MAJOR ARTICLE

MSG-01: A Randomized, Double-Blind, Placebo-Controlled Trial of Caspofungin Prophylaxis Followed by Preemptive Therapy for Invasive Candidiasis in High-Risk Adults in the Critical Care Setting

Luis Ostrosky-Zeichner,[1] Shmuel Shoham,[2] Jose Vazquez,[3] Annette Reboli,[4] Robert Betts,[5] Michelle A. Barron,[6] Mindy Schuster,[7] Marc A. Judson,[8] Sanjay G. Revankar,[9] Juan Pablo Caeiro,[10] Julie E. Mangino,[11] David Mushatt,[12] Roger Bedimo,[13] Alison Freifeld,[14] Minh Hong Nguyen,[15] Carol A. Kauffman,[16] William E. Dismukes,[17] Andrew O. Westfall,[18] Jeanna Beth Deerman,[17] Craig Wood,[19] Jack D. Sobel,[9] and Peter G. Pappas[17]

[1]University of Texas Medical School at Houston and Memorial Hermann Texas Medical Center, Houston; [2]Johns Hopkins University School of Medicine, Baltimore, Maryland; [3]Georgia Regents University, Augusta; [4]Cooper Medical School of Rowan University, Camden, New Jersey; [5]University of Rochester Medical Center, New York; [6]University of Colorado Denver, Aurora; [7]Perleman School of Medicine, University of Pennsylvania, Philadelphia; [8]Albany Medical College, New York; [9]Wayne State University, Detroit, Michigan; [10]Baylor College of Medicine, Houston, Texas; [11]The Ohio State University Medical Center, Columbus; [12]Tulane University School of Medicine, New Orleans, Louisiana; [13]Veterans Affairs North Texas Health Care System, Dallas; [14]University of Nebraska Medical Center, Omaha; [15]University of Pittsburgh, Pennsylvania; [16]University of Michigan Medical School and Veterans Affairs Ann Arbor Healthcare System; [17]School of Medicine and [18]School of Public Health, University of Alabama at Birmingham; and [19]Merck & Co, Inc, North Wales, Pennsylvania

(See the Editorial Commentary by Muldoon and Denning on pages 1227–9.)

Background. Invasive candidiasis is the third most common bloodstream infection in the intensive care unit (ICU) and is associated with morbidity and mortality. Prophylaxis and preemptive therapy are attractive strategies for this setting.

Methods. We conducted a multicenter, randomized, double-blind, placebo-controlled trial of caspofungin as antifungal prophylaxis in 222 adults who were in the ICU for at least 3 days, were ventilated, received antibiotics, had a central line, and had 1 additional risk factor (parenteral nutrition, dialysis, surgery, pancreatitis, systemic steroids, or other immunosuppressants). Subjects' (1,3)-β-D-glucan levels were monitored twice weekly. The primary endpoint was the incidence of proven or probable invasive candidiasis by EORTC/MSG criteria in patients who did not have disease at baseline. Patients who had invasive candidiasis were allowed to break the blind and receive preemptive therapy with caspofungin. The preemptive approach analysis included patients all patients who received study drug, including those positive at baseline.

Results. The incidence of proven/probable invasive candidiasis in the placebo and caspofungin arms was 16.7% (14/84) and 9.8% (10/102), respectively, for prophylaxis ($P = .14$), and 30.4% (31/102) and 18.8% (22/117), respectively, for the preemptive approach ($P = .04$); however, this analysis included patients with baseline disease. There were no significant differences in the secondary endpoints of mortality, antifungal use, or length of stay. There were no safety differences.

Conclusions. Caspofungin was safe and tended to reduce the incidence of invasive candidiasis when used for prophylaxis, but the difference was not statistically significant. A preemptive therapy approach deserves further study.

Clinical Trials Registration. NCT00520234.

Keywords. invasive candidiasis; ICU; prophylaxis; preemptive therapy; caspofungin.

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Correspondence: Luis Ostrosky-Zeichner, MD, FACP, FIDSA, University of Texas Medical School at Houston and Memorial Hermann Texas Medical Center, 6431 Fannin, MSB 2.112, Houston, TX 77030 (luis.ostrosky-zeichner@uth.tmc.edu).

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Invasive candidiasis (IC) is the third most common bloodstream infection in the intensive care unit (ICU) and is independently associated with mortality [1, 2]. Prophylaxis for this infection in selected adults would appear appropriate [3–5], as it has been shown to be useful in other clearly defined high-risk populations such as orthotropic liver transplant recipients [6].

There have been no large or multicenter studies to establish efficacy and safety of IC prophylaxis in ICU settings [6]. There are 3 methodologically sound single-center studies that have explored this issue as well as several meta-analyses [4, 7–10]. Taken together, these data suggest that prophylaxis may be useful in high-risk subjects, but a multicenter study is still lacking.

In an effort to identify ICU patients who are at high risk for developing IC, we conducted 2 retrospective analyses of subjects admitted to ICUs to determine risk factors for the development of IC using modified European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the Mycoses Study Group (EORTC/MSG) definitions [11]. A clinical prediction rule requiring mechanical ventilation AND a central venous catheter AND broad-spectrum antibiotics on any of days 1 through 3 of ICU admission AND 1 of the following risk factors: parenteral nutrition, dialysis, major surgery, pancreatitis, systemic steroids, or other immunosuppressive agents applied to 18% of subjects, providing an incidence of IC of 10% [12]; this was in contrast to our previous clinical prediction rule [13] that applied to only 8% of ICU patients with an incidence of 13%.

A recent advance in medical mycology has been the availability of serum diagnostic markers such as (1,3)-β-D-glucan (BG), which is a component of the fungal cell wall [14]. The latest version of the EORTC/MSG criteria for the diagnosis of fungal infections has incorporated BG as microbiological support [11]. Using BG as part of the diagnostic criteria of IC in this study allows for higher sensitivity in the detection of this disease, as well as exploring the strategy of preemptive or early antifungal therapy in subjects for whom prophylaxis is unsuccessful. This is also particularly interesting in the face of recent research showing that time to therapy has a definite impact on the outcome of the disease [15] and a proof-of-concept study showing the value of BG-driven therapy [16].

We chose caspofungin for prophylaxis as 1 of 3 echinocandins that is approved for the treatment of IC, is well tolerated, and is active against all species of *Candida* (including fluconazole-resistant strains). Development of resistance to echinocandins is uncommon [17, 18].

We conducted the first multicenter, randomized, double-blind, placebo-controlled trial of caspofungin prophylaxis followed by BG-directed preemptive therapy for IC in high-risk adults in the critical care setting.

METHODS

Study Type

This was a phase 4 multicenter, randomized, double-blind, placebo-controlled study with 2 arms (caspofungin prophylaxis vs placebo), followed by preemptive therapy for subjects who develop proven or probable IC (Table 1). The flow and phases of the study are shown in Figure 1.

Objectives

The primary objective of this study was to evaluate the efficacy of caspofungin as prophylaxis for IC in high-risk ICU patients by comparing the incidence of proven and probable IC in subjects receiving caspofungin with the incidence in those receiving placebo. The secondary objectives were to (1) prospectively verify the performance of a clinical prediction rule for IC, (2) evaluate the safety of caspofungin, (3) evaluate the effect of a preemptive therapy approach, (4) evaluate the effect of prophylaxis and preemptive therapy on all-cause mortality, and (5) evaluate effects of prophylaxis and preemptive therapy on ICU and hospital length of stay (LOS).

Endpoints

The primary endpoint was the incidence of proven and probable IC based on modified EORTC/MSG criteria, which include serologic evidence (Table 1) as assessed by the data review committee (DRC) in the modified intention-to-treat (MITT) population. The secondary endpoints included incidence of proven IC, time to development of proven or probable IC, initiation

Table 1. Definitions of Proven and Probable Invasive Candidiasis

Definition	Parameters
Proven invasive candidiasis	Blood culture that yields *Candida* spp OR histopathologic or cytopathologic examination of a needle aspiration or biopsy specimen from a normally sterile site excluding mucous membranes showing yeast cells OR recovery of a yeast by culture from a sample obtained by a sterile procedure (including a freshly [<24 h] placed drain) from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process.
Probable invasive candidiasis	Serum BG levels >80 pg/mL in 2 consecutive samples AND 1 of the following: 1. Temperature >38°C or <36°C. 2. Hypotension defined as systolic BP <90 mm Hg or a significant drop (40 mm Hg) in BP from baseline. 3. WBC count >12 000 cells/μL.

Abbreviations: BG, (1,3)-β-D-glucan; BP, blood pressure; WBC, white blood cell.

Source: Modified from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the Mycoses Study Group (EORTC/MSG) criteria [11].

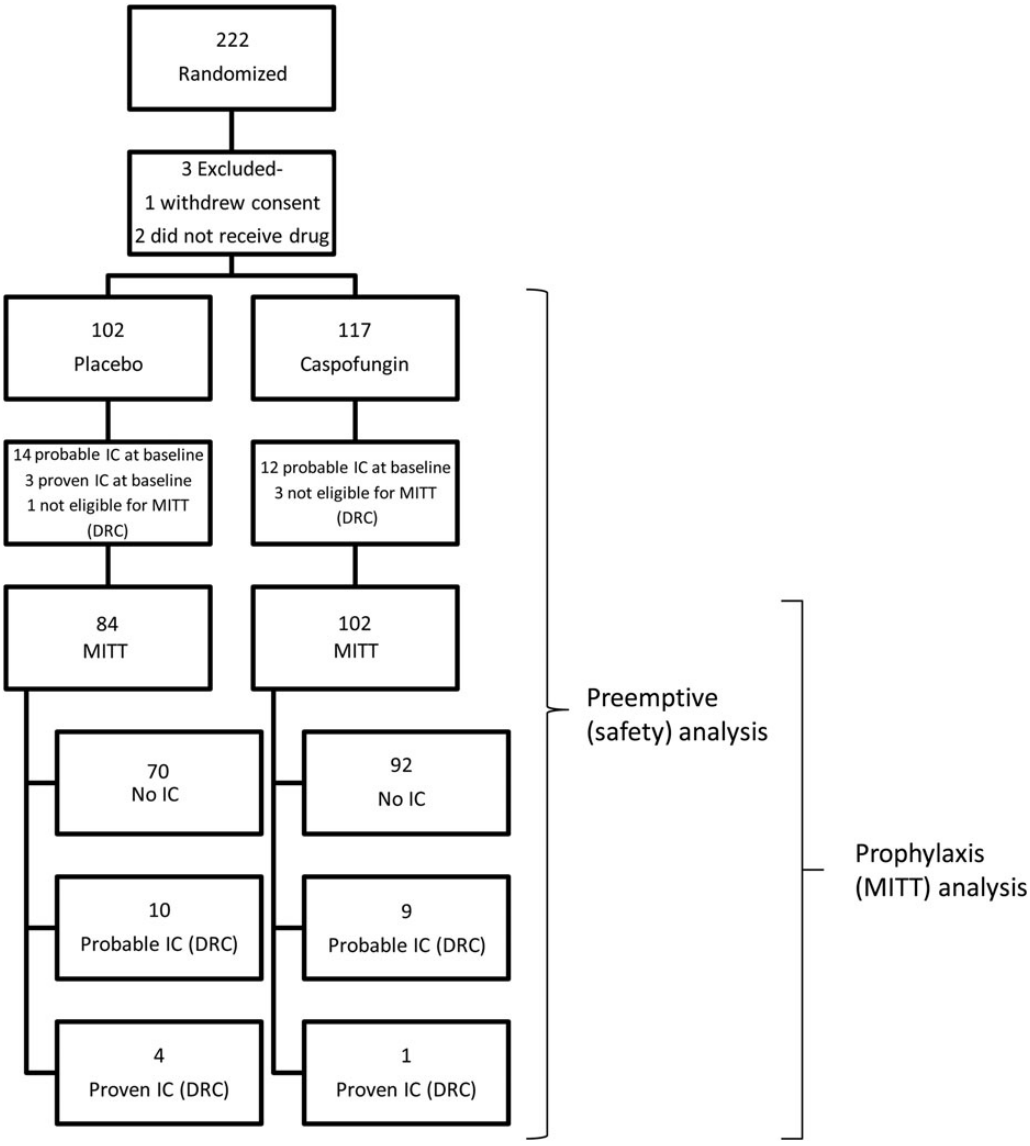

Figure 1. Analysis populations and patient disposition. A total of 222 patients were enrolled. Three patients were excluded from the analysis because 1 had a problem in the documentation of the informed consent and the other 2 did not receive study drug. The preemptive/safety population included 117 patients in the caspofungin arm and 102 in the placebo arm. For the prophylaxis population, 15 patients were excluded from the analysis for the caspofungin arm and 18 from the placebo arm, leaving 102 patients for the caspofungin arm and 84 for the placebo arm. Abbreviations: DRC, data review committee; IC, invasive candidiasis; MITT, modified intention to treat.

of systemic antifungal therapy within 7 days of ending prophylaxis, all-cause mortality within 7 days of ending prophylaxis, and hospital metrics (LOS in the hospital and ICU). There were 2 primary safety endpoints: the proportion of subjects who discontinued study therapy due to a drug-related adverse event and the proportion of subjects with 1 or more serious drug-related adverse events (AEs). Secondary safety endpoints also included all-cause mortality through end of study and incidence of drug-related AEs.

Patients

Adult patients from 15 ICUs in the United States were enrolled. Inclusion criteria were as follows: (1) nonpregnant subjects ≥18 years of age, (2) admitted to the ICU during the preceding 3 days (minimum of 48 hours in ICU) and expected to stay in the ICU for at least another 48 hours, and (3) meeting the following conditions of the clinical prediction rule for IC [12]: use of mechanical ventilation on any of days 1 through 3 of ICU admission AND use of a central venous catheter on

any of days 1 through 3 of ICU admission AND use of any broad-spectrum antibiotic (ie, one with activity against ≥2 bacterial classes) on any of days 1 through 3 of ICU admission AND at least 1 of the following risk factors: use of parenteral nutrition on any of days 1 through 3 of ICU admission, any type of dialysis on any of days 1 through 3 of ICU admission, any major surgery (performed under general anesthesia) within 7 days prior to or on ICU admission, diagnosis of pancreatitis (by computed tomography or lipase level >1000 U/L) within 7 days prior to or on ICU admission, use of systemic steroids (>1 dose of prednisone equivalent to ≥20 mg/day) within 7 days prior to or on ICU admission, or use of any other immunosuppressive agents (>1 dose) within 7 days prior to or on ICU admission.

Patients were excluded from the study if they met any of the following exclusion criteria: allergy or intolerance to echinocandins, absolute neutrophil count <500 cells/μL, AIDS, aplastic anemia or chronic granulomatous disease, moderate or severe hepatic insufficiency, pregnancy or lactation, subjects likely to die within 24 hours of enrollment, antifungal therapy within 10 days prior to study, documentation of an active invasive fungal infection upon enrollment, previous enrollment in this study, and an investigational agent within the 10 days prior to entry.

Intervention

The study design can be seen in Figure 1. For the prophylaxis phase, subjects were randomized to either caspofungin 70 mg intravenous loading dose followed by 50 mg intravenous or 0.9% saline placebo intravenous daily. During this phase of the study, subjects were be followed for the duration of their ICU stay or for a maximum of 28 days, with follow-up visits at 1 week and 2 weeks, and a final visit upon hospital discharge. When subjects met the primary endpoint (proven or probable IC), investigators were allowed to break the blind and subjects receiving placebo were started on therapy with caspofungin. Subjects receiving caspofungin were allowed to continue or to switch to other agents. Blood cultures were performed per standard of care and BG levels were drawn twice weekly starting at baseline and until the follow-up. Serum samples were shipped overnight and BG levels were measured at a central laboratory (Beacon Diagnostics, Falmouth, Massachusetts) using the Fungitell kit. Results were reported to investigators in real time. A BG result of ≥80 pg/mL was considered positive and triggered an immediate repeat test.

Data and Safety Monitoring Board

Adverse events were monitored by the investigators on a daily basis. The severity and relationship of AEs to the study drug was determined by the investigator using standardized definitions. Drug was discontinued in subjects who developed any clinical or laboratory AE that was felt to be definitely, probably, or possibly related to study drug for which interruption of therapy was clinically indicated (usually grade 3 or 4 toxicity). All severe AEs (SAEs) were reported to the coordinating center within 24 hours. The data and safety monitoring board (DSMB) met by teleconference on a quarterly basis and reviewed the incidence of AEs and SAEs on a treatment-blinded fashion, with prespecified thresholds to stop the study. The DSMB recommended continuation of the study to full accrual.

Data Review Committee

A DRC reviewed every case in a blinded fashion at the end of the study for eligibility, adjudication to the appropriate analysis population, and outcome. Each subject was reviewed by 2 DRC members and if they agreed, the subject was adjudicated. If they disagreed, the case was reviewed by the full committee in a teleconference and adjudicated by consensus. DRC members did not review subjects treated at their own institution.

Statistical Analysis and Considerations

The primary endpoint for the prophylaxis phase was the incidence of proven and probable IC based on the modified EORTC/MSG criteria as assessed by the DRC on the prophylaxis (MITT) population. An analysis of the outcomes on the safety population was planned for the preemptive therapy approach. Other endpoints include the incidence of proven IC, time to development of proven or probable IC, initiation of systemic antifungal therapy within 7 days of end of prophylaxis, all-cause mortality within 7 days of end of prophylaxis, and hospital metrics.

With an estimated incidence of IC of 20% in the placebo arm and ≤5% in the prophylaxis arm, with a 2-sided type I error of 5%, a sample size of 111 subjects per arm would achieve 80% power to detect this difference of ≥15%. This sample size estimate is based on the Fisher exact test for comparing 2 binomial populations. The sample size needed for the Mantel-Haenszel (Cochran) test was estimated to be in the range of 77 to 85, depending upon risk ratio and variance assumptions in the 2 Acute Physiology and Chronic Health Evaluation II (APACHE II) strata. Thus, enrollment of a minimum of 85 evaluable subjects per arm was required. With an estimated 30% of subjects not being evaluable due to premature discontinuation or loss to follow-up, it was estimated that 222 subjects would be required to be enrolled into this study. Block randomization was stratified by APACHE II score (≤20 or >20).

The primary analysis population was the MITT population, defined as all subjects who received at least 1 dose of study drug and did not have an active invasive fungal infection (proven or probable) documented at enrollment. The preemptive approach or safety population included all subjects who were randomized and who received at least 1 dose of study drug.

The primary analysis was a comparison of those subjects with proven and probable IC between the 2 prophylaxis arms of the study in the MITT population. Differences in the incidence of IC were tested using the Cochran–Mantel-Haenszel test with stratification by APACHE II group (≤20 or >20). The secondary analyses examined differences in time to event using Kaplan-Meier estimates of survival curves with log-rank test of treatment differences and analyses of effects of clinical covariates on incidence rate and time-to-event outcomes with logistic regression and Cox proportional hazard models, respectively. A casewise deletion approach for missing data points was used.

The 5 safety endpoints included in the safety analyses were incidence of AEs, incidence of SAEs, incidence of drug-related SAEs, discontinuation of therapy because of a drug-related AE, and all-cause mortality through end of study. Fisher exact tests were used to examine differences in the proportion of subjects experiencing the different safety endpoints in the 2 treatment arms. All SAEs and drug-related AEs were characterized by subject. AEs and SAEs were coded using MEDRA software, version 10. Statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, North Carolina).

Ethics

This study was conducted following Good Clinical Practice guidelines. Informed consent was obtained prior to any study procedures from all patients or their designee, according to institutional practice. This study was reviewed and approved by the institutional review board at each institution. This study was registered and its results are available at ClinicalTrials.gov under registration number NCT00520234.

RESULTS

Patient Flow, Disposition, and Baseline Characteristics

The study was conducted from August 2007 to March 2010. Screening logs show that approximately 16 000 patients with an ICU stay >3 days were evaluated during that period. A sampling of 1766 patients not enrolled showed that 73% did not meet the clinical prediction rule, 6% had received previous antifungals, 5% were excluded due to the Child-Pugh score, 5% were outside of the enrollment window, and 11% had a variety of exclusion criteria. As Figure 1 shows, 222 patients were enrolled in the trial, of whom 3 were excluded from the analysis (1 patient in whom consent was not properly documented per local practices and 2 patients who never received drug). Therefore, the preemptive approach /safety population included 219 patients and the prophylaxis population included 186 patients, after 33 patients were excluded for having IC at baseline or were found not to be eligible by the DRC. As seen in Table 2, the study arms were well balanced in terms of age,

Table 2. Baseline Characteristics and Reasons for Intensive Care Unit Admission

	Preemptive Approach/Safety Population		Prophylaxis/MITT Population	
Variable	Caspofungin (n = 117)	Placebo (n = 102)	Caspofungin (n = 102)	Placebo (n = 84)
Male sex, %	60.7	59.8	62.7	59.5
Age, y, mean (SD)	58.2 (17.6)	56.7 (16.6)	57.7 (17.4)	55.4 (16.8)
Race/ethnicity, %				
White	66.7	58.8	66.7	60.7
Non-Hispanic	93.2	92.2	93.1	90.5
APACHE II score, mean (SD)	25.3 (8.0)	25.1 (8.7)	25.0 (8.1)	24.9 (8.6)
Primary reason for ICU admission, %				
Cardiovascular	4.3	5.9	2.9	4.8
CV surgery	13.7	14.7	12.7	16.7
GI surgery	10.3	11.8	10.8	9.5
Infections	0.9	1.0	1.0	1.2
Metabolic	1.7	1.0	2.0	0
Neurologic	5.1	6.9	4.9	7.1
Pancreatitis	5.1	2.9	5.9	3.6
Renal	4.3	0	4.9	0
Respiratory failure	36.8	37.3	38.2	40.5
Shock	11.1	9.8	9.8	7.1
Trauma	6.0	7.8	5.9	8.3
Other	0.9	1.0	1.0	1.2

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CV, cardiovascular; GI, gastrointestinal; ICU, intensive care unit; MITT, modified intention to treat; SD, standard deviation.

Table 3. Study Endpoints and Outcomes

Variable	Prophylaxis/MITT Population		
	Caspofungin (n = 102)	Placebo (n = 84)	*P* Value
Incidence of proven or probable IC by DRC, %	9.8	16.7	.14
Incidence of proven IC by DRC, %	1.0	4.8	.11
Use of antifungals within 7 d EOT, %	13.7	17.9	.35
All-cause mortality within 7 d EOT, %	16.7	14.3	.78

Abbreviations: DRC, data review committee; EOT, end of therapy; IC, invasive candidiasis; MITT, modified intention to treat.

sex, race, ethnicity, APACHE II scores, and indications for ICU admission.

Endpoints

The incidence of proven and probable IC was 9.8% in patients receiving caspofungin vs 16.7% in those receiving placebo ($P = .14$; Table 3). The incidence of proven IC was 4.8% in the placebo arm vs 1.0% in the caspofungin arm ($P = .11$). There were no significant differences in antifungal drug use within 7 days, all-cause mortality within 7 days, time to invasive candidiasis, or ICU/hospital LOS between the 2 groups.

Preemptive Approach Analysis

When the primary endpoint was assessed using the preemptive approach/safety population, the incidence of proven/probable IC was 18.8% for caspofungin vs 30.4% for placebo ($P = .04$). The incidence appears to be higher because this analysis includes patients who were retrospectively found to be positive at baseline. We believe that including those patients does comply with the intent and concept of preemptive therapy; however, these results should be taken with caution. The incidence of proven IC was 0.9% for caspofungin vs 6.9% for placebo ($P = .02$). As with the primary analysis, there were no statistically significant differences in antifungal drug use within 7 days, all-cause mortality within 7 days, and ICU LOS, time to invasive candidiasis, or hospital LOS between the 2 groups.

Breakthrough Cases and BG Data

The one proven IC case in the caspofungin arm was a case of a paraesophageal abscess with *Candida albicans*, *Candida krusei*, and *Candida tropicalis* in a patient with an esophageal injury. The 7 proven IC cases in the placebo arm included 5 cases of candidemia (2 *C. albicans*, 1 *Candida glabrata*, 1 *Candida parapsilosis*, and 1 not identified to the species level), 1 case of *C. albicans* empyema, and 1 intra-abdominal abscess with *C. albicans*.

Seven of the 8 (87.5%) proven IC cases had at least 1 positive BG value. All probable cases were adjudicated on the basis of 2 positive BG values and signs and symptoms. The mean BG values were 88.1 (SD, 114.1) pg/mL in patients with no IC, 402.1 (SD, 730.5) pg/mL in patients with probable IC, and 296.6 (SD, 194.3) pg/mL in patients with proven IC. Of note, subjects with proven and probable IC had a significantly longer mean LOS in the ICU compared with patients who did not have IC (proven, 27.4 [SD, 12.2] days vs no IC, 12.9 [SD, 9.1] days, $P < .001$; and probable, 19.4 [SD, 13.6] days vs no IC, 12.9 [SD, 9.1] days, $P < .001$). Proven IC cases also had a significantly longer mean LOS in the ICU compared with probable IC cases (27.4 [SD, 12.2] days vs 19.4 [SD, 13.6] days, respectively; $P = .048$). There was no statistically significant difference in mean baseline, mean final, and mean change values as well as mean slope of BG curves among patients treated with caspofungin or placebo in the preemptive therapy approach analysis.

Table 4. Safety and Adverse Events

Events	Caspofungin (n = 117)	Placebo (n = 102)	Total (N = 219)
No. of adverse events	517	372	889
Subjects with adverse events	106 (90.6)	87 (85.3)	193 (88.1)
No. of severe adverse events	43	33	76
Subjects with severe adverse events	33 (28.2)	28 (27.5)	61 (27.9)
Severe adverse events related to study drug	1 (0.9)	0	1 (0.5)
Study discontinuations related to study drug	2 (1.7)	2 (2)	4 (1.8)
Deaths through end of study	24 (20.5)	16 (15.7)	40 (18.3)

Data are presented as No. (%).

Safety

As shown in Table 4, 88.1% of subjects enrolled in the study experienced an AE. There were no statistically significant differences in the incidence of AEs or SAEs among the 2 study groups. Only 1 SAE was judged by the investigator to be related to the study drug (facial flushing and edema related to caspofungin administration). Mortality was slightly higher in the caspofungin arm (20.5% vs 15.7% in the placebo arm), but the difference was not statistically significant ($P = .39$).

DISCUSSION

This is the first randomized, multicenter, double-blind, placebo-controlled trial of antifungal prophylaxis with an echinocandin for the prevention of IC in high-risk ICU patients. In addition, this study serves as a proof-of-concept model for preemptive antifungal therapy based on the detection of early infection by BG, following the single-center observations of Hanson et al [16].

Antifungal prophylaxis in the ICU is controversial as it has only been studied in single-center studies or meta-analyses. Eggimann et al showed that critically ill nonneutropenic adults with gastrointestinal leakage were at risk for *Candida* peritonitis and that fluconazole prophylaxis reduced this risk [7]. Garbino et al [8] studied 220 adults who were receiving mechanical ventilation in an ICU for at least 3 days, and they demonstrated that fluconazole was associated with an overall reduction in *Candida* from 7% to 3%. Finally, Pelz et al enrolled 260 nonneutropenic adult surgical subjects from a single ICU in a double-blind randomized comparison of fluconazole at 400 mg/day with placebo as prophylaxis for candidiasis [9]. Fluconazole reduced the rate of IC infections from 15% to 8.5% ($P = .07$). When a time-to-event analysis was performed, the difference in the treatment groups achieved a statistical significance of .01 by the log-rank test. The meta-analysis by Shorr et al [4] concluded that prophylactic fluconazole administration for prevention of mycoses in surgical ICU subjects appears to decrease the rate of IC, but the strategy does not improve survival.

Our study successfully identified a population at high risk for IC, showing that our clinical prediction rule [12] provided an incidence of proven/probable IC of 16.7% in the placebo arm of the prophylaxis population and 30.4% in the placebo arm for the safety population. Although this incidence is higher than that resulting from any predictive model in the literature to date, it still resulted in a possibly underpowered study for the primary analysis population. Another interesting finding is that cases of IC based on BG positivity were diagnosed earlier than expected based on previous studies.

The primary endpoint for prophylaxis was not met. It is problematic to determine if indeed there was no benefit to antifungal prophylaxis, or if the lack of a statistically significant difference was related to the study being underpowered due to lower-than-expected incidence of IC in the MITT analysis. Nevertheless, data from the secondary analyses point to an overall positive effect of the intervention. These analyses should be interpreted with caution because the baseline incidence of disease appears to be slightly higher in the placebo arm and because most of the cases are driven by positive BG.

Although we do not have a definitive answer for the value of antifungal prophylaxis, this study is perhaps most interesting as a proof-of-concept demonstration of the feasibility and value of targeted preemptive antifungal therapy with caspofungin in high-risk ICU patients. When considering the overall/safety population, which more closely reflects clinical scenarios in which cases with disease are not excluded upfront, all differences were significant, finding an overall decrease in the incidence of IC. Nevertheless the benefits of such an intervention remain to be studied as, although not powered to do so, we failed to find an effect of either intervention in secondary outcomes of clinical and economical interest, such as antifungal use or LOS.

The limitations of this study include a highly selective population, a lower-than-expected incidence of IC in the primary analysis resulting in a possibly underpowered study, the differences in the proportion of baseline BG positivity, the use of BG to define probable IC, and the lack of randomization and blinding in the preemptive therapy analysis. Also, the lack of widespread availability of BG testing in real time may be considered a limitation in the applicability of these interventions.

There were no significant differences in safety parameters. The study showed the expected number of unrelated AEs in ICU-based studies and only 1 SAE was probably related to the study drug. This study provides additional data regarding the safety of caspofungin in critically ill patients. There was a slightly higher mortality in the caspofungin arm. Although not statistically significant, this parameter needs to be carefully monitored in future studies.

In conclusion, caspofungin was safe but did not reduce the incidence of invasive candidiasis when used for prophylaxis. There was a numerical difference, but the difference was not statistically significant. A preemptive therapy approach deserves further study. The value of these interventions remains to be determined.

Notes

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References

1. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis **2004**; 39:309–17.
2. Gudlaugsson O, Gillespie S, Lee K, et al. Attributable mortality of nosocomial candidemia, revisited. Clin Infect Dis **2003**; 37:1172–7.
3. Rex JH, Wingard JR, Wenzel R, Herbrecht R, Sobel J, Edwards JE Jr. The design of clinical trials that evaluate antifungal prophylaxis and combination therapy: introduction and overview. Clin Infect Dis **2004**; 39(suppl 4):S165–9.
4. Shorr AF, Chung K, Jackson WL, Waterman PE, Kollef MH. Fluconazole prophylaxis in critically ill surgical patients: a meta-analysis. Crit Care Med **2005**; 33:1928–35; quiz 36.
5. Ostrosky-Zeichner L. Prophylaxis or preemptive therapy of invasive candidiasis in the intensive care unit? Crit Care Med **2004**; 32:2552–3.
6. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis **2009**; 48: 503–35.
7. Eggimann P, Francioli P, Bille J, et al. Fluconazole prophylaxis prevents intra-abdominal candidiasis in high-risk surgical patients. Crit Care Med **1999**; 27:1066–72.
8. Garbino J, Lew DP, Romand JA, Hugonnet S, Auckenthaler R, Pittet D. Prevention of severe *Candida* infections in nonneutropenic, high-risk, critically ill patients: a randomized, double-blind, placebo-controlled trial in patients treated by selective digestive decontamination. Intensive Care Med **2002**; 28:1708–17.
9. Pelz RK, Hendrix CW, Swoboda SM, et al. Double-blind placebo-controlled trial of fluconazole to prevent candidal infections in critically ill surgical patients. Ann Surg **2001**; 233:542–8.
10. Playford EG, Webster AC, Sorrell TC, Craig JC. Antifungal agents for preventing fungal infections in non-neutropenic critically ill and surgical patients: systematic review and meta-analysis of randomized clinical trials. J Antimicrob Chemother **2006**; 57:628–38.
11. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis **2008**; 46:1813–21.
12. Ostrosky-Zeichner L, Pappas PG, Shoham S, et al. Improvement of a clinical prediction rule for clinical trials on prophylaxis for invasive candidiasis in the intensive care unit. Mycoses **2011**; 54:46–51.
13. Ostrosky-Zeichner L, Sable C, Sobel J, et al. Multicenter retrospective development and validation of a clinical prediction rule for nosocomial invasive candidiasis in the intensive care setting. Eur J Clin Microbiol Infect Dis **2007**; 26:271–6.
14. Karageorgopoulos DE, Vouloumanou EK, Ntziora F, Michalopoulos A, Rafailidis PI, Falagas ME. Beta-D-glucan assay for the diagnosis of invasive fungal infections: a meta-analysis. Clin Infect Dis **2011**; 52:750–70.
15. Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. Clin Infect Dis **2006**; 43:25–31.
16. Hanson KE, Pfeiffer CD, Lease ED, et al. Beta-D-glucan surveillance with preemptive anidulafungin for invasive candidiasis in intensive care unit patients: a randomized pilot study. PLoS One **2012**; 7: e42282.
17. Kartsonis NA, Nielsen J, Douglas CM. Caspofungin: the first in a new class of antifungal agents. Drug Resist Updat **2003**; 6:197–218.
18. Denning DW. Echinocandin antifungal drugs. Lancet **2003**; 362: 1142–51.