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Antifungal Activities of Posaconazole, Ravuconazole, and Voriconazole Compared to Those of Itraconazole and Amphotericin B against 239 Clinical Isolates of *Aspergillus* spp. and Other Filamentous Fungi: Report from SENTRY Antimicrobial Surveillance Program, 2000

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Posaconazole, ravuconazole, and voriconazole are new triazole derivatives that possess potent, broad-spectrum antifungal activity. We evaluated the in vitro activity of these investigational triazoles compared with that of itraconazole and amphotericin B against 239 clinical isolates of filamentous fungi from the SENTRY Program, including *Aspergillus* spp. (198 isolates), *Fusarium* spp. (7 isolates), *Penicillium* spp. (19 isolates), *Rhizopus* spp. (4 isolates), *Mucor* spp. (2 isolates), and miscellaneous species (9 isolates). The isolates were obtained from 16 different medical centers in the United States and Canada between January and December 2000. In vitro susceptibility testing was performed using the microdilution broth method outlined in the National Committee for Clinical Laboratory Standards M38-P document. Overall, posaconazole was the most active compound, inhibiting 94% of isolates at a MIC of ≤1 μg/ml, followed by voriconazole (91%), amphotericin B (89%), ravuconazole (88%), and itraconazole (70%). All three new triazoles demonstrated excellent activity (MIC, ≤1 μg/ml) against *Aspergillus* spp. (114 *Aspergillus fumigatus*, 22 *Aspergillus niger*, 13 *Aspergillus flavus*, 9 *Aspergillus versicolor*, 8 *Aspergillus terreus*, and 32 *Aspergillus* spp.): posaconazole (98%), voriconazole (98%), ravuconazole (92%), amphotericin B (89%), and itraconazole (72%). None of the triazoles were active against *Fusarium* spp. (MIC at which 50% of the isolates tested were inhibited [MIC_{50}], >8 μg/ml) or *Mucor* spp. (MIC_{50}, >8 μg/ml). Posaconazole and ravuconazole were more active than voriconazole against *Rhizopus* spp. (MIC_{50}, 1 to 2 μg/ml versus >8 μg/ml, respectively). Based on these results, all three new triazoles exhibited promising activity against *Aspergillus* spp. and other less commonly encountered isolates of filamentous fungi. The clinical value of these in vitro data remains to be seen, and in vitro-in vivo correlation is needed for both new and established antifungal agents. Surveillance efforts should be expanded in order to monitor the spectrum of filamentous fungal pathogens and their in vitro susceptibility as these new antifungal agents are introduced into clinical use.

Although *Candida* spp. and *Cryptococcus neoformans* remain the most common causes of invasive opportunistic mycotic infection (14, 15, 35), serious infections due to *Aspergillus* spp. and other filamentous fungi are emerging as prominent causes of infectious morbidity and mortality worldwide (5, 11, 13, 27). Invasive aspergillosis occurs at a rate of 12.4 cases per million people per year in the United States (35). Dasbach et al. (4) estimated that invasive aspergillosis increased by approximately eightfold between 1976 and 1996, with over 10,000 cases and a cost of $548 million annually in the United States. Likewise, an expanding number of hyaline filamentous fungi (e.g. *Fusarium*, *Acremonium*, *Penicillium*, and *Scedosporium* species), Zygomycetes, and dematiaceous filamentous fungi (e.g., *Bipolaris*, *Alternaria*, and *Exophiala* species) pose additional threats to the ever-increasing population of immunocompromised hosts in hospitals and the community (13, 27, 29, 35).

Current diagnostic and therapeutic approaches fall short in addressing the problem of filamentous fungal infections (5, 13, 16). Although amphotericin B remains the standard therapy for these infections, therapeutic outcomes are suboptimal (3, 13, 37, 39). Clearly, there is a need for alternative antifungal agents to address these serious infections (7, 12, 13, 17, 38).

Although ongoing antimicrobial surveillance systems have provided useful information regarding the spectrum of pathogens and the antifungal susceptibility of yeasts causing invasive fungal infections (1, 15, 30, 31, 33), there is little, if any, such information for the filamentous fungi (29, 35). Expansion of existing surveillance programs to include filamentous fungi will provide information regarding the frequency of various species causing invasive disease and in vitro susceptibility testing of these opportunistic pathogens against both new and established antifungal agents will provide data that may have important implications for antifungal drug treatment regimens in the appropriate clinical setting.

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The SENTRY Antimicrobial Surveillance Program has documented the spectrum and activity of various antifungal agents against *Candida* spp. on a global scale since 1997 (6, 30–33). In January 2000, the SENTRY Surveillance Program was expanded to include monitoring of *Aspergillus* spp. and other filamentous fungi causing invasive mycoses in hospitalized patients. Clinical isolates from 16 different medical centers were sent to the University of Iowa for characterization, including antifungal susceptibility testing. In this study, we report the results of the first 12 months of filamentous fungal pathogen surveillance in the SENTRY Program (United States and Canada) and compare the in vitro activity of three new triazole antifungal agents, posaconazole, ravuconazole, and voriconazole, with that of itraconazole and amphotericin B using the National Committee for Clinical Laboratory Standards (NCCLS) M38-P microdilution method (23).

MATERIALS AND METHODS

Organisms. A total of 239 clinical isolates of filamentous fungi were obtained from 16 different medical centers in the United States (14 centers) and Canada (2 centers) between January and December 2000. The isolates were obtained from a variety of sources, including sputum, bronchoscopy, and tissue biopsy specimens. The collection included the following isolates: *Aspergillus fumigatus*, (114 isolates), *Aspergillus niger* (22 isolates), *Aspergillus flavus* (13 isolates), *Aspergillus versicolor* (9 isolates), *Aspergillus terreus* (8 isolates), *Aspergillus* spp. (32 isolates), *Penicillium* spp. (19 isolates), *Fusarium* spp. (7 isolates), *Rhizopus* spp. (4 isolates), *Mucor* spp. (2 isolates), *Paecilomyces* spp. (2 isolates), *Trichosporon* spp. (2 isolates), and one isolate each of *Acremonium* sp., *Biopolaris* sp., *Chrysosporium* sp., *Geotrichum* sp., and *Wangiella dermatitidis*. All isolates were stored as spore suspensions in sterile distilled water at room temperature until they were used in the study. Before testing, each isolate was subcultured at least twice on potato dextrose agar (Remel, Lenexa, Kans.) to ensure its viability and purity.

Antifungal drugs. Posaconazole (Schering-Plough Research Institute, Kenilworth, N.J.), ravuconazole (Bristol-Myers Squibb, Wallingford, Conn.), voriconazole (Pfizer Pharmaceutical Group, New York, N.Y.), itraconazole (Janssen, Beerse, Belgium) and amphotericin B (Sigma Chemical Co., St. Louis, Mo.) were all obtained as reagent-grade powders from their respective manufacturers. Stock solutions were prepared in polyethylene glycol (posaconazole and itraconazole) and dimethyl sulfoxide (ravuconazole, voriconazole, and amphotericin B). All drugs were diluted in RPMI 1640 medium (Sigma Chemical Co.) buffered to pH 7.0 with 0.165 M morpholinepropanesulfonic acid (MOPS) buffer (Sigma) and dispensed into 96-well microdilution trays. The recommendations stated in NCCLS document M38-P were followed for the dilution of each antifungal agent (23). Trays containing an aliquot of 0.1 ml in each well of appropriate drug solution (2× final concentration) were sealed and stored at −70°C until they were used. The final ranges of drug concentrations tested were 0.008 to 8 μg/ml for all five antifungal agents.

Susceptibility testing. MICs were determined by the NCCLS M38-P broth microdilution methodology (23). Briefly, each isolate was grown on potato dextrose agar slants at 35°C for a period of 7 days. The fungal colonies were then covered with 1 ml of sterile 0.85% saline and gently scraped with a sterile pipette. The resulting suspensions were transferred to sterile tubes, and heavy particles were allowed to settle. The turbidity of the conidial spore suspensions was measured at 530 nm and was adjusted to obtain a final inoculum of 0.4×10^4 CFU/ml. To determine the final inoculum, an appropriate dilution was performed and an aliquot (0.01 ml) was plated on potato dextrose agar (Remel). Plates were incubated at 30°C and were examined daily for the presence of fungal colonies. The microdilution trays were incubated at 35°C, and MICs were read at 48 h. Drug-free controls were included in each tray. Following incubation, MIC endpoints were interpreted with the aid of a reading mirror. Only wells that showed no growth (optically clear) or approximately 75% reduction in growth compared to that of drug-free controls were recorded as the MIC.

Quality control. Quality control was ensured by testing the following strains recommended in the NCCLS M38-P document (23): *A. flavus* ATCC 204304, *Candida parapsilosis* ATCC 22019, and *Candida krusei* ATCC 6258. All results were within the recommended limits.

RESULTS AND DISCUSSION

The antifungal activities of posaconazole, ravuconazole, voriconazole, itraconazole, and amphotericin B against 198 isolates of *Aspergillus* spp. are shown in Table 1. Posaconazole, ravuconazole, and voriconazole were all highly active against *A. fumigatus* (98 to 100% susceptible at a MIC of ≤1 μg/ml), *A. flavus* (100%), *A. terreus* (100%), and *Aspergillus* spp. (91 to 94%). Among the 198 isolates of *Aspergillus* species tested, 98% were inhibited by ≤1 μg/ml of posaconazole and voriconazole, followed by ravuconazole (92%), amphotericin B (89%), and itraconazole (72%). Notably, only 25% of *A. terreus* isolates were inhibited by ≤1 μg/ml of amphotericin B compared to 92% of all other *Aspergillus* species.

The new triazoles were less active against the miscellaneous filamentous fungi (Table 2). None of the triazoles, including itraconazole, were active against *Fusarium* spp. (MIC at which 50% of the isolates tested were inhibited [MIC_{50}], >8 μg/ml) or *Mucor* spp. (MIC_{50}, >8 μg/ml). Although the number of isolates was small, posaconazole, ravuconazole, and voriconazole were more active against isolates of *Pencillium* spp. (MIC_{90}, 1 μg/ml), *Paecilomyces* spp. (MIC_{50}, 0.12 to 2 μg/ml), *Trichosporon* spp. (MIC_{50}, 0.12 to 1 μg/ml), *Acremonium* sp. (MIC, 0.5 to 1 μg/ml), *Bipolaris* sp. (MIC, 0.5 to 1 μg/ml), *Geotrichum* sp. (MIC, 0.06 to 0.5 μg/ml) and *W. dermatitidis* (MIC, 0.06 to 1 μg/ml). Posaconzole and ravuconazole were more active than voriconazole against *Rhizopus* spp. (MIC_{50}, 1 to 2 μg/ml versus >8 μg/ml, respectively).

Overall, 94% of the 239 filamentous fungi tested were inhibited by ≤1 μg/ml of posaconazole, followed by voriconazole (91%), amphotericin B (89%), ravuconazole (88%), and itraconazole (70%) (data not shown).

These findings agree with those published earlier with smaller numbers of filamentous fungal isolates (8–10, 18, 19, 21, 25, 34). We found that all three investigational triazoles were more active than itraconazole against all of the *Aspergillus* species tested. In almost every instance, the in vitro potencies of posaconazole, ravuconazole, and voriconazole were comparable to one another and slightly greater than that of amphotericin B. Our findings for voriconazole against *Rhizopus* spp. and for all three new triazoles against *Fusarium* spp. and *Mucor* spp. are in agreement with previously published in vitro data (8–10, 18, 19, 21, 25, 34, 36). However, clinical studies of refractory mycoses treated with voriconazole or posaconazole documented success rates of 38 and 50%, respectively, in treatment of invasive fusariosis (R. Y. Hachem, I. I. Raad, C. M. Afif, R. Negroni, J. Graybill, S. Hadley, H. Kantarjian, S. Adams, and G. Mukwaya, 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1009, 2000; J. R. Perfect, I. Lutsar, A. Gonzalez-Ruiz, 38th Ann. Meeting Infect. Dis. Soc. Am., abstr. 303, 2000).

These promising in vitro data do seem to be corroborated by encouraging in vivo results from experimental models and early clinical studies although additional data correlating in vitro activity with clinical outcome are clearly needed (2, 20, 22, 26, 28, 36; B. Dupont, D. E. Denning, H. Lode, S. Yanren, P. F. Troke, and N. Sarantis, 36th ICAAC, abstr. F81, 1995; Hachem et al. 40th ICAAC)). Pharmacokinetic studies with all three new triazoles have demonstrated peak concentrations of >5 μg/ml in plasma, with sustained levels exceeding 1 μg/ml

TABLE 1. In vitro susceptibilities of 198 isolates of *Aspergillus* species to amphotericin B, itraconazole, and three investigational triazole antifungal agents

Organism (no. tested) and antifungal agent	MIC (μg/ml)			% Susceptible at MIC (μg/ml) of:				
	Range	50%	90%	0.25	0.5	1	2	4
A. fumigatus (114)								
Amphotericin B	0.5–4	1	1	0	2	98	99	100
Itraconazole	0.25–2	1	2	2	24	77	100	100
Posaconazole	0.03–1	0.25	0.5	81	99	100	100	100
Ravuconazole	0.25–4	0.5	0.5	16	95	98	99	100
Voriconazole	0.12–4	0.25	0.5	88	98	99	99	100
A. niger (22)								
Amphotericin B	0.25–1	1	1	9	46	100	100	100
Itraconazole	0.5–2	2	2	0	9	36	100	100
Posaconazole	0.25–1	0.5	1	41	82	100	100	100
Ravuconazole	0.5–4	1	2	0	14	50	96	100
Voriconazole	0.25–2	0.5	1	14	73	96	100	100
A. flavus (13)								
Amphotericin B	1–2	1	2	0	0	62	100	100
Itraconazole	0.25–1	0.5	1	8	69	100	100	100
Posaconazole	0.12–1	0.25	0.5	54	92	100	100	100
Ravuconazole	0.12–1	0.5	1	8	62	100	100	100
Voriconazole	0.06–1	0.5	1	23	92	100	100	100
A. versicolor (9)								
Amphotericin B	1–2	1		0	0	89	100	100
Itraconazole	0.5–2	2		0	11	33	100	100
Posaconazole	0.06–2	0.5		33	67	78	100	100
Ravuconazole	0.12–2	1		11	44	89	100	100
Voriconazole	0.25–2	0.5		44	56	89	100	100
A. terreus (8)								
Amphotericin B	1–4	2		0	0	25	88	100
Itraconazole	0.25–0.5	0.5		25	100	100	100	100
Posaconazole	0.06–0.25	0.12		100	100	100	100	100
Ravuconazole	0.25–0.5	0.25		50	100	100	100	100
Voriconazole	0.25–0.5	0.25		75	100	100	100	100
Aspergillus spp. (32)								
Amphotericin B	0.12–2	1	2	3	3	75	100	100
Itraconazole	0.5–>8	1	2	0	25	72	94	97
Posaconazole	0.06–>8	0.25	1	63	81	94	94	94
Ravuconazole	0.12–>8	0.5	1	31	66	91	94	97
Voriconazole	0.12–>8	0.25	1	50	78	94	94	97
All isolates (198)								
Amphotericin B	0.12–4	1	2	2	6	89	99	100
Itraconazole	0.25–>8	1	2	2	27	72	99	99
Posaconazole	0.03–>8	0.25	0.5	70	92	98	99	99
Ravuconazole	0.12–>8	0.5	1	17	78	92	99	99
Voriconazole	0.06–>8	0.25	0.5	67	90	98	99	99

(24, 28; D. M. Grasela, S. J. Olsen, V. Mummaneni, P. Rolan, L. Christopher, J. Norton, O. H. Hadjilambris, and M. R. Marino, 40th ICAAC, abstr. 839, 2000; B. E. Patterson and P. E. Coates, 35th ICAAC, abstr. F78, 1995)). Thus, the dosing regimens for these agents result in concentrations in plasma that exceed the MICs for 92 to 98% of *Aspergillus* species and 88 to 94% of all of the tested filamentous fungi (Tables 1 and 2).

We have also provided further evidence for the feasibility of the NCCLS M38-P broth microdilution method for comparing the activity of both new and established antifungal agents and for testing larger numbers of filamentous fungal isolates in the context of an antifungal surveillance program. Continued longitudinal surveillance efforts of this type using standardized susceptibility testing methods will provide the means with which to track the emergence of antifungal resistance over time among *Aspergillus* species and other filamentous fungal pathogens. The role of such testing in clinical decision-making, however, must await further studies establishing a correlation between in vitro MIC data and clinical outcome. Until such information is available, routine in vitro susceptibility testing of filamentous fungi as a prelude to clinical decision-making is not warranted (23).

Recently, Espinel-Ingroff et al. (10) reported that the NCCLS M38-P microdilution method was able to reliably differentiate between susceptible and potentially resistant strains

TABLE 2. In vitro susceptibilities of 41 isolates of miscellaneous filamentous fungi to amphotericin B, itraconazole, and three investigational triazole antifungal agents

Organism (no. tested) and antifungal agent	MIC (μg/ml)			% Susceptible at MIC (μg/ml) of:				
	Range	50%	90%	0.25	0.5	1	2	4
Penicillium spp. (19)								
Amphotericin B	0.12–2	1	1	16	42	95	100	100
Itraconazole	0.12–2	0.5	2	16	63	89	100	100
Posaconazole	0.03–1	0.25	1	74	89	100	100	100
Ravuconazole	0.03–1	0.5	1	42	74	100	100	100
Voriconazole	0.06–>8	0.5	1	26	74	95	95	95
Fusarium spp. (7)								
Amphotericin B	1–2	1		0	0	86	100	100
Itraconazole	0.5–>8	>8		0	14	14	14	14
Posaconazole	0.25–>8	>8		14	29	29	29	43
Ravuconazole	0.5–>8	>8		0	14	29	29	29
Voriconazole	0.5–>8	8		0	14	29	29	43
Rhizopus spp. (4)								
Amphotericin B	0.5–1	1		0	25	100	100	100
Itraconazole	4–>8	4		0	0	0	0	50
Posaconazole	1–4	2		0	0	25	75	100
Ravuconazole	1–8	1		0	0	50	75	75
Voriconazole	>8	>8		0	0	0	0	0
Mucor spp. (2)								
Amphotericin B	0.5	0.5		0	100	100	100	100
Itraconazole	>8	>8		0	0	0	0	0
Posaconazole	>8	>8		0	0	0	0	0
Ravuconazole	>8	>8		0	0	0	0	0
Voriconazole	>8	>8		0	0	0	0	0
Paecilomyces spp. (2)								
Amphotericin B	0.5	0.5		0	100	100	100	100
Itraconazole	0.25–0.5	0.25		50	100	100	100	100
Posaconazole	0.12–0.5	0.12		50	100	100	100	100
Ravuconazole	1–8	1		0	0	50	50	50
Voriconazole	2–8	2		0	0	0	50	50
Trichosporon spp. (2)								
Amphotericin B	0.06–8	0.06		50	50	50	50	50
Itraconazole	8–>8	8		0	0	0	0	0
Posaconazole	1–>8	1		0	0	50	50	50
Ravuconazole	0.12–>8	0.12		50	50	50	50	50
Voriconazole	0.05–>8	0.5		0	50	50	50	50
Acremonium sp. (1)								
Amphotericin B	2			0	0	0	100	100
Itraconazole	>8			0	0	0	0	0
Posaconazole	1			0	0	100	100	100
Ravuconazole	0.5			0	100	100	100	100
Voriconazole	0.5			0	100	100	100	100
Bipolaris sp. (1)								
Amphotericin B	0.25			100	100	100	100	100
Itraconazole	0.25			100	100	100	100	100
Posaconazole	0.05			0	100	100	100	100
Ravuconazole	1			0	0	100	100	100
Voriconazole	0.5			0	100	100	100	100
Chrysosporium sp. (1)								
Amphotericin B	0.06			100	100	100	100	100
Itraconazole	0.5			0	100	100	100	100
Posaconazole	0.12			100	100	100	100	100
Ravuconazole	>8			0	0	0	0	0
Voriconazole	>8			0	0	0	0	0
Geotrichum sp. (1)								
Amphotericin B	0.25			100	100	100	100	100
Itraconazole	0.5			0	100	100	100	100
Posaconazole	0.25			100	100	100	100	100
Ravuconazole	0.06			100	100	100	100	100
Voriconazole	0.03			100	100	100	100	100
Wangiella dermatitidis (1)								
Amphotericin B	1			0	0	100	100	100
Itraconazole	1			0	0	100	100	100
Posaconazole	0.06			100	100	100	100	100
Ravuconazole	1			0	0	100	100	100
Voriconazole	0.12			100	100	100	100	100

of *Aspergillus* species for itraconazole and possibly for the new triazoles as well. Espinel-Ingroff et al. (10) noted that cross-resistance between itraconazole and the newer triazoles was not universal and may vary according to the strain of *Aspergillus* and the specific triazole being tested. Our results support these findings and are most notable for *A. fumigatus*, of which ≥95% of 114 isolates were inhibited by ≤0.5 μg/ml of posaconazole, ravuconazole, and voriconazole compared to only 24% with itraconazole (Table 1).

In summary, we found that posaconazole, ravuconazole, and voriconazole all exhibit excellent in vitro activity against *Aspergillus* spp. and several less common filamentous fungi. These agents are more active than amphotericin B against *Aspergillus* spp. and offer important advantages over itraconazole in terms of spectrum and potency. Continued surveillance for emerging resistance and continued development of these exciting new agents is encouraged.

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REFERENCES

1. **Brandt, M. E., M. A. Pfaller, R. A. Hajjeh, R. J. Hamil, P. G. Pappas, A. L. Reingold, D. Rimland, and D. W. Warnock.** 2001. Trends in antifungal drug susceptibility of *Cryptococcus neoformans* isolates from the United States: 1992 to 1994 and 1996 to 1998. Antimicrob. Agents Chemother. **45:**3065–3069.
2. **Cacciapuoti, A., D. Loebenberg, E. Corcoran, F. Menzel, Jr., E. L. 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.
3. **Caillot, D., L. Mannone, B. Cuisenier, and J.-F. Couaillier.** 2001. Role of early diagnosis and aggressive surgery in the management of invasive pulmonary aspergillosis in neutropenic patients. Clin. Microbiol. Infect. **7**(Suppl. 2)**:**54–61.
4. **Dasbach, E. J., G. M. Davies, and S. M. Teutsch.** 2000. Burden of aspergillosis-related hospitalizations in the United States. Clin. Infect. Dis. **31:**1524–1528.
5. **Denning, D. W., A. Marinas, J. Cohen.** 1998. An EORTC multicentre prospective survey of invasive aspergillosis in haematological patients: diagnosis and therapeutic outcome. EORTC Invasive Fungal Infections Cooperative Group. J. Infect. **37:**173–180.
6. **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.
7. **Dismukes, W. E.** 2000. Introduction to antifungal drugs. Clin. Infect. Dis. **30:**653–657.
8. **Espinel-Ingroff, A.** 1998. Comparison of in vitro activities of the new triazole SCH 56592 and the echinocandins MK-0991 (L-743, 872) and LY 303366 against opportunistic filamentous and dimorphic fungi and yeasts. J. Clin. Microbiol. **36:**2950–2956.
9. **Espinel-Ingroff, A.** 2001. In vitro fungicidal activities of voriconazole, itraconazole, and amphotericin B against opportunistic moniliaceous and dematiaceous fungi. J. Clin. Microbiol. **39:**954–958.
10. **Espinel-Ingroff, A., M. Bartlett, V. Chaturvedi, M. Ghannoum, K. C. Hazen, M. A. Pfaller, and T. J. Walsh.** 2001. Optimal susceptibility testing conditions for detection of azole resistance in *Aspergillus* spp.: NCCLS collaborative evaluation. Antimicrob. Agents Chemother **45:**1828–1835.
11. **Groll, A. H., P. M. Shah, C. Metzel, M. Schneider, F. Just-Nuebling, and K. Huebner.** 1996. Trends in the post-mortem epidemiology of invasive fungal infections at a university hospital. J. Infect. **33:**23–32.
12. **Groll, A. H., and T. J. Walsh.** 1997. Potential new antifungal agents. Curr. Opin. Infect. Dis. **10:**449–458.
13. **Groll, A. H., and T. J. Walsh.** 2001. Uncommon opportunistic fungi: new nosocomial threats. Clin. Microbiol. Infect. **7**(Suppl. 2)**:**8–24.
14. **Hajjeh, R. A., M. E. Brandt, and R. W. Pinner.** 1995. Emergence of cryptococcal disease: epidemiologic perspectives 100 years after its discovery. Epidemiol. Rev. **17:**303–320.
15. **Kao, A. S., M. E. Brandt, W. R. Pruitt, L. A. Conn, B. A. Perkins, D. S. Stevens, W. S. Baughman, A. L. Reingold, G. A. Rothrock, M. A. Pfaller, R. W. Pinner, and R. A. Hajjeh.** 1999. The epidemiology of candidemia in two United States cities: results of a population-based active surveillance. Clin. Infect. Dis. **29:**1164–1170.
16. **Klont, R. R., J. F. G. M. Meis, and P. E. Verweij.** 2001. Critical assessment of issues in the diagnosis of invasive aspergillosis. Clin. Microbiol. Infect. **7**(Suppl. 2)**:**32–37.
17. **Lin, S.-J., J. Schranz, and S. M. Teutsch.** 2001. Aspergillosis case-fatality rate: systematic review of the literature. Clin. Infect. Dis. **32:**358–366.
18. **Marco, F., M. A. Pfaller, S. A. Messer, and R. N. Jones.** 1998. Antifungal activity of a new triazole, voriconazole (UK-109, 496), compared with three other antifungal agents tested against clinical isolates of filamentous fungi. Med. Mycol. **36:**433–436.
19. **Marco, F., M. A. Pfaller, S. A. Messer, and R. N. Jones.** 1998. In vitro activity of a new triazole antifungal agent, Sch 56592, against clinical isolates of filamentous fungi. Mycopathologia **141:**73–77.
20. **Martin, M. V., J. Yates, and C. A. Hitchcock.** 1997. Comparison of voriconazole (UK-109, 496) and itraconazole in prevention and treatment of *Aspergillus fumigatus* endocarditis in guinea pigs. Antimicrob. Agents Chemother. **41:**13–16.
21. **McGinnis, M. R., L. Pasarell, D. A. Sutton, A. W. Fothergill, C. R. Cooper, Jr., and M. G. Rinaldi.** 1997. In vitro evaluation of voriconazole against some clinically important fungi. Antimicrob. Agents Chemother. **41:**1832–1834.
22. **Murphy, M., E. M. Bernard, T. Ishimaru, and D. Armstrong.** 1997. Activity of voriconazole (UK-109, 496) against clinical isolates of *Aspergillus* species and its effectiveness in an experimental model of invasive pulmonary aspergillosis. Antimicrob. Agents Chemother. **41:**696–698.
23. **National Committee for Clinical Laboratory Standards.** 1998. Reference method for broth dilution antifungal susceptibility testing of conidium-forming filamentous fungi. Proposed standard M38-P. National Committee for Clinical Laboratory Standards, Wayne, Pa.
24. **Nomier, A. A., P. Kumari, M. J. Hilbert, S. Gupta, D. Loebenberg, A. Cacciapuoti, R. Hare, G. H. Miller, C.-C. Lin, and M. N. Cayen.** 2000. Pharmacokinetics of SCH 56592, a new azole broad-spectrum antifungal agent, in mice, rats, rabbits, dogs, and cynomolgus monkeys. Antimicrob. Agents Chemother. **44:**727–731.
25. **Oakley, K. L., C. B. Moore, and D. W. Denning.** 1997. In vitro activity of SCH 56592 and comparison with activities of amphotericin B and itraconazole against *Aspergillus* spp. Antimicrob. Agents Chemother. **41:**1124–1126.
26. **Oakley, K. L., G. Morrissey, and D. W. Denning.** 1997. Efficacy of SCH 56592 in a temporarily neutropenic murine model of invasive aspergillosis with an itraconazole-susceptible and an itraconazole-resistant isolate of *Aspergillus fumigatus*. Antimicrob. Agents Chemother. **41:**1503–1507.
27. **Perfect, J. R., and W. A. Schell.** 1996. The new fungal opportunists are coming. Clin. Infect. Dis. **22**(Suppl. 2)**:**S112-S118.
28. **Petraitine, R., V. Petraitis, A. H. Groll, T. Sein, S. Piscitelli, M. Candelario, A. Field-Ridley, N. Avila, J. Bacher, and T. J. Walsh.** 2001. Antifungal activity and pharmacokinetics of posaconazole (SCH 56592) in treatment and prevention of experimental invasive pulmonary aspergillosis: correlation with galactomannan antigenemia. Antimicrob. Agents Chemother. **45:**857–869.
29. **Pfaller, M. A.** 1998. The epidemiology of invasive mycoses—narrowing the gap. Clin. Infect. Dis. **27:**1148–1150.
30. **Pfaller, M. A., R. N. Jones, G. V. Doern, H. S. Sader, R. J. Hollis, and S. A. Messer.** 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.
31. **Pfaller, M. A., R. N. Jones, G. V. Doern, A. C. Fluit, J. Verhoef, H. S. Sader, S. A. Messer, A. Houston, S. Coffman, and R. J. Hollis.** 1999. International

surveillance of bloodstream infections dues to *Candida* species in the European SENTRY Program: species distribution and antifungal susceptibility including the investigational triazole and echinocandin agents. Diagn. Microbiol. Infect. Dis. **35:**19–25.

32. **Pfaller, M. A., R. N. Jones, G. V. Doern, H. S. Sader, S. A. Messer, A. Houston, S. Coffman, and R. J. Hollis.** 2000. Bloodstream infections due to *Candida* species: SENTRY antimicrobial surveillance program in North America and Latin America, 1997–1998. Antimicrob. Agents Chemother. **44:**747–751.
33. **Pfaller, M. A., D. J. Diekema, R. N. Jones, H. S. Sader, A. C. Fluit, R. J. Hollis, and S. A. Messer.** 2001. International surveillance of bloodstream infections due to *Candida* species: Frequency of occurrence and in vitro susceptibility to fluconazole, ravuconazole, and voriconazole among isolates collected from 1997 through 1999 in the SENTRY Antimicrobial Surveillance Program. J. Clin. Microbiol. **39:**3254–3259.
34. **Radford, S. A., E. M. Johnson, and D. W. Warnock.** 1997. In vitro studies of activity of voriconazole (UK-109,4 96), a new triazole antifungal agent, against emerging and less common mold pathogens. Antimicrob. Agents Chemother. **41:**841–843.
35. **Rees, J. R., R. W. Pinner, R. A. Hajjeh, M. E. Brandt, and A. L. Reingold.** 1998. The epidemiological features of invasive mycolic infections in the San Francisco Bay area, 1992–1993: results of a population-based laboratory active surveillance. Clin. Infect. Dis. **27:**1138–1147.
36. **Sheehan, D. J., C. A. Hitchcock, and C. M. Sibley.** 1999. Current and emerging azole antifungal agents. Clin. Microbiol. Rev. **12:**40–79.
37. **Tolleman, J., L. Klingspor, and O. Ringdén.** 2001. Liposomal amphotericin B (AmBisome) for fungal infectons in immunocompromised adults and children. Clin. Microbiol. Infect. **7**(Suppl. 2)**:**68–79.
38. **Walsh, T. J., J. W. Hiemenz, and E. Anaissie.** 1996. Recent progress and current problems in treatment of invasive fungal infections in neutropenic patients. Infect. Dis. Clin. N. Am. **10:**365–400.
39. **Wingard, J. R., P. Kubilis, L. Lee, G. Yee, M. White, L. Walshe, R. Bowden, E. Anaissie, J. Hiemenz, and J. Lister.** 1999. Clinical surveillance of nephrotoxicity in patients treated with amphotericin B for suspected or proven aspergillosis. Clin. Infect. Dis. **29:**1402–1407.