/2	100	8	16/ND[d]	0	2	64/ND	0	814	0.5/2	99
	Itraconazole		0.12/0.25	55		0.5/ND	0		0.25/ND	0		0.12/0.25	4
	Voriconazole		0.03/0.06	100		0.5/ND	71		0.5/ND	100		0.03/0.06	99
	Ravuconazole		0.03/0.12	100		1/ND	71		0.12/ND	100		0.03/0.12	99
	Amphotericin B		2/4	42		1/ND	60		1/ND	50		2/4	43[c]
	5FC		0.12/0.25	99		0.12/ND	100		0.25/ND	50		0.12/0.25	99
C. tropicalis (597)	Fluconazole	585	0.5/2	100	7	16/ND	0	5	>64/ND	0	597	0.5/2	98
	Itraconazole		0.12/0.5	59		1/ND	0		>8/ND	0		0.12/0.5	58
	Voriconazole		0.03/0.12	100		1/ND	50		>8/ND	0		0.06/0.12	99
	Ravuconazole		0.03/0.12	99		2/ND	33		>8/ND	0		0.03/0.12	98
	Amphotericin B		1/2	57		1/ND	50		1/ND	50		1/2	57[c]
	5FC		0.5/1	93		0.25/ND	100		0.5/ND	100		0.25/1	93
C. krusei (131)	Fluconazole	6	8/ND	100	65	32/32	0	60	64/64	0	131	32/64	5
	Itraconazole		0.25/ND	17		0.5/1	2		1/1	2		0.5/1	2
	Voriconazole		0.12/ND	100		0.25/0.5	100		0.5/1	98		0.5/0.5	99
	Ravuconazole		0.25/ND	100		0.25/0.5	98		0.5/1	98		0.5/0.5	98
	Amphotericin B		1/ND	50		4/8	6		4/8	2		4/8	7[c]
	5FC		0.25/ND	67		16/32	5		16/32	2		16/32	6
C. dubliniensis (88)	Fluconazole	78	0.12/0.25	100	6	32/ND	0	4	>64/ND	0	88	0.25/16	89
	Itraconazole		0.06/0.12	91		0.12/ND	50		0.5/ND	0		0.06/0.25	84
	Voriconazole		0.007/0.03	100		0.25/ND	100		0.5/ND	100		0.007/0.03	100
	Ravuconazole		0.007/0.03	100		0.06/ND	100		0.06/ND	100		0.007/0.03	100
	Amphotericin B		1/1	100		0.12/ND	100		0.5/ND	100		0.25/0.5	100
	5FC		0.06/0.06	100		0.06/ND	100		0.06/ND	100		0.06/0.06	100
C. guilliermondi (85)	Fluconazole	68	4/8	100	14	16/32	0	2	>64/ND	0	85	4/16	81
	Itraconazole		0.5/1	7		1/1	0		4/ND	0		1/1	7
	Voriconazole		0.12/0.25	100		0.25/0.5	100		2/ND	0		0.12/0.25	98
	Ravuconazole		0.25/0.5	97		0.5/1	100		4/ND	0		0.25/1	98
	Amphotericin B		0.25/1	100		0.5/1	100		0.5/ND	50		0.5/1	99
	5FC		0.12/0.5	100		0.12/0.25	100		0.06/ND	100		0.12/0.5	100
C. lusitaniae (58)	Fluconazole	57	0.5/2	100	1	16	0				58	0.5/2	98
	Itraconazole		0.12/0.25	51		2	0					0.12/0.25	50
	Voriconazole		0.007/0.015	100		0.5	100					0.007/0.015	100
	Ravuconazole		0.015/0.06	100		2	0					0.015/0.06	98
	Amphotericin B		0.5/1	98		0.5	100					0.5/1	98
	5FC		0.06/0.12	91		0.06	100					0.06/0.12	93

[a] Fluconazole susceptibility categories are defined in the footnote to Table 1. *n* represents the number of isolates tested in each category. %S, percent susceptible: fluconazole MIC, ≤8 μg/ml; 5FC MIC, ≤4 μg/ml; itraconazole MIC, ≤0.12 μg/ml; all other MICs, ≤1 μg/ml.

[b] Amphotericin B MICs were determined by Etest.

[c] $P < 0.001$ compared to amphotericin B activity against *C. albicans*.

[d] ND, not determined (fewer than 10 isolates).

ally all of the *Candida* spp. tested. Although the MICs of ravuconazole and voriconazole for *C. albicans* and *C. glabrata* isolates that were resistant to fluconazole and itraconazole (RR phenotype) were also found to be elevated, those isolates that were resistant to fluconazole alone (RS phenotype) and those for which fluconazole MICs were 16 to 32 μg/ml, were susceptible to ≤1 μg of both ravuconazole and voriconazole per ml. As reported by Perea et al. (12), high-level fluconazole-resistant strains of *C. albicans* commonly display multiple mechanisms of resistance, including overexpression of MDR1 and CDR efflux pumps as well as alterations in the target enzyme and overexpression of the genes encoding the enzyme.

TABLE 3. Cross-resistance among approved and investigational triazoles

Species	Antifungal agent	Fluconazole/itraconazole susceptibility category[a]	n[b]	Cumulative % inhibited at MIC (μg/ml) of:						
				0.12	0.25	0.5	1	2	4	8
C. albicans	Voriconazole	RR	37	0	2.7	10.8	18.9[c]	37.8	40.5	40.5
		RS	38	2.6	26.3	55.3	94.7[c]	100		
	Ravuconazole	RR	32	12.5	18.8	25.0	40.6[c]	43.8	46.9	46.9
		RS	38	50.0	89.5	97.4	100[c]			
C. glabrata	Voriconazole	RR	70	0	0	0	11.4	55.7	78.6	97.1
		RS	1	0	0	100				
	Ravuconazole	RR	64	0	0	0	9.4	42.2	71.9	92.2
		RS	1	0	0	0	100			
C. krusei	Voriconazole	RR	39	0	15.4	79.5	100[d]			
		RS	19	0	26.3	89.5	94.7[d]	94.7	100	
	Ravuconazole	RR	35	0	17.1	88.6	100[d]			
		RS	18	0	33.3	88.9	94.4[d]	94.4	100	

[a] R/R, fluconazole MIC of ≥64 μg/ml and itraconazole MIC of ≥1 μg/ml; RS, fluconazole MIC of ≥64 μg/ml and itraconazole MIC of ≤0.12 μg/ml.
[b] n, number of isolates tested in each category.
[c] $P < 0.001$ for difference in percent inhibited in RR versus RS.
[d] $P > 0.05$ for difference in percent inhibited in RR versus RS.

Such isolates have been shown to be less susceptible to multiple azoles, including itraconazole and voriconazole (12). *C. albicans* strains demonstrating the RS phenotype probably do not overexpress CDR genes or have target enzyme alterations (12) and thus are more likely to be susceptible to azoles other than fluconazole. *C. glabrata* isolates with the RR phenotype are well known to overexpress CDR genes (29), so it is not surprising that these isolates would be resistant to the new triazoles as well.

In contrast to the findings with *C. albicans* and *C. glabrata*, high-level resistance to fluconazole and itraconazole was observed in *C. krusei* isolates without concomitant resistance to ravuconazole and voriconazole. Both of the new triazoles were equally active against both RR and RS phenotypes. These findings imply different mechanisms of resistance to azoles in *C. krusei* compared to other *Candida* spp. The fact that *C. krusei* bloodstream infection isolates tested in this study were not only resistant to fluconazole and itraconazole, but also were resistant to amphotericin B and 5FC, is noteworthy and suggests that the new triazoles may be important agents in the treatment of infections due to *C. krusei*.

Consistent with these in vitro results, in vivo studies have demonstrated efficacy in treating infections due to *Candida* spp. with voriconazole (24, 26) and ravuconazole (8, 9). Pharmacokinetic studies have demonstrated excellent oral bioavailability for both agents and peak concentrations in plasma of 2 to 6 μg/ml, with sustained levels exceeding 1 μg/ml for the entire dosing interval (24, 26; D. M. Grasela et al., 40th ICAAC). Thus, the oral (ravuconazole and voriconazole) and parenteral (voriconazole) dosing regimens result in concentrations of ravuconazole and voriconazole in plasma that exceed the MICs for 98% of *Candida* spp.

In summary, we have demonstrated that ravuconazole and voriconazole are more potent than the four approved systemic antifungal agents against a large collection of recent clinical isolates of *Candida*. While cross-resistance is a concern with strains of *C. albicans* and *C. glabrata* that are capable of expressing multiple mechanisms of resistance, both agents are promising as new and important additions to the antifungal armamentarium.

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REFERENCES

1. **Barry, A. L., and S. D. Brown.** 1996. In vitro studies of two triazole antifungal agents (voriconazole [UK-109,496] and fluconazole) against *Candida* species. Antimicrob. Agents Chemother. **40:**1948–1949.
2. **Barry, A. L., M. A. Pfaller, S. D. Brown, A. Espinel-Ingroff, M. A. Ghannoum, C. Knapp, R. P. Rennie, J. H. Rex, and M. G. Rinaldi.** 2000. Quality control limits for broth microdilution susceptibility tests of ten antifungal agents. J. Clin. Microbiol. **38:**3457–3459.
3. **Cacciapuoti, A., D. Loebenberg, E. Corconan, F. Menzel, Jr., E. I. Moss, Jr., C. Norris, M. Michalski, K. Raynor, J. Halpern, C. Mendrick, B. Arnold, B. Antonacci, R. Parmegiani, T. Yarosh-Tomaine, G. H. Miller, and R. S. Hare.** 2000. In vitro and in vivo activities of SCH 56592 (posaconazole), a new triazole antifungal agent against *Aspergillus* and *Candida*. Antimicrob. Agents Chemother. **44:**2017–2022.
4. **Diekema, D. J., M. A. Pfaller, S. A. Messer, A. Houston, R. J. Hollis, G. V. Doern, R. N. Jones, and The SENTRY Participants Group.** 1999. In vitro activities of BMS-207147 against over 600 contemporary clinical bloodstream isolates of *Candida* species from the SENTRY Antimicrobial Surveillance Program in North America and Latin America. Antimicrob. Agents Chemother. **43:**2236–2239.
5. **Espinel-Ingroff, A.** 1998. In vitro activity of the new triazole voriconazole (UK-109,496) against opportunistic filamentous and dimorphic fungi and common and emerging yeast pathogens. J. Clin. Microbiol. **36:**198–202.
6. **Espinel-Ingroff, A., K. Boyle, and D. J. Sheehan.** 2001. In vitro antifungal activities of voriconazole and reference agents as determined by NCCLS methods: review of the literature. Mycopathologia **150:**101–115.
7. **Fung-Tomc, J. C., E. Huczko, B. Minassian, and D. P. Bonner.** 1998. In vitro activity of a new oral triazole, BMS-207147 (ER-30346). Antimicrob. Agents Chemother. **42:**313–318.
8. **Hata, K., J. Kimura, H. Miki, T. Toyosawa, T. Nakamura, and K. Katsu.** 1996. In vitro and in vivo activities of ER-30346, a novel oral triazole with a broad antifungal spectrum. Antimicrob. Agents Chemother. **40:**2237–2242.

9. **Hata, K., J. Kimura, H. Miki, T. Toyosawa, M. Moriyama, and K. Katsu.** 1996. Efficacy of ER-30346, a novel oral triazole antifungal agent, in experimental models of aspergillosis, candidiasis, and cryptococcosis. Antimicrob. Agents Chemother. **40:**2243–2247.
10. **Marco, F., M. A. Pfaller, S. Messer, and R. N. Jones.** 1998. In vitro activities of voriconazole (UK-109,496) and four other antifungal agents against 394 clinical isolates of *Candida* spp. Antimicrob. Agents Chemother. **42:**161–163.
11. **National Committee for Clinical Laboratory Standards.** 1997. Reference method for broth dilution antifungal susceptibility testing of yeast. Approved standard M27-A. National Committee for Clinical Laboratory Standards, Wayne, Pa.
12. **Perea, S., J. L. López-Ribot, W. R. Kirkpatrick, R. K. McAtee, R. A. Santillán, M. Martinez, D. Calabrese, D. Sanglard, and T. F. Patterson.** 2001. Prevalence of molecular mechanisms of resistance to azole antifungal agents in *Candida albicans* strains displaying high-level fluconazole resistance isolated from human immunodeficiency virus-infected patients. Antimicrob. Agents Chemother. **45:**2676–2684.
13. **Pfaller, M. A., S. A. Messer, R. J. Hollis, R. N. Jones, G. V. Doern, M. E. Brandt, and R. A. Hajjeh.** 1998. In vitro susceptibilities of *Candida* bloodstream isolates to the new triazole antifungal agents BMS-207147, SCh 56592, and voriconazole. Antimicrob. Agents Chemother. **42:**3242–3244.
14. **Pfaller, M. A., R. N. Jones, S. A. Messer, M. B. Edmond, and R. P. Wenzel.** 1998. National surveillance of nosocomial bloodstream infection due to species of *Candida* other than *Candida albicans*: frequency of occurrence and antifungal susceptibility in the SCOPE Program. Diagn. Microbiol. Infect. Dis. **30:**121–129.
15. **Pfaller, M. A., S. A. Messer, A. Houston, M. S. Rangel-Frauso, T. Wiblin, H. M. Blumberg, J. E. Edwards, W. Jarvis, M. A. Martin, H. C. Neu, L. Saiman, J. E. Patterson, J. C. Dibb, C. M. Roldan, M. G. Rinaldi, and R. P. Wenzel.** 1998. National Epidemiology of Mycoses Survey: a multicenter study of strain variation and antifungal susceptibility among isolates of *Candida* species. Diagn. Microbiol. Infect. Dis. **31:**289–296.
16. **Pfaller, M. A., R. N. Jones, G. V. Doern, H. S. Sader, R. J. Hollis, and S. A. Messer for the SENTRY Participant Group.** 1998. International surveillance of bloodstream infections due to *Candida* species: frequency of occurrence and antifungal susceptibilities of isolates collected in 1997 in the United States, Canada, and South America for the SENTRY Program. J. Clin. Microbiol. **36:**1886–1889.
17. **Pfaller, M. A., S. A. Messer, and A. Bolmstrom.** 1998. Evaluation of Etest for determining in vitro susceptibility of yeast isolates to amphotericin B. Diagn. Microbiol. Infect. Dis. **32:**223–227.
18. **Pfaller, M. A., D. J. Diekema, R. N. Jones, H. S. Sader, A. C. Fluit, R. J. Hollis, S. A. Messer, and The SENTRY Participant Group.** 2001. International surveillance of bloodstream infections due to *Candida* species: frequency of occurrence and in vitro susceptibilities to fluconazole, ravuconazole, and voriconazole of isolates collected from 1997 through 1999 in the SENTRY Antimicrobial Surveillance Program. J. Clin. Microbiol. **39:**3254–3259.
19. **Pfaller, M. A., S. A. Messer, R. J. Hollis, and R. N. Jones.** 2001. In vitro activities of posaconazole (Sch 56592) compared with those of itraconazole and fluconazole against 3,685 clinical isolates of *Candida* spp. and *Cryptococcus neoformans*. Antimicrob. Agents Chemother. **45:**2862–2864.
20. **Rex, J. H., M. A. Pfaller, J. N. Galgiani, M. S. Bartlett, A. Espinel-Ingroff, M. A. Ghannoum, M. Lancaster, F. C. Odds, M. G. Rinaldi, T. J. Walsh, and A. L. Barry for the Subcommittee on Antifungal Susceptibility Testing of the National Committee for Clinical Laboratory Standards.** 1997. Development of interpretive breakpoints for antifungal susceptibility testing: conceptual framework and analysis of in vitro-in vivo correlation data for fluconazole, itraconazole and *Candida* infections. Clin. Infect. Dis. **24:**235–247.
21. **Rex, J. H., T. J. Walsh, J. D. Sobel, S. G. Filler, P. G. Pappas, W. E. Dismukes, and J. E. Edwards.** 2000. Practice guidelines for the treatment of candidiasis. Clin. Infect. Dis. **30:**662–678.
22. **Rex, J. H., M. A. Pfaller, T. J. Walsh, V. Chaturvedi, A. Espinel-Ingroff, M. A. Ghannoum, L. L. Gosey, F. C. Odds, M. G. Rinaldi, D. J. Sheehan, and D. W. Warnock.** 2001. Antifungal susceptibility testing: practical aspects and current challenges. Clin. Microbiol. Rev. **14:**643–658.
23. **Ruhnke, M., A. Schmidt-Westhausen, and M. Trautmann.** 1997. In vitro activities of voriconazole (UK-109,496) against fluconazole-susceptible and -resistant *Candida albicans* isolates from oral cavities of patients with human immunodeficiency virus infection. Antimicrob. Agents Chemother. **41:**575–577.
24. **Sabo, J. A., and S. M. Abdel-Rahman.** 2000. Voriconazole: a new triazole antifungal. Ann. Pharmacother. **34:**1032–1043.
25. **Sheehan, D. J., C. A. Hitchcock, and C. M. Sibley.** 1999. Current and emerging azole antifungal agents. Clin. Microbiol. Rev. **12:**40–79.
26. **Verweij, P. E., B. E. de Pauw, and J. F. Meis.** 1999. Voriconazole. Curr. Opin. Anti-Infect. Investig. Drugs **1:**361–372.
27. **Wanger, A., K. Mills, P. W. Nelson, and J. H. Rex.** 1995. Comparison of Etest and National Committee for Clinical Laboratory Standards broth macrodilution method for antifungal susceptibility testing: enhanced ability to detect amphotericin B-resistant *Candida* isolates. Antimicrob. Agents Chemother. **39:**2520–2522.
28. **Warren, N. G., and K. C. Hazen.** 1999. *Candida*, *Cryptococcus*, and other yeasts of medical importance, p. 1184–1199. *In* P. R. Murray, E. J. Baron, M. A. Pfaller, F. C. Tenover, and R. H. Yolken (ed.), Manual of clinical microbiology, 7th ed. ASM Press, Washington, D.C.
29. **White, T. C., K. A. Marr, and R. A. Bowden.** 1998. Clinical, cellular, and molecular factors that contribute to antifungal drug resistance. Clin. Microbiol. Rev. **11:**382–402.