

Phase 2, Randomized, Dose-Ranging Study Evaluating the Safety and Efficacy of Anidulafungin in Invasive Candidiasis and Candidemia

David S. Krause,^{1*} John Reinhardt,² Jose A. Vazquez,³ Annette Reboli,⁴ Beth P. Goldstein,¹ Michele Wible,¹ and Timothy Henkel¹

Vicuron Pharmaceuticals Inc., King of Prussia, Pennsylvania¹; Christiana Care Health Services, Newark, Delaware²; Wayne State University School of Medicine, Detroit, Michigan³; and University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden, Camden, New Jersey⁴

Received 29 October 2003/Returned for modification 23 December 2003/Accepted 9 February 2004

This study evaluated the safety and efficacy of anidulafungin, a novel echinocandin, in patients with invasive candidiasis, including candidemia. A total of 123 eligible patients were randomized to one of three intravenous regimens, 50, 75, or 100 mg once daily. Treatment continued for 2 weeks beyond resolution or improvement of signs and symptoms. The primary efficacy criterion was a successful global response rate (i.e., clinical and microbiological success) in the evaluable population at the follow-up (FU) visit, 2 weeks after end of therapy (EOT). One hundred twenty (120) patients received at least one dose of anidulafungin; 68 were evaluable. Review of adverse events and laboratory data indicated no dose response for safety parameters. Non-*albicans* *Candida* species accounted for approximately one-half of all isolates. Success rates at EOT were 84, 90, and 89% in the 50-, 75-, and 100-mg groups, respectively. At FU, the success rates were 72, 85, and 83%. Phase 3 studies of anidulafungin for the treatment of invasive candidiasis and candidemia are warranted.

Candida species are the fourth most common cause of bloodstream infection, accounting for 8 to 15% of all nosocomial bloodstream infections in the United States (5, 8, 14), and are associated with significant morbidity and an attributable mortality of up to 38% (7). The incidence of candidemia is increasing due to a variety of factors, including iatrogenic immunosuppression, increasingly invasive technologies, and the use of broad-spectrum antibiotics (6, 11). In addition, the epidemiology of candidemia is evolving, with greater representation of non-*albicans* *Candida* species (13, 16).

Anidulafungin is a novel cyclic lipopeptide of the echinocandin class, with a spectrum of antifungal activity that includes *Candida* (all species, including strains resistant to azoles and amphotericin B) and *Aspergillus* spp. (12, 15). Anidulafungin is not metabolized by the liver and is not eliminated in the urine, nor is it a substrate, inhibitor, or inducer of the enzymes in the cytochrome P450 system. No dosage adjustments appear to be required for patients with any degree of hepatic or renal insufficiency or for patients receiving concomitant medications (J. Dowell, M. Stogniew, and D. Krause, 13th Eur. Congr. Clin. Microbiol. Infect. Dis., Clin. Microbiol. Infect. 9(Suppl. 1):1222, 2003; M. Stogniew, F. Pu, T. Henkel, and J. Dowell, 13th Eur. Congr. Clin. Microbiol. Infect. Dis., Clin. Microbiol. Infect. 9(Suppl. 1):1222, 2003; D. Thye, T. Kilfoil, G. Kilfoil, and T. Henkel, Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-1392, 2002). The half-life of anidulafungin is 1 day, and the provision of a loading dose on day 1 at twice the daily maintenance dose allows steady-state plasma levels to be achieved after 24 h (J. Dowell, W. Knebel, T. Ludden, M. Stogniew, D. Krause, and T. Henkel,

Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-1575, 2003).

This phase 2 study was designed to evaluate the safety and efficacy of anidulafungin in patients with invasive candidiasis, including candidemia, and to identify the optimal dose of anidulafungin for such infections.

MATERIALS AND METHODS

The study protocol was reviewed and approved by the institutional review board of each institution prior to implementation. All patients provided written informed consent prior to study entry. Research was conducted according to good clinical practices and in compliance with the U.S. Code of Federal Regulations.

Adult patients ≥ 18 years of age with an expected survival of >72 h were considered for enrollment. Diagnostic criteria for invasive candidiasis were two-fold: (i) blood or tissue sample culture positive for *Candida* and (ii) the presence of at least one sign or symptom of infection within 4 days prior to treatment initiation. Acceptable indicators included inflammation at the site of infection, elevated ($>38.6^{\circ}\text{C}$ on one occasion or $>37.8^{\circ}\text{C}$ on two occasions at least 4 h apart) or subnormal ($<35.5^{\circ}\text{C}$ once) body temperature, and systolic blood pressure of <100 or ≥ 30 mm Hg below baseline. Patients who had received therapeutic doses of antifungal therapy (defined as a cumulative dose greater than or equal to any of the following: 1.6 mg of amphotericin/kg of body weight or 10 mg of a lipid-based formulation/kg, 1,600 mg of fluconazole, 800 mg of itraconazole, 800 mg of ketoconazole, or 120 mg of caspofungin) within 7 days of enrollment were excluded from the study unless the patient had been designated a treatment failure on the prior therapy. Pregnant or lactating women were excluded from the study, as were patients with known hypersensitivity to echinocandin excipients.

Eligible patients were randomized equally (in blocks of three) via an interactive voice response system to one of three treatment arms: 50, 75, or 100 mg once daily. At each dose level, patients received a loading dose of twice the daily maintenance dose given as a single infusion on day 1. All infusions were to be given at a rate of 1 mg/min at the same time each day. Treatment continued for 2 weeks after resolution of the infection, and blood and tissue cultures were negative, or presumed to be negative if not obtainable, to a maximum of 42 days. Clinical signs and symptoms were assessed at baseline, daily during treatment, at the end of therapy (EOT), and at a follow-up (FU) visit 2 weeks after the EOT. Adverse events and concomitant medication use data were collected at each study visit. Hematology and clinical-chemistry parameters were examined periodically during treatment and at the EOT and FU visits. Blood cultures were

* Corresponding author. Mailing address: Vicuron Pharmaceuticals Inc., 455 S. Gulph Rd., Suite 310, King of Prussia, PA 19406. Phone: (610) 491-2206. Fax: (610) 491-2298. E-mail: dkrause@vicuron.com.

TABLE 1. Patient populations

Characteristic	No. of patients			Total
	Anidulafungin dose group (mg)			
	50	75	100	
Randomized	42	40	41	123
Never received study drug	2	0	1	3
ITT	40	40	40	120
No baseline pathogen	3	0	1	4
MITT	37	40	39	116
<10 days of anidulafungin ^a	9	8	8	25
Concomitant antifungal therapy before EOT	3	1	1	5
Indeterminate clinical-microbiological response	0	1	2	3
Evaluable at EOT	25	30	28	83
Concomitant antifungal therapy before FU	1	3	1	5
Indeterminate clinical-microbiological response	6	1	3	10
Evaluable at FU	18	26	24	68

^a Patients who received at least 5 days of anidulafungin and had a clinical response of failure at EOT were not excluded from the evaluable populations.

performed on day 1, periodically as clinically indicated, and again at FU. Catheter management was at the discretion of the investigator.

The prospectively defined primary measure of efficacy was global response in evaluable (per protocol) patients at the FU visit. A successful global response required successful clinical and microbiological responses. A successful clinical response required resolution of signs and symptoms of infection and no need for additional antifungal therapy (cure) or, in order to allow for a switch to oral therapy (EOT only), significant improvement of signs and symptoms and the need for additional antifungal therapy (improvement). A successful microbiological response was defined as a negative culture from a normally sterile site that was previously positive for *Candida* (proven eradication) or inability to obtain cultures in a patient with a clinical response of success (presumed eradication). Secondary efficacy analyses included global response at EOT, as well as clinical response and microbiological response at EOT and FU. The evaluable population consisted of those patients with confirmed *Candida* infection who received at least 10 doses of study medication (or failed after ≥ 5 doses) and who were without protocol violations. Investigators assigned a clinical response of success (cure or improvement) or failure at EOT and FU; however, patients evaluated as having a response of failure at any earlier time were carried forward as failure at all later time points. Patients graded as clinically improved but requiring further antifungal therapy (i.e., other than anidulafungin) at EOT were no longer evaluable at FU. Patients with missing data or who were inevaluable were considered failures for an intent-to-treat (ITT) analysis. All safety analyses were performed on an ITT basis, i.e., including those patients receiving at least one dose of the study drug. In this phase 2 study, no formal statistical comparisons between treatment arms were planned for either efficacy or safety parameters. Only descriptive statistics are presented.

RESULTS

Patient disposition and analysis populations. Enrollment took place between August 2001 and November 2002 at 24 investigative sites in the United States. One-hundred twenty patients, 40 per treatment arm, received at least one dose of anidulafungin. (Table 1). Sixty-eight (55%) patients completed the study. Of those patients not completing the study, the majority of withdrawals were due to the 33 fatalities.

The modified ITT (MITT) population consisted of 116 patients whose baseline cultures yielded at least one *Candida* species (Table 1). Eighty-three patients were clinically evaluable at EOT, and 68 were clinically evaluable at FU. The reasons for nonevaluability included <10 days of treatment with anidulafungin (other than failure after ≥ 5 doses) (25

TABLE 2. Baseline characteristics of ITT population

Characteristic	Value for anidulafungin dose group (mg) ^a		
	50	75	100
Age [median yr (range)]	52 (18–88)	54 (21–87)	59 (26–88)
Sex			
Male [n (%)]	13 (33)	21 (53)	18 (45)
Female [n (%)]	27 (68)	19 (48)	22 (55)
Wt (median [kg])	68.9	76.1	70.6
APACHE II score (mean \pm SD)	13.4 \pm 8.3	18.6 \pm 9.7	15.0 \pm 8.2
APACHE II score ≥ 20 [n (%)]	7 (18)	12 (30)	10 (25)
Absolute neutrophil count of <500 [n (%)]	7 (18)	5 (13)	4 (10)
Diabetes mellitus [n (%)]	13 (33)	12 (30)	11 (28)
Prior systemic antifungal treatment [n (%)]	23 (58)	28 (70)	31 (78)

^a Forty patients per group.

patients), use of additional antifungal therapy prior to the EOT or FU visit for a reason other than treatment failure (10 patients), and indeterminate clinical response, e.g., failure to return for either the EOT or FU visit (13 patients).

Characteristics of the study population. The baseline characteristics of the 120 patients in the ITT population are presented in Table 2. The three dosage groups were generally well matched with respect to age, gender, and weight; however, patients in the 75- and 100-mg groups had higher APACHE II scores than those in the lowest-dosage group. Overall, $\sim 25\%$ of the study population had Acute Physiology and Chronic Health Evaluation (APACHE) II scores of ≥ 20 . Diabetes mellitus was the single most common underlying medical condition.

The majority of patients (94%) were enrolled with candidemia. One patient had a prosthetic joint (hip) infection; no patients had endocarditis or endophthalmitis. Twelve (10%) patients qualified for the study based on a tissue sample positive for *Candida*, five (4%) of whom also presented with candidemia. *Candida albicans*, the most prevalent species, was isolated from 53% of the patients. However, *C. glabrata* was also prominent (31% of patients). Infections due to *C. parapsilosis* and *C. tropicalis* occurred less frequently (Table 3). Ten

TABLE 3. Distribution of baseline *Candida* species by treatment group^a

Species or source	No. of patients (%)			Total
	Anidulafungin dose group (mg)			
	50	75	100	
<i>C. albicans</i>	20 (54)	20 (50)	22 (56)	62 (53)
<i>C. glabrata</i>	11 (30)	10 (25)	15 (38)	36 (31)
<i>C. parapsilosis</i>	6 (16)	4 (10)	1 (3)	11 (9)
<i>C. tropicalis</i>	1 (3)	6 (15)	3 (8)	10 (9)
<i>C. krusei</i>	2 (5)	3 (8)	0	5 (4)
Other species	2 (5)	0	1 (3)	3 (3)
Blood	36 (97)	37 (93)	36 (92)	109 (94)
Tissue	1 (3)	7 (18)	4 (10)	12 (10)
Both	0	4 (10)	1 (3)	5 (4)

^a 10 patients had multiple species isolated at baseline. There were 37, 40, and 39 members of the MITT population in the 50-, 75-, and 100-mg groups, respectively (total, 116).

TABLE 4. Successful responses by treatment group^a

Endpoint	No. of subjects with response/ No. of subjects in the population (%) for anidulafungin dose group (mg)		
	50	75	100
Global response			
EOT	21/25 (84)	27/30 (90)	25/28 (89)
FU	13/18 (72)	22/26 (85)	20/24 (83)
Clinical response			
EOT	22/25 (88)	27/30 (90)	25/28 (89)
FU	13/18 (72)	22/26 (85)	20/24 (83)
Microbiological response ^b			
EOT	21/25 (84)	28/30 (93)	25/28 (89)
FU	14/18 (78)	22/26 (85)	21/24 (88)

^a Results are presented for evaluable patients.

^b Analyzed on a per-patient basis

patients presented with multiple species (nine patients with two species and one patient with three species). Of 47 patients with a central catheter or arterial line at the time of infection, 22 (46%) had the line removed or changed prior to receipt of the study drug.

The median numbers of anidulafungin doses administered per patient were 14.0, 15.0, and 14.0 in the three dosage groups (range, 2 to 61).

Global and clinical responses. At EOT and FU (the primary times of interest), there were trends toward higher success rates in the higher-dose groups than in the 50-mg-dose group (Table 4). The percentage of patients with a successful clinical response mirrored the results for the global response. The difference in the numbers of patients in the evaluable population at EOT and FU is largely due to patients who were reported as improved but were placed on an oral antifungal agent ($n = 10$) or had an indeterminate (e.g., lost to follow-up) clinical or microbiological response ($n = 5$). At FU, all patients graded as clinical successes were cures, with the exception of one patient evaluated as improvement (50-mg group).

Microbiological response. Microbiological success rates at both EOT and FU also yielded higher success rates in the higher-dosage groups (Table 4). Only two patients, one in the 50-mg group (*C. krusei* candidemia) and one in the 100-mg group (*C. albicans* and *C. parapsilosis* infection of hip prosthesis), had culture-proven persistent infection at the EOT visit. Seven additional patients had presumed persistent infection, two in the 50-mg group, one in the 75-mg group, and four in the 100-mg group. All but one of these presumed persistent infections represented a bloodstream infection. Only one patient (100-mg group) experienced a proven microbiologic recurrence of *C. albicans* infection between EOT and FU.

Safety analyses. Events considered to be related to treatment (according to investigator attribution) were reported by ≤ 2 (5%) patients in each dose group, with the exception of hypokalemia, reported by four (10%) patients in the 50-mg dose group (Table 5). The most common events, irrespective of relationship to treatment, were hypotension (13%), vomiting (13%), constipation (11%), nausea (11%), and pyrexia (11%). No dose-response relationship was observed for these or any other events.

Overall, 46% of the patients experienced at least one serious adverse event. Thirty-three (33) deaths occurred in the study, 12 in the 50-mg group, 10 in the 75-mg group, and 11 in the

100-mg group. Fourteen of the deaths occurred while the patients were on the study drug: four, four, and six, respectively, in the three study groups. The most commonly reported causes of death were cardiac arrest, multiorgan failure, and (nonfungal) sepsis, each occurring in four patients. Only three serious adverse events were reported as either probably or possibly related to treatment: a nonfatal, nonneutropenic fever with onset on day 11 and two episodes of seizure, both of which occurred in patients with complicated comorbid conditions.

No systemic infusion-related adverse reactions occurred following administration of $>1,700$ doses of anidulafungin. In addition, no anaphylactic reactions or hemolytic episodes occurred.

There was no dose-response relationship with respect to the appearance of adverse events, either overall or by severity, seriousness, or relationship to treatment. Analysis of laboratory values for hematology and serum chemistries did not reveal any areas of clinical concern or any dose-response relationships.

DISCUSSION

Until recently, chemotherapeutic options for the treatment of invasive candidiasis included agents associated with significant toxicity (1, 2, 3, 10) or which lacked activity against the full spectrum of *Candida* species (4, 11, 19). In addition, the relatively constant attributable mortality rate of 30 to 40% associated with invasive candidiasis and candidemia is a major concern (7, 17, 18). Therefore, there is a need for new, more efficacious, and safer antifungal agents (20). The echinocandins have emerged as a novel class of antifungal agents with potential for comparable or superior antifungal efficacy and an improved safety profile.

The present study evaluated the safety and efficacy of anidulafungin, a new echinocandin, in patients diagnosed with candidemia and invasive candidiasis. Our study enrolled a repre-

TABLE 5. Safety summary

Adverse event	No. of patients (%) from anidulafungin dose group (mg)		
	50	75	100
Any event	38 (95)	38 (95)	38 (95)
Related event ^a	11 (28)	11 (28)	12 (30)
Hypokalemia	4 (10)	2 (5)	2 (5)
Increased GGT	1 (3)	0	2 (5)
Hypomagnesemia	1 (3)	1 (3)	1 (3)
Serious event ^b	20 (50)	17 (43)	18 (45)
Death	12 (30)	10 (25)	11 (28)
Sepsis ^c	4 (10)	2 (5)	0
Cardiac arrest ^c	1 (3)	3 (8)	1 (3)
Respiratory distress ^c	0	2 (5)	3 (8)
Multiorgan failure	3 (8)	1 (3)	0
Septic shock	1 (3)	2 (5)	0

^a Considered by the investigator to have a probable or possible relationship to treatment with anidulafungin. Related adverse events occurring in at least two patients overall are displayed. GGT, gamma glutamyl transferase.

^b Serious adverse events reported by ≥ 2 patients in any treatment group are presented.

^c Three cases of respiratory distress, two cases of sepsis, and one cardiac arrest were nonfatal.

sentative sample of patients with candidemia. The distribution of baseline pathogens mirrored recent surveys of candidemia, with half of all isolates being non-*albicans* *Candida* species (13, 16). Although patients in the two higher-dosage groups had higher APACHE II scores at baseline than those in the lowest-dosage group, a higher success rate was observed in the higher-dosage groups. However, there was no dose response with respect to adverse events, nor did systemic infusion reactions occur. The small sample size of this study precludes definitive conclusions comparing dosage groups, however.

The limitations of this study include the absence of a standard care comparator and of investigator blinding. In the absence of a comparator, or of a group of patients who did not receive antifungal therapy, we cannot be sure that the responses obtained are not due solely to other factors, such as catheter removal or supportive care. However, the efficacy of anidulafungin in the 100-mg dosage group of patients appears to be as high or higher than that observed in other recent trials using caspofungin, amphotericin B, and/or fluconazole (9, 17, 18). In a similar population, caspofungin yielded an 81% success rate among patients evaluable for analysis (9). Larger studies will be needed to explore differences in response rates by species, since, as for other echinocandins, higher MICs are observed for *C. parapsilosis* than for other species (12).

Anidulafungin was well tolerated in this population of patients with significant underlying medical conditions and comorbidities.

The encouraging results of this trial are the first reported for anidulafungin in invasive *Candida* infection. Randomized, controlled phase 3 studies of the 100-mg dosage regimen are warranted for this indication to confirm these results.

ACKNOWLEDGMENTS

This study was funded by Vicuron Pharmaceuticals Inc.

We acknowledge Michael Pfaller and Richard Hollis from the University of Iowa for providing central reference laboratory services for analysis of *Candida* isolates and Regina Jurewicz for manuscript preparation. We also thank Peter Pappas of the University of Alabama for critical review of the manuscript.

This study was performed on behalf of the Anidulafungin Invasive Candidiasis Study Group. In addition to the authors, the members of the Anidulafungin Invasive Candidiasis Study Group are A. Gabrielli (Gainesville, Fla.), T. Alferrez (New Orleans, La.), C. Cook (Columbus, Ohio), P. Eder (Baltimore, Md.), C.-B. Hsiao (Buffalo, N.Y.), A. Karchmer (Boston Mass.), T. Kerkering (Richmond, Va.), D. Kett (Miami, Fla.), M. Y. Khan (Phoenix, Az.), M. Kollef (St. Louis, Mo.), A. Luteran (Mobile, Ala.), R. Martindale (Augusta, Ga.), R. Fang and D. Mueller (Lackland Air Force Base, Tex.), S. Chapman (Jackson, Miss.), J. Daller (Galveston, Tex.), Y. S. Kim (Philadelphia, Pa.), P. G. Pappas (Birmingham, Ala.), J. R. Perfect (Durham, N.C.), L. Proia (Chicago, Ill.), D. Graham (Springfield, Ill.), J. Raffalli (Valhalla, N.Y.), J. Rex (Houston, Tex.), B. Segal (Buffalo, N.Y.), J. Solomkin (Cincinnati, Ohio), M. Zervos (Royal Oak, Mich.), A. Quartin (Miami, Fla.), and D. McKinsey (Kansas City, Mo.).

REFERENCES

- Anaissie, E. J., R. O. Darouiche, D. Abi-Said, O. Uzun, J. Mera, L. O. Gentry, T. Williams, D. P. Kontoyiannis, C. L. Karl, and G. P. Bodey. 1996. Management of invasive candidal infections: results of a prospective, randomized, multicenter study of fluconazole versus amphotericin B and review of the literature. *Clin. Infect. Dis.* **23**:964–972.
- Anaissie, E. J., S. E. Vartivarian, D. Abi-Said, O. Uzun, H. Pinczowski, D. P. Kontoyiannis, P. Khoury, K. Papadakis, A. Gardner, I. I. Raad, J. Gilbreath, and G. P. Bodey. 1996. Fluconazole versus amphotericin B in the treatment of hematogenous candidiasis: a matched cohort study. *Am. J. Med.* **101**:170–176.
- Bates, D. W., L. Su, D. T. Yu, G. M. Chertow, D. L. Seger, D. R. J. Gomes, E. J. Dasbach, and R. Platt. 2001. Mortality and costs of acute renal failure associated with amphotericin B therapy. *Clin. Infect. Dis.* **32**:686–693.
- Cuenca-Estrella, M., E. Mellado, T. M. Diaz-Guerra, A. Monzón, and J. L. Rodríguez-Tudela. 2000. Susceptibility of fluconazole-resistant clinical isolates of *Candida* spp. to echinocandin LY303366, itraconazole and amphotericin B. *J. Antimicrob. Chemother.* **46**:475–477.
- Edmond, M. B., S. E. Wallace, K. McClish, M. A. Pfaller, R. N. Jones, and R. P. Wenzel. 1999. Nosocomial bloodstream infections in United States hospitals: a three-year analysis. *Clin. Infect. Dis.* **29**:239–244.
- Fridkin, S. K., and W. R. Jarvis. 1996. Epidemiology of nosocomial fungal infections. *Clin. Microbiol. Rev.* **9**:499–511.
- Gudlaugsson, O., S. Gillespie, K. Lee, J. Vande Berg, J. Hu, S. Messer, L. Herwaldt, M. Pfaller, and D. Diekmann. 2003. Attributable mortality of nosocomial candidemia, revisited. *Clin. Infect. Dis.* **37**:1172–1177.
- Kao, A. S., M. E. Brandt, W. R. Pruitt, L. A. Conn, B. A. Perkins, D. S. Stephens, 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.
- Mora-Duarte, J., R. Betts, C. Rotstein, A. L. Colombo, L. Thompson-Moya, J. Smetana, R. Lupinacci, C. Sable, N. Kartsonis, and J. Perfect for the Caspofungin Invasive Candidiasis Study Group. 2002. Comparison of caspofungin and amphotericin B for invasive candidiasis. *N. Engl. J. Med.* **347**:2020–2029.
- Nguyen, M. H., J. E. Peacock, Jr., D. C. Tanner, A. J. Morris, M. L. Nguyen, D. R. Snyderman, M. M. Wagener, and V. L. Yu. 1995. Therapeutic approaches in patients with candidemia. *Arch. Intern. Med.* **155**:2429–2435.
- Odds, F. C. 1996. Epidemiological shifts in opportunistic and nosocomial *Candida* infections: mycological aspects. *Int. J. Antimicrob. Agents* **6**:141–144.
- Ostrosky-Zeichner, L., J. H. Rex, P. G. Pappas, R. J. Hamill, R. A. Larsen, H. W. Horowitz, W. G. Powderly, N. Hyslop, C. A. Kauffman, J. Cleary, J. E. Mangina, and L. Lee. 2003. Antifungal susceptibility survey of 2,000 bloodstream *Candida* isolates in the United States. *Antimicrob. Agents Chemother.* **47**:3149–3154.
- Pappas, P. G., J. H. Rex, J. Lee, R. J. Hamill, R. A. Larsen, W. Powderly, C. A. Kauffman, N. Hyslop, J. E. Mangino, S. Chapman, H. W. Horowitz, J. E. Edwards, and W. E. Dismukes for the National Institute of Allergy and Infectious Diseases Mycoses Study Group. 2003. A prospective observational study of candidemia: epidemiology, therapy, and influence on mortality in hospitalized adult and pediatric patients. *Clin. Infect. Dis.* **37**:634–643.
- Pfaller, M. A., D. J. Diekmann, 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.
- Pfaller, M. A., F. Marco, S. A. Messer, and R. N. Jones. 1998. In vitro activity of two echinocandin derivatives, LY303366 and MK-0991 (L-743,792), against clinical isolates of *Aspergillus*, *Fusarium*, *Rhizopus*, and other filamentous fungi. *Diagn. Microbiol. Infect. Dis.* **20**:251–255.
- Rangel-Frausto, M. S., T. Wible, H. M. Blumberg, L. Saiman, J. Patterson, M. Rinaldi, M. Pfaller, J. E. Edwards, Jr., W. Jarvis, J. Dawson, R. P. Wenzel, and the NEMIS Study Group. 1999. National Epidemiology of Mycoses Survey (NEMIS): variations in rates of bloodstream infections due to *Candida* species in seven surgical intensive care units and six neonatal intensive care units. *Clin. Infect. Dis.* **29**:253–258.
- Rex, J. H., J. E. Bennett, A. M. Sugar, P. G. Pappas, C. M. van der Horst, J. E. Edwards, R. G. Washburn, W. M. Scheld, A. W. Karchmer, A. P. Dine, M. J. Levenstein, and C. D. Webb for the Candidemia Study Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group. 1994. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. *N. Engl. J. Med.* **331**:1325–1330.
- Rex, J. H., P. G. Pappas, A. W. Karchmer, J. Sobel, J. E. Edwards, S. Hadley, C. Brass, J. A. Vazquez, S. W. Chapman, H. W. Horowitz, M. Zervos, D. McKinsey, J. Lee, T. Babinchak, R. W. Bradsher, J. D. Cleary, D. M. Cohen, L. Danziger, M. Goldman, J. Goodman, E. Hilton, N. E. Hyslop, D. H. Kett, J. Lutz, R. H. Rubin, W. M. Scheld, M. Schuster, B. Simmons, D. K. Stein, R. G. Washburn, L. Mautner, T.-C. Chu, H. Panzer, R. B. Rosenstein, and J. Booth for the National Institute of Allergy and Infectious Diseases Mycoses Study Group. 2003. A randomized and blinded multicenter trial of high-dose fluconazole plus placebo versus fluconazole plus amphotericin B as therapy for candidemia and its consequences in nonneutropenic subjects. *Clin. Infect. Dis.* **36**:1221–1228.
- Singh, N. 2001. Changing spectrum of invasive candidiasis and its therapeutic implications. *Clin. Microbiol. Infect.* **7**(Suppl. 2):1–7.
- Walsh, T. J. 2002. Echinocandins—an advance in the primary treatment of invasive candidiasis. *N. Engl. J. Med.* **347**:2070–2072.