Open-Label, Randomized Comparison of Itraconazole versus Caspofungin for Prophylaxis in Patients with Hematologic Malignancies

Gloria N. Mattiuzzi,^{1*} Gladys Alvarado,¹ Francis J. Giles,¹ Luis Ostrosky-Zeichner,² Jorge Cortes,¹ Susan O'Brien,¹ Srdan Verstovsek,¹ Stefan Faderl,¹ Xian Zhou,³ Issam I. Raad,^{4,5} B. Nebiyu Bekele,³ G. J. Leitz,⁶ Ivonne Lopez-Roman,¹ and Elihu H. Estey¹

Departments of Leukemia,¹ Biostatistics and Applied Mathematics,³ Infectious Disease,⁴ and Infectious Disease–Infection Control,⁵ The University of Texas M. D. Anderson Cancer Center, and Laboratory of Mycology Research, Division of Infectious Diseases, Department of Internal Medicine, and Center for the Study of Emerging and Re-emerging Pathogens, The University of Texas Houston Medical School,² Houston, Texas, and Ortho Biotech Products, L.P., Bridgewater, New Jersey⁶

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Invasive fungal infection remains the most common cause of infectious death in acute leukemia. In this open-label, randomized study, we compared the efficacy and safety of caspofungin with that of intravenous itraconazole for antifungal prophylaxis in patients undergoing induction chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome. Of 200 patients, 192 were evaluable for efficacy (86 for itraconazole, 106 for caspofungin). Duration of prophylaxis (median, 21 days [range, 1 to 38 days]), demographics, and prognostic factors were similar in both groups. Ninety-nine patients completed antifungal prophylaxis without developing fungal infection (44 [51%] with itraconazole, 55 [52%] with caspofungin). Twelve patients developed documented invasive fungal infections, five in the itraconazole group (four with candidemia and one with *Aspergillus* pneumonia), and seven in the caspofungin group (two with candidemia, two with disseminated trichosporon species, two with *Aspergillus* pneumonia, and one with disseminated *Fusarium* spp). Two patients in the itraconazole group and four in the caspofungin group died of fungal infection ($P = 0.57$). Grade 3 to 4 adverse event rates were comparable between groups; the most common event in both was reversible hyperbilirubinemia. No evidence of cardiovascular toxicity from intravenous itraconazole was noted among patients older than 60. In conclusion, intravenous itraconazole and caspofungin provided similar protection against invasive fungal infection during induction chemotherapy, and both drugs were well tolerated.

Despite advances in antifungal prophylaxis and treatment, invasive fungal infection remains the most common infectious cause of death among patients with acute leukemia. In our recent review of causes of death among patients undergoing induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS), invasive fungal infection was the most common, and aspergillosis, alone or in combination with bacterial infection, was the most common fungal infection (12).

At The University of Texas M. D. Anderson Cancer Center, we routinely use antifungal prophylaxis for patients with newly diagnosed AML or high-risk MDS undergoing induction chemotherapy. Given the high risk of mortality associated with invasive fungal infections, particularly aspergillosis, we find antifungal prophylaxis to be preferable to no prophylaxis for patients at high risk of developing such infections. Prophylactic fluconazole has been shown to significantly reduce the number of yeast infections and the need for empirical amphotericin B in such patients (19). Unfortunately, none of the prophylactic antifungal regimens in current use are demonstrably superior for preventing invasive aspergillosis (13–15), and thus both an

effective regimen and a way of identifying patients at particular risk of invasive fungal infection are still needed.

Caspofungin is the first of the echinocandin class of antifungal agents to be made available in the United States. Caspofungin acts by inhibiting the synthesis of β -(1-3)-D-glucan, a component of fungal cell walls. Caspofungin is fungicidal in vitro and in vivo against most isolates of *Candida* spp. and is fungistatic against *Aspergillus* spp. However, caspofungin is not active against *Cryptococcus neoformans*, *Trichosporon* spp., or *Fusarium* spp. (5, 11). Its apparently low toxicity and lack of known drug interactions make caspofungin an attractive parenteral alternative to more traditional forms of antifungal prophylaxis.

In a previous study at the M. D. Anderson Cancer Center, we found intravenous itraconazole to be a viable option for antifungal prophylaxis in patients with hematologic malignancies (15). One important advantage of this drug is that it is available in both intravenous and oral formulations. However, itraconazole and its major metabolite, hydroxyitraconazole, inhibit the cytochrome P4503A4 isoenzyme system, which can complicate drug administration.

In this study, we compared the efficacy and safety of caspofungin with that of our standard agent for antifungal prophylaxis, intravenous itraconazole, in patients with AML or high-risk MDS who were undergoing induction chemotherapy.

* Corresponding author. Mailing address: Department of Leukemia, Unit 428, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030. Phone: (713) 745-2723. Fax: (713) 745-4612. E-mail: gmattiuz@mdanderson.org.

MATERIALS AND METHODS

Patient characteristics. Patients aged 15 years or older with a new diagnosis of AML or high-risk MDS were eligible. Exclusion criteria were pregnancy, lactation or (for women of childbearing potential) unwillingness to use effective contraception throughout the study, a history of anaphylaxis attributed to azole compounds, and evidence of proven or probable fungal infection according to the criteria of the European Organization for Research and Treatment of Cancer's Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases' Mycoses Study Group (EORTC/MSG) (2). Enrolled patients were considered not evaluable if they completed less than 3 days of therapy or if they showed evidence of invasive fungal infection during the first 24 h of therapy.

This open-label, randomized, single-institution study was approved by the institutional review board of The University of Texas M. D. Anderson Cancer Center. Patients or legally authorized representatives provided written informed consent before the initiation of prophylaxis.

Study protocol. After stratification by age (≤ 59 or ≥ 60 years old), performance status (≤ 2 or ≥ 3 on the Zubrod scale), and the presence or absence of overt nonfungal infections on day 1 of induction, chemotherapy-eligible patients were randomly assigned via the dynamic allocation scheme of Pocock and Simon (18) to receive either itraconazole (200 mg intravenously [i.v.] in a 1-h infusion twice a day for 2 consecutive days, followed by 200 mg i.v. once daily) or caspofungin (50 mg i.v. in a 1-h infusion once daily). Prophylaxis was continued until (i) the absolute neutrophil count exceeded $0.5 \times 10^9/\text{liter}$ on 2 consecutive days; (ii) complete response, death, or change in anti-leukemia therapy because of persistent disease; (iii) appearance of proven or probable invasive fungal infection according to the EORTC/MSG criteria; (iv) unacceptable toxicity; or (v) 35 days had elapsed from the start of prophylaxis.

Antibacterial prophylaxis (levofloxacin, 500 mg per os daily) and antiviral prophylaxis (valacyclovir, 500 mg per os daily) were administered to all patients while their neutrophil counts were less than $0.5 \times 10^9/\text{liter}$. No other antifungal agents were allowed during the period of prophylaxis. Patients older than 50 years were offered the opportunity to undergo induction chemotherapy in a protected environment (i.e., in HEPA-filtered rooms).

At the onset of fever, blood samples were obtained for culture, and additional samples were collected if the fever persisted. Chest radiographs were obtained upon enrollment and at the onset of fever or signs or symptoms of pulmonary compromise. If fever persisted, chest radiographs were obtained every 3 to 4 days. Bronchoalveolar lavage specimens were obtained for culture from patients with radiographic evidence of extensive pulmonary infiltrates or those who developed new pulmonary infiltrates while receiving antibacterial agents. Computed tomography (CT) scans were obtained at the discretion of the treating physician. Serodiagnostic tests for fungal infection were not routinely used.

Because i.v. itraconazole has been associated with negative inotropic effects and congestive heart failure (1), patients assigned to the itraconazole group who were older than 60 years or had a history of cardiovascular disease were to undergo multiple gated acquisition (MUGA) scanning or echocardiography, once on day 1 of prophylaxis and again upon discharge, to evaluate the ejection fraction.

Definitions. Success was defined as the completion of prophylaxis without the development of documented invasive fungal infection during the period of prophylaxis. Fungal infection was considered "documented" on the basis of culture (blood, sputum, or bronchoalveolar fluid samples), radiographic, and clinical (neutropenia or fever) evidence of infection. All infections in the "documented" category met the criteria for either "proven" or "probable" infection according to the EORTC/MSG criteria (2). Patients were diagnosed with "possible fungal infection" if a culture-negative fever persisted for 3 days despite a change from levofloxacin to imipenem or ceftazidime and if they developed radiographic findings that indicated pneumonia (2).

Statistical considerations. In statistical terms, the study objective was to increase the proportion of patients without fungal infection from 0.4 to 0.6. With a two-sided test, a significance level of 0.05, a power of 0.8, and no interim analysis, the estimated sample size to reveal such an effect was 190 (95 patients in each of the two groups).

Data for eligible patients were summarized by using standard descriptive statistics and frequency tabulation. Associations between categorical variables were assessed via cross-tabulation, chi-squared tests, and Fisher's exact tests. Differences in continuous variables (age; creatinine, albumin, or bilirubin level; absolute neutrophil count; and number of days of prophylaxis) were compared for the two treatment groups via Student's *t* test (21). Patients who received at least one dose of study drug were included in the primary analysis (modified intent-to-treat group). A subset of patients who received study drug for at least

3 days and had no protocol violations were included in the efficacy analysis (evaluable group).

Univariate and multivariate logistic regression models were used to assess the treatment effect on the rate of fungal infection. Survival curves were estimated using the method of Kaplan and Meier (10). Log-rank tests were used to assess differences in time to failure or survival between groups (9). Univariate and multivariate Cox proportional hazards regression (HR) models were used to assess the relationship between prognostic factors and time of death during induction chemotherapy (4). Predictive variables in the Cox model were selected by forward stepwise selection based on a *P* value of <0.05 and then by allowing any variable ($P < 0.05$) previously deleted to reenter the final model. All statistical analyses were performed with SAS 8.0 or S-plus 2000 (3). All tests of statistical significance were two-sided, with a type I error rate of 5%.

RESULTS

Patients. Between June 2001 and January 2003, 200 patients were registered in the study. Three patients were excluded because they never received a study drug, leaving 197 patients for the primary analysis (90 in the itraconazole group and 107 in the caspofungin group). All of these patients had received at least one dose of the study drug. The median duration of prophylaxis was 21 days in both groups (range, 1 to 38 days). Chemotherapy regimens for most patients (184) included high-dose cytarabine (given with idarubicin, fludarabine, or topotecan); the rest included gemtuzumab (11 patients) or idarubicin (2 patients).

The two treatment groups were similar in demographic characteristics and prognostic factors (Table 1). Most of the patients in both groups (92% in the itraconazole group and 86% in the caspofungin group) underwent induction chemotherapy in a protected (i.e., HEPA-filtered) environment. The complete response rate to chemotherapy was similar in the two groups (57% in the itraconazole group versus 64% in the caspofungin group; $P = 0.33$).

Outcomes. Five patients were excluded from the efficacy analysis, two who had received concomitant fluconazole with the study drug and three who received less than 3 days of study drug because the treating physicians did not wish to continue prophylaxis in the presence of persistent fever. These latter three patients were excluded from the efficacy analysis, because in our opinion these patients did not receive enough study drug for that drug to be evaluable as prophylaxis (as opposed to systemic antifungal treatment, which would of course influence outcome). Thus, a total of 192 patients (86 patients in the itraconazole group and 106 patients in the caspofungin group) were evaluated for efficacy. Antifungal prophylaxis was considered successful (i.e., patients showed no evidence of proven, probable, or possible invasive fungal infection) in 99 of the 192 patients, 44 (51%) in the itraconazole group, and 55 (52%) in the caspofungin group (95% confidence interval, 0.42% to 0.62%; $P = 0.92$) (Table 2).

For those patients who did develop proven or probable fungal infection, the median time to failure of antifungal prophylaxis was 15 days in the i.v. itraconazole group (range, 3 to 19 days) and 19 days in the caspofungin group (range, 8 to 21 days) ($P = 0.75$). Twelve patients developed documented invasive fungal infections, five in the itraconazole group and seven in the caspofungin group (Table 3). Of the five patients in the itraconazole group, four had candidemia (one with *Candida krusei*, one with *C. albicans*, and two with *C. glabrata*) and one had *Aspergillus* pneumonia. Infections in three of the four

TABLE 1. Patient characteristics

Characteristic ^a	Treatment group		P value
	Itraconazole	Caspofungin	
No. of patients randomized ^b	92	108	
No. of patients evaluated (MITT)	90	107	
Age, yrs			
Median	60	64	0.17
Range	17–82	22–82	
Sex, no. (%)			
Male	56 (62)	69 (64)	0.74
Female	34 (38)	38 (36)	
Underlying disease, no. (%)			
AML	71 (79)	77 (72)	0.26
MDS	19 (21)	30 (28)	
Zubrod performance status, no. (%)			
0–2	87 (97)	102 (95)	0.64
≥3	3 (3)	5 (5)	
Protective environment, no. (%)	83 (92)	92 (86)	0.17
Nonfungal infection at start of study, no. (%)	20 (22)	17 (16)	0.26
Baseline serum creatinine level, mg/dl			
Median	0.95	1.0	0.53
Range	0.6–3.2	0.5–6.6	
Baseline total bilirubin level, mg/dl			
Median	0.5	0.5	0.81
Range	0.1–2.3	0.1–2.7	
Baseline albumin level, g/dl			
Median	3.3	3.3	0.60
Range	1.4–4.4	1.4–4.6	
Baseline absolute neutrophil count, per μ l			
Median	1,051	2,530	0.89
Range	0–30,789	0–7,992	
Baseline absolute lymphocyte count, per μ l			
Median	1,694	1,608	0.82
Range	416–20,280	0–15,246	
Chemotherapy regimens, no. (%)			
High dose with cytarabine	85 (94)	99 (92)	0.59
Other	5 (6)	8 (8)	

^a MITT, modified intent to treat; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome.

^b Three patients who were randomized but never received the study drug were excluded from the primary analysis.

patients with candidemia resolved after treatment with liposomal amphotericin B (L-AmB) at 5 mg per kg of body weight per day; subsequent blood cultures from the fourth patient, also given L-AmB, were not positive for candida, but that patient developed *Aspergillus* pneumonia and died with resistant leukemia and pneumonia despite treatment with high-dose L-AmB. Subsequent susceptibility testing (3a) revealed

that three of the four *Candida* isolates showed dose-dependent susceptibility to itraconazole, and the fourth was resistant (*C. glabrata*; MIC > 4 μ g/ml).

Of the seven patients given caspofungin who developed documented invasive fungal infections (Table 3), two patients developed candidemia; infection in one (*C. parapsilosis*) resolved after treatment with L-AmB, but the other patient (with *C. albicans* and *C. glabrata*) developed concomitant *Aspergillus* pneumonia and died with neutropenia despite high-dose L-AmB. Two other patients had disseminated *Trichosporon* infection. Both were treated with L-AmB. One patient achieved complete remission and resolution of the infection, and the other patient died with persistent neutropenia and *Trichosporon* infection and concomitant vancomycin-resistant enterococcus sepsis. Two patients had *Aspergillus* pneumonia; infection in one patient (who also achieved complete remission) resolved upon treatment with L-AmB, but the other patient (for whom induction chemotherapy failed) died despite treatment with L-AmB. The seventh patient developed *Fusarium* cellulitis that resolved after complete remission and treatment with voriconazole.

Comparable proportions of patients in each group (34% in the itraconazole group and 37% in the caspofungin group) withdrew because of persistent fever or pulmonary infiltrates of uncertain etiology and with no evidence to support the diagnosis of proven or probable invasive fungal infection. Of these 69 patients, 50 (75%) were given L-AmB as empirical therapy; 11 (16%) were given caspofungin in combination with voriconazole (3 patients) or L-AmB (8 patients); and 4 patients were given voriconazole only. Four of the 69 patients were later found to have bacterial infections, for which appropriate treatment was given. None of the other 65 patients subsequently developed proven or probable invasive fungal infections. Twelve additional patients (eight in the itraconazole group and four in the caspofungin group) were withdrawn from the study because of probable drug-related adverse events (Table 2 and the section on side effects below).

Mortality. Fourteen patients (seven in each treatment group) died during induction chemotherapy. None of the deaths were related to the study drugs. Two patients in the itraconazole group and four patients in the caspofungin group died of fungal infections ($P = 0.57$) (Table 4). In two of those six cases, documented fungal infections were diagnosed more than 10 days after discontinuation of the prophylactic antifungal agent. In the Cox multivariate analysis, being female (HR = 4.83; $P = 0.01$), having a high baseline bilirubin level (HR = 4.66; $P = 0.001$), and having a high serum creatinine level (HR = 1.48; $P = 0.038$) were associated with an increased risk of death after adjustment for the type of antifungal prophylaxis (HR = 1.22; $P = 0.71$).

Side effects. More patients in the itraconazole group were withdrawn from the study because of probable drug-related adverse events (eight [9%] in the itraconazole group versus four [4%] in the caspofungin group), but this difference was not statistically significant ($P = 0.12$). Hyperbilirubinemia (all at grade 3 or lower, all reversible) was the most common adverse event reported in both groups, occurring in six patients in the itraconazole group and in four patients in the caspofungin group.

Forty-six patients in the itraconazole group who were older

TABLE 2. Outcomes

Patient criterion	No. of patients (%) in treatment group:		P value
	Itraconazole	Caspofungin	
Total randomized	92	108	
Did not receive study drug	2	1	
Total evaluated (intent-to-treat group) ^a	90	107	
Excluded from efficacy analysis			
Received concomitant fluconazole ^b	2	0	
Received less than 3 days of prophylaxis ^c	2	1	
Evaluated for efficacy	86	106	
Completed prophylaxis with no evidence of documented fungal infection	44 (51)	55 (52)	0.92
Developed documented invasive fungal infection	5 (6)	7 (6)	0.83
Developed persistent fever or pulmonary infiltrates of unknown etiology	29 (34)	40 (37)	0.56
Withdrew because of side effects	8 (9)	4 (5)	0.12

^a Among the intent-to-treat group, antifungal prophylaxis was considered successful in 45 patients in the itraconazole group (50%) and in 56 patients in the caspofungin group (52%; $P = 0.85$).

^b Use of a second triazole represented a protocol violation.

^c Less than 3 days' treatment was thought to be insufficient for evaluating the drug as prophylaxis (rather than treatment).

than 60 years or had a history of cardiovascular disease were to undergo MUGA scanning or echocardiography, once on day 1 of prophylaxis and again upon discharge, to evaluate the ejection fraction. Twenty-nine of those 46 patients had both studies performed, and none showed significant reductions in ejection fraction after the completion of prophylaxis ($P = 0.249$; data not shown). Of the other 17 patients who had had only one MUGA scan or echocardiogram, only one patient (who had had an ejection fraction of 30% before prophylaxis) developed clinical signs of congestive heart failure, which resolved with treatment.

DISCUSSION

Our findings show that i.v. itraconazole and caspofungin provided comparable protection against invasive fungal infections among patients with newly diagnosed AML or high-risk MDS who were undergoing induction chemotherapy. The ob-

jective of the study, to increase the proportion of patients without fungal infections from 40% to 60%, was not met.

This trial was designed to assess the superiority of caspofungin over itraconazole. Failure to show superiority cannot, in and of itself, be used as the basis for claiming similarity for two compounds. However, when no difference was observed between the two treatments, we then applied Bayesian methods to assess the similarity of the two treatments in terms of their ability to prevent invasive fungal infection (8a). This Bayesian analysis (not the lack of superiority) led us to conclude similarity between the two treatments. Specifically, we assessed the probability that caspofungin would be at most 2.5%, 5%, or 10% worse at preventing invasive fungal infection than itraconazole. Assuming a standard beta distribution and the observed rates of invasive fungal infections (5 of 86 patients in the itraconazole group and 7 of 106 patients in the caspofungin group), the posterior probabilities that caspofungin would be at most 2.5% worse than itraconazole are 70%, at most 5% worse, 89%; and at most 10% worse, 99.5%.

This is the first randomized trial of caspofungin for prophylaxis in patients with hematologic malignancies. Despite devel-

TABLE 3. Types of documented fungal infections

Documented infection	No. of patients in treatment group:	
	Itraconazole (n = 86)	Caspofungin (n = 106)
Yeasts		
<i>Candida krusei</i>	1	
<i>C. glabrata</i>	2	
<i>C. parapsilosis</i>		1
<i>Trichosporon</i> spp.		2
Molds		
<i>Aspergillus versicolor</i>	1	
<i>A. fumigatus</i>		2
<i>Fusarium</i> spp.		1
Mixed infections		
<i>C. albicans</i> + <i>C. glabrata</i> + <i>A. versicolor</i>		1
<i>C. albicans</i> + <i>A. terreus</i>	1	
Total	5	7

TABLE 4. Mortality

Cause of death	No. of patients from treatment group:	
	Itraconazole (n = 86)	Caspofungin (n = 106)
Non-infection-related deaths	4	2
Infection-related deaths		
Sepsis (unknown pathogen)	1	1
Disseminated <i>Trichosporon</i> + VRE ^a		1
sepsis		
<i>Aspergillus</i> pneumonia	1	2
<i>Aspergillus</i> pneumonia + candidemia (<i>C. albicans</i>)	1 ^a	
<i>Curvularia</i> spp. pneumonia		1 ^b

^a Infection was documented 10 days after itraconazole had been discontinued.

^b Infection was documented 20 days after caspofungin had been discontinued.

^c VRE, vancomycin-resistant enterococcus.

oping neutropenia, roughly half of the patients in each treatment group completed the 35-day antifungal prophylaxis period without requiring empirical antifungal treatment. Both drugs were well tolerated, with only 13 patients (7%) experiencing toxicity requiring drug discontinuation. Intravenous itraconazole did not result in significant reduction in cardiac function.

The rate of documented fungal infections in this study was comparable to that observed in previous clinical trials done at M. D. Anderson (13–15). Interestingly, two patients in the caspofungin group in our current study developed *Trichosporon* infection and one developed *Fusarium* infection, findings that support the lack of in vitro activity of the echinocandins against *Trichosporon* spp. and *Fusarium* spp. (5, 6, 22). Breakthrough trichosporonosis has also been reported in a patient given caspofungin (8). Our findings also suggest that an agent other than caspofungin should be used when colonization or infection with *Trichosporon* spp. or *Fusarium* spp. is suspected. Our findings confirm reports of the safety of caspofungin given for the treatment of invasive fungal infections (16, 20) and studies indicating that i.v. itraconazole is both effective and well tolerated when given as prophylaxis for invasive fungal infections in patients with hematologic malignancies (7).

The development of breakthrough candidemia (1 patient with *C. parapsilosis* and 1 with *C. albicans* and *C. glabrata*) on caspofungin prophylaxis suggests that caspofungin, like other antifungal agents, may not be as effective in the setting of neutropenia. An alternative explanation is the resistance of these two strains in vitro; *C. parapsilosis* is known to have variable susceptibility to caspofungin (17).

The limitations of the current study include the small numbers of patients, the lack of blinding, and the lack of standardized CT scans or serologic tests (not available during the study period) for the definitive diagnosis of invasive fungal infection. Another potential shortcoming was the lack of a placebo group. However, given the high risk of morbidity and mortality from invasive fungal infections in the patient population studied (12), we did not consider use of a placebo group ethical under these conditions.

In conclusion, given the comparable activity of the two agents, the choice of i.v. itraconazole versus caspofungin should be individualized. Specifically, for patients with known liver dysfunction or those to be given chemotherapy that is hepatotoxic or known to interact with other drugs metabolized by the liver, caspofungin may be the more appropriate choice for antifungal prophylaxis. However, itraconazole can also be given orally, which would free the recipient from the inconvenience and expense of having to receive infusions. In addition, itraconazole is effective against infections due to *Trichosporon* spp. but caspofungin is not. Local institutional flora should be taken into consideration when selecting antifungal prophylaxis.

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REFERENCES

- Ahmad, S. R., S. J. Singer, and B. G. Leissa. 2001. Congestive heart failure associated with itraconazole. *Lancet* 357:1766–1767.
- Ascioglu, S., J. H. Rex, B. de Pauw, J. E. Bennett, J. Bille, F. Crockaert, D. W. Denning, J. P. Donnelly, J. E. Edwards, Z. Erjavec, D. Fiere, O. Lortholary,

- J. Maertens, J. F. Meis, T. F. Patterson, J. Ritter, D. Selleslag, P. M. Shah, D. A. Stevens, T. J. Walsh, and Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer Mycoses Study Group of the National Institute of Allergy and Infectious Diseases. 2002. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin. Infect. Dis.* 34:7–14.
- Becker, R. A., J. M. Chambers, and A. R. Wilks. 1988. The new S language. Wadsworth, Pacific Grove, Calif.
- Clinical and Laboratory Standards Institute. 2002. Reference method for broth dilution, antifungal susceptibility testing of yeasts. Document M27-A2. Clinical and Laboratory Standards Institute, Wayne, Pa.
- Cox, D. R. 1972. Regression models and life tables. *J. R. Stat. Soc.* 34:187–220.
- Denning, D. W. 2003. Echinocandin antifungal drugs. *Lancet* 362:1142–1151.
- Espinel-Ingroff, A. 1998. Comparison of in vitro activities of the new triazole SCH56592 and the echinocandins MK-0991 (L-743,872) and LY303366 against opportunistic filamentous and dimorphic fungi and yeasts. *J. Clin. Microbiol.* 36:2950–2956.
- Glasmeier, A., A. Prentice, M. Gorschluter, S. Engelhart, C. Hahn, B. Djulbegovic, and I. G. Schmidt-Wolf. 2003. Itraconazole prevents invasive fungal infections in neutropenic patients treated for hematologic malignancies: evidence from a meta-analysis of 3,597 patients. *J. Clin. Oncol.* 21:4615–4626.
- Goodman, D., E. Pamer, A. Jakubowski, C. Morris, and K. Sepkowitz. 2002. Breakthrough trichosporonosis in a bone marrow transplant recipient receiving caspofungin acetate. *Clin. Infect. Dis.* 35:E35–E36.
- Harrell, F. E., Jr., and Y. C. Shih. 2001. Using full probability models to compute probabilities of actual interest to decision makers. *Int. J. Technol. Assess. Health Care* 17:17–26.
- Hosmer, D. W., and S. Lemeshow. 1999. Applied survival analysis. Wiley, New York, N.Y.
- Kaplan, E. L., and P. Meier. 1958. Nonparametric estimations from incomplete observations. *J. Am. Stat. Assoc.* 53:457–481.
- Keating, G. M., and B. Jarvis. 2001. Caspofungin. *Drugs* 61:1121–1129.
- Mattiuzzi, G., G. Alvarado, R. Alvarez, et al. 2003. Causes of death in patients with acute myelogenous leukemia and high-risk myelodysplastic syndrome undergoing induction chemotherapy. *Blood* 102:878a.
- Mattiuzzi, G. N., E. Estey, I. Raad, F. Giles, J. Cortes, Y. Shen, D. Kontoyiannis, C. Koller, M. Munsell, M. Beran, and H. Kantarjian. 2003. Liposomal amphotericin B versus the combination of fluconazole and itraconazole as prophylaxis for invasive fungal infections during induction chemotherapy for acute myelogenous leukemia and myelodysplastic syndrome. *Cancer* 97:450–456.
- Mattiuzzi, G. N., H. Kantarjian, S. Faderl, J. Lim, D. Kontoyiannis, D. Thomas, W. Wierda, I. Raad, G. Garcia-Manero, X. Zhou, A. Ferrajoli, N. Bekele, and E. Estey. 2004. Amphotericin B lipid complex as prophylaxis of invasive fungal infections in patients with acute myelogenous leukemia and myelodysplastic syndrome undergoing induction chemotherapy. *Cancer* 100:581–589.
- Mattiuzzi, G. N., H. M. Kantarjian, S. O'Brien, D. P. Kontoyiannis, F. Giles, X. Zhou, J. Lim, B. N. Bekele, S. Faderl, J. Cortes, S. Pierce, G. J. Leitz, I. Raad, and E. Estey. 2004. Intravenous itraconazole for prophylaxis of systemic fungal infections in patients with acute myelogenous leukemia and high-risk myelodysplastic syndrome undergoing induction chemotherapy. *Cancer* 100:568–573.
- Mora-Duarte, J., R. Betts, C. Rotstein, A. L. Colombo, L. Thompson-Moya, J. Smietana, R. Lupinacci, C. Sable, N. Kartsonis, J. Perfect, and Caspofungin Invasive Candidiasis Study Group. 2002. Comparison of caspofungin and amphotericin B for invasive candidiasis. *N. Engl. J. Med.* 347:2020–2029.
- 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. Mangino, and J. Lee. 2003. Antifungal susceptibility survey of 2,000 bloodstream *Candida* isolates in the United States. *Antimicrob. Agents Chemother.* 47:3149–3154.
- Pocock, S. J., and R. Simon. 1975. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 31:103–115.
- Rex, J. H., E. J. Anaissie, E. Boutati, E. Estey, and H. J. Kantarjian. 2002. Systemic antifungal prophylaxis reduces invasive fungal infections in acute myelogenous leukemia: a retrospective review of 833 episodes of neutropenia in 322 adults. *Leukemia* 16:1197–1203.
- Sable, C. A., B. Y. Nguyen, J. A. Chodakewitz, and M. J. DiNubile. 2002. Safety and tolerability of caspofungin acetate in the treatment of fungal infections. *Transplant. Infect. Dis.* 4:25–30.
- Snedecor, G. W., and W. G. Cochran. 1980. Statistical methods, 7th ed. Iowa State University Press, Ames, Iowa.
- Uzun, O., S. Kocagoz, Y. Cetinkaya, S. Arikan, and S. Unal. 1997. In vitro activity of a new echinocandin, LY303366, compared with those of amphotericin B and fluconazole against clinical yeast isolates. *Antimicrob. Agents Chemother.* 41:1156–1157.