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Micafungin and caspofungin pharmacodynamics in patients with candidemia

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Candidemia is an important cause of health care-associated bloodstream infections. Appropriate antifungal therapy is crucial to reduce morbidity and mortality. A previous randomized clinical trial compared the clinical effectiveness of caspofungin 50 mg, micafungin 100 mg (M100), and micafungin 150 mg (M150) in treating invasive candidiasis and candidemia. M100 treatment success was non-inferior to caspofungin, while M150 yielded less favourable clinical and mycological responses. Pharmacodynamic (PD) variables were explored to assess the effect of caspofungin, M100 and M150 on the following outcomes: mycological eradication, clinical success, days to eradication, recurrence, and emergent infection for cases of candidemia only from the aforementioned clinical trial. Univariate and multivariate analyses were performed to evaluate the ratio of area under the concentration curve to minimum inhibitory concentration [AUC:MIC] for the treatment arms. AUC:MIC >1500 conferred better mycological eradication, but an inverse relationship between micafungin and mycological eradication based on an AUC:MIC ≥7500 was found. M150 required more days to eradication than M100 ($p<0.03$) and caspofungin ($p<0.02$). A correlation was also noted for days to eradication with several other risk factors, including race, *Candida parapsilosis*, and neutropenia.

Key words: Micafungin and caspofungin, echinocandins,

INTRODUCTION

Candidemia is the most common invasive fungal infection encountered in the hospital setting (Pfaller and Diekema, 2007). Candidemia previously ranked fourth among causes of nosocomial bloodstream infections but is the third most common cause of such infections in the intensive care unit (Bow et al., 2010; Kuhn et al., 2002; Ostrosky-Zeichner et al., 2007; Wisplinghoff et al., 2006). However, a recent point prevalence study of nosocomial infections in 2015 in the United States underscored its importance, as it was the second most common cause of nosocomial bloodstream infection (Magill et al., 2018). Its incidence is rising and is associated with increased costs

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for patient management through increased length of stay, as well as with significant morbidity and mortality (Pfaller and Diekema, 2007; Andes et al., 2011; Fridkin, 2005; Nucci et al., 2010; Pappas et al., 2003; Wisplinghoff et al., 2004; Morgan et al., 2005; Zilberberg et al., 2008). Studies have shown that inadequate antifungal therapy is associated with higher mortality (Bow et al., 2010; Wisplinghoff et al., 2006; Ibrahim et al., 2000; Kumar et al., 2009; Kumar et al., 2006; Pappas et al., 2009). Efforts to optimize antifungal therapy for the treatment of candidemia are well founded.

Echinocandins are a class of antifungals that are non-competitive inhibitors of the synthesis of β-(1,3)-D-glucan (Walker et al., 2010). Echinocandins have favourable toxicity profiles and potent activity against most Candida species (Andes et al., 2011; Andes et al., 2010; Kuse et al., 2007; Mora-Duarte et al., 2002; Ostrosky-Zeichner et al., 2005; Pfaller et al., 2008; Reboli et al., 2007).

Two echinocandins were assessed in the first head-to-head echinocandin randomized clinical trial for invasive candidiasis, conducted by Pappas et al. (2007). This double blind multicenter randomized clinical trial compared caspofungin with micafungin at two different dosages (100 and 150 mg) and demonstrated the non-inferiority of micafungin to caspofungin at four time points: the end of intravenous (IV) therapy (the primary endpoint), the end of all antifungal therapy, two weeks after the end of therapy, and six weeks after the end of therapy. Of note, micafungin proved to be more efficacious than caspofungin against *Candida parapsilosis* candidemia (Pappas et al., 2007).

Although no significant difference in overall efficacy was observed between micafungin and caspofungin, surprisingly, the higher dose of micafungin (150 mg, M150) was somewhat less effective than the lower dose (100 mg, M100) at primary end point of the end of blinded intravenous therapy. M150 produced slightly lower response rates, slower time to eradication of *Candida* bloodstream infections (median time to eradication of three versus two days), and higher rates of persistently positive blood cultures (Pappas et al., (2007). One explanation for these observations of higher efficacy, faster eradication of candidemia and lower rate of persistence of candidemia may be the pharmacodynamic (PD) properties of M100 compared to those of M150.

The aim of this study was to explore PD modelling for candidemia of M100, compared to M150, and secondarily of caspofungin, in order to correlate the PD effect of these agents with clinical outcome and eradication of candidemia. It was hoped that this assessment may provide a rationale for the somewhat greater clinical efficacy of M100 compared to M150 in treating candidemia thus providing a clinical correlate to the *in-vitro* paradoxical effect noted with the echinocandins (Chamilos et al., 2007; Clemons et al., 2006; Paderu et al., 2007). It was also aimed to verify the comparable clinical response rates and eradication times of candidemia for micafungin and caspofungin. PD variables of area under the inhibitory curve (AUC) and minimum inhibitory concentrations (MIC) as well as the AUC:MIC ratio of the drugs were also examined to assess differences in success rates among the *Candida* species causing candidemia in the original trial.

PATIENTS AND METHODS

Patient data were extracted from the previously referenced clinical trial conducted by Pappas et al. (2007. As described in the original study, patients were ≥18 years of age and stratified by Acute Physiology and Chronic Health Evaluation (APACHE) II score and region. The population for the present study consisted only of patients with candidemia from the original study, defined as having at least one positive blood culture for *Candida* organisms. All bloodstream non-Candida yeast infections were excluded, as well as those patients with *Candida* isolated from a sterile body and invasive candidiasis only. Individuals with candidemia and concomitant invasive candidiasis were included, but only the candidemia infection was analyzed.

Baseline demographic data (age, sex, race, weight) and patient risk factors for candidemia were recorded from the original study to be included in this analysis. Baseline information was defined as the day of study enrolment. Five study outcomes were evaluated: mycological eradication, clinical success at end of therapy (EOT), recurrence, emergent fungal infection and days to eradication (DTE). Clinical response at the end of intravenous study drug therapy (EOT) as previously defined was used (Pappas et al., 2007).

Mycological response was categorized as *Candida* eradication or persistence. Eradication was defined as an absence of the infecting *Candida* spp. from the bloodstream as documented by two negative blood culture samples obtained at least 24 h apart. Persistence implied the continued presence of the baseline fungal pathogen in follow up blood cultures after the initiation of antifungal therapy or when cultures could not be obtained (e.g. death). Emergent fungal infection was defined as a proven invasive fungal infection diagnosed more than 72 h after the first dose of intravenous study drug caused by another species in a blood culture than the one or ones identified at baseline.

A fungal infection with the same species as the baseline infection, but at a different site, was counted as an emergent invasive infection only if it was diagnosed during blinded intravenous therapy. Recurrent fungal infection was defined as having positive blood cultures of the same species as the infection diagnosed at enrollment (baseline) that required additional systemic antifungal therapy. For the EOT response as defined earlier, patients were divided into clinical successes versus failures as per the original study. Clinical success, partial response, stabilization and failure were as previously published (Pappas et al., 2007). Adjudication of response for candidemia was independently performed by a Data Review Panel (DRP). As previously reported, patients were randomized in a 1:1:1 ratio to one of three daily intravenous treatment groups: M100, M150, or caspofungin (70 mg on day 1 and 50 mg daily thereafter) (Pappas et al., 2007).

In vitro susceptibility testing for all isolates was performed (National Committee for Clinical Laboratory Standards, 2002) and these data were recorded for the following *Candida* spp. categories: *Candida albicans, Candida tropicalis, C. parapsilosis, Candida glabrata, Candida krusei,* and “others”. MICs were determined after 24 h of incubation. The 24-h MIC was utilized to calculate the AUC:MIC for each of the study drugs. The AUC:MIC was equal to the 24-h area under the curve (AUC) over the 24-h MIC for a given species. AUC:MICs were calculated based on estimated steady

state 24-h AUC and MIC for the *Candida* isolate causing the bloodstream infection. The predicted steady state AUC values were estimated based on the patient creatinine clearance and body weight in a fashion similar to pharmacokinetic data previously published by Amsden et al. (1993).

Only patients with available susceptibility data performed for the baseline *Candida* pathogen and sufficient data to generate AUC:MIC were utilized in the present analysis. Patients with missing microbiological data were excluded. Two patients, one in the caspofungin arm and one in the M100 arm, with missing weights precluded AUC calculation and were excluded. AUC:MIC values were calculated employing the population pharmacokinetic methods utilized by Amsden et al. (1993).

Briefly, the AUC:MIC was equal to the 24 h estimated steady state area under the concentration curve over the 24 h MIC of the organism. The estimated AUC was based on the patient's calculated creatinine clearance and weight. For the purpose of AUC:MIC calculation, height for all patients was assumed to be 161 cm for women and 170 cm for men as individual patients from North America as well as AUC:MIC Europe and South America were enrolled in the original study. Patients with missing follow up blood cultures were adjudicated as failures. For the AUC:MIC calculation, creatinine clearance was estimated by means of the Cockcroft-Gault formula (Cockcroft and Gault, 1976) . Real body weights were employed rather than ideal body weight.

Statistical analyses were performed as follows: categorical variables expressed as percentages were compared using the chi-square and Fisher's exact tests, while normally distributed continuous variables (presented as means with standard deviations) were analyzed with a one way ANOVA test. Non-normally distributed variables such as APACHE II scores, were assessed by the Kruskal Wallis test.

Univariate logistic regression models were created from which the odds ratios for eradication (ORE) for the following risk factors were estimated: study drug; organism (*C. parapsilosis* vs. other species); type of infection and catheter removal. Univariate logistic regression was also used to examine the effect of AUC:MIC of the study medications (M100 and M150) on mycological response for the DRP assessed outcome data.

Subsequently, multivariable logistic regression models were used to investigate the effect of treatment arm in conjunction with risk factors on clinical response, mycological response, recurrence and emergent fungal infection. A backward stepwise logistic regression procedure was employed to select significant risk factors from the following list: age, gender, race, weight, hematologic malignancy, solid tumor, chemotherapy within 30 days, radiation within 2 weeks, solid organ transplantation, hematopoietic stem cell transplant, graft versus host disease, hemodialysis, treatment arm, Apache II score, corticosteroid use within 2 weeks, neutropenia at baseline, diabetes, type of infection, catheter removal, organism type and average AUC:MIC. Thereafter, multivariate logistic regression was also undertaken to examine the effect of treatment on mycological and EOT responses with the various correlated risk factors. The analysis focused on an AUC:MIC threshold of 3000 (<3000 versus ≥3000).

Univariate and multivariable generalized linear Poisson regression was used to determine the effects of treatment on days to eradication (DTE).

For all the models, estimates with a Wald test P value less than 0.05 was considered as statistically significant (used to determine the significance of an exploratory variable in a statistical model). Kaplan-Meier plots were employed to assess cumulative eradication probability versus DTE for various AUC:MIC cut points from 50 to 1000 for caspofungin and 50 to 17500 for M100 and M150. A Log-rank p value less than 0.05 was considered as statistically significant. Finally, the probability of having eradication in the groups for the issue of catheter removal versus no catheter removal was also compared using Kaplan-Meier plots. Stata version 12 (StataCorp 2011, Release 12, College Station, Texas StataCorp LP) was used for all the analyses.

RESULTS

The disposition of patients is as shown in Figure 1. The intention to treat (ITT) population consisted of 593 patients randomized to one of the 3 arms of the study (Reboli et al., 2007). Thereafter, the modified intention to treat (MITT-those who received one dose of the test drug) population was further reduced by assessing only patients with candidemia and available AUC:MIC data. The final allocated subject number (436 patients) was as follows: M100 (n=149), M150 (n=152), and caspofungin (n=135).

The patient demographic characteristics and risk factors for candidemia in the treatment arms are shown in Table 1. There was a statistically significant weight difference in the patient groups, with the M100 group having the lowest mean weight (p=0.002). With regards to risk factors for candidemia, no statistically significant differences between groups were noted, except for: surgery within two weeks of enrolment (more frequent in the caspofungin arm, p=0.04); kidney disease (most common in the M100 arm, p=0.03); and bacteremia (most common in the M150 arm, p=0.02). Finally, there was a significant difference in the AUC:MIC distribution across the 3 arms as noted in Table 1. The caspofungin arm had the fewest number of patients with higher AUC:MICs, ≥1500 (1 patient; p<0.001).

A specific breakdown of *Candida* isolates producing candidemia in each arm and their susceptibilities are included in Table 2. *C. parapsilosis* was singled out due to its decreased susceptibility to echinocandins. When comparing *C. parapsilosis* vs. other *Candida* spp., the distribution differed significantly, with the caspofungin group possessing the highest frequency of *C. parapsilosis* (p=0.01).

Five study outcomes were evaluated: mycological eradication, clinical success at EOT, recurrence, emergent fungal infection and DTE. Assessments of the aforementioned outcomes were independently undertaken by the DRP. The outcomes and death rates across the three treatment arms are shown in Table 3.

To examine the effect of AUC:MIC on mycological eradication, AUC:MIC cut points ranging from 150 to 12500 were explored with univariate logistic regression (Table 4). Keeping in mind that caspofungin had only 1 patient with an AUC:MIC ≥1500 as noted in Table 1 (and in fact this one caspofungin patient had an AUC:MIC ≥3000), these data really reflect the AUC:MIC values for M100 and M150. An odds ratio of eradication (ORE) of 2.19 (95% confidence interval [CI] 1.06-4.55) for patients with an AUIC ≥1500 versus those with an AUIC <1500, indicating that patients with an AUIC ≥1500 had a twofold greater chance for successful *Candida* eradication (p=0.04). No significant dichotomy between higher

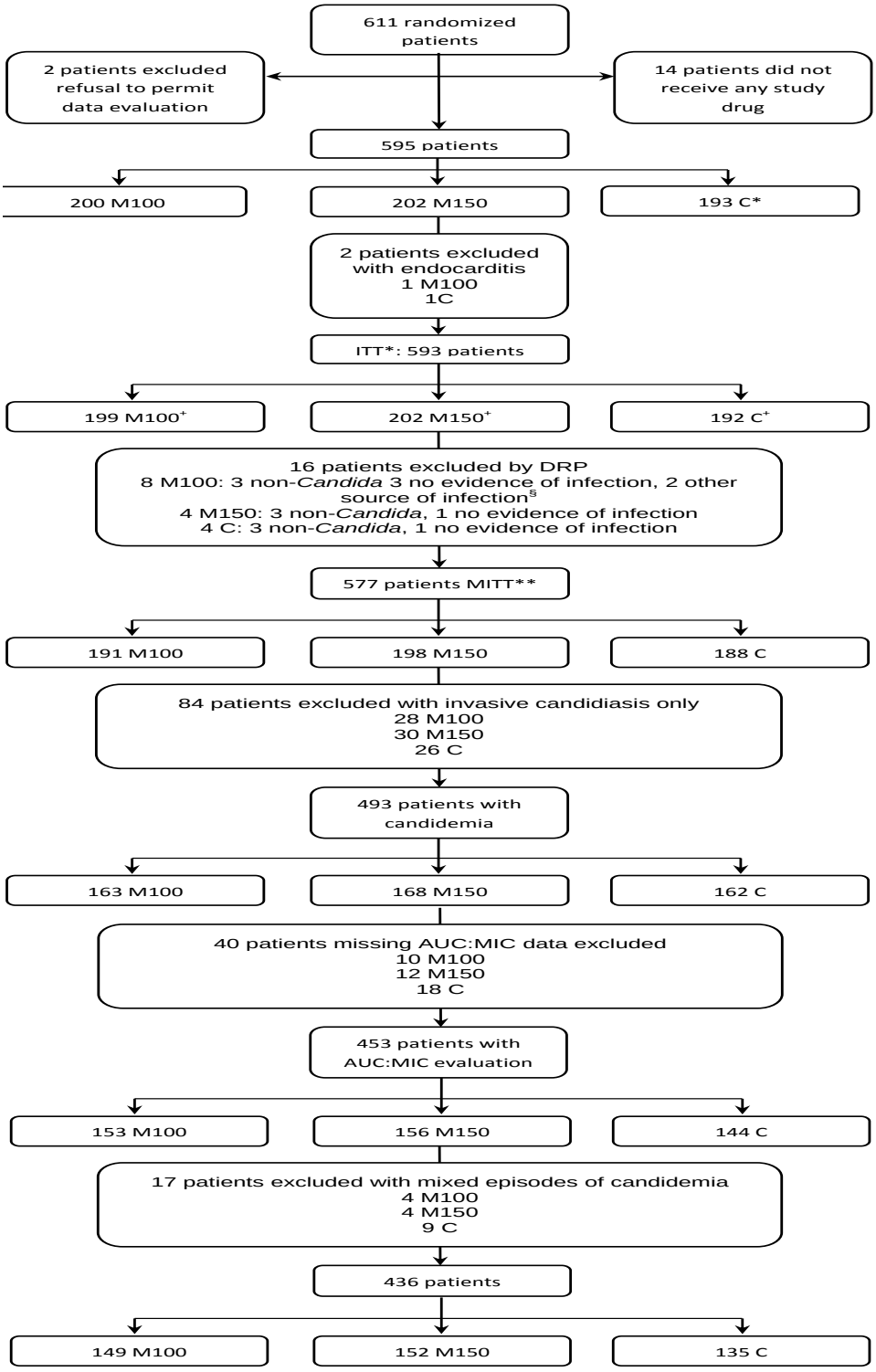

Figure 1. Consort table. *ITT: Intention to treat, +M100: micafungin; M150: micafungin 150; C: caspofungin. §2 other source of infection: 1 Morganella morganii sepsis, 1 Staphylococcal bacteremia with possible endocarditis. **MITT: modified intention to treat.

AUC:MICs and poorer mycological eradication was observed for micafungin. However, as indicated in Table 4, decreased OREs were noted when a threshold of AUC:MIC ≥7500 for micafungin, thus signifying inferior

Table 1. Demographic characteristics of the treatment groups.

Risk factors	Caspofungin n = 135 (%)	Micafungin 100 n = 149 (%)	Micafungin 150 n = 152 (%)	P value
Age	55.4 (±16.8)	57.1 (±16.5)	54.6 (±16.5)	0.43
Gender				
Male	79 (58.52)	87 (58.39)	90 (59.21)	0.99
Female	56 (41.48)	62 (41.61)	62 (40.79)	
Race				
White	87 (64.44)	104 (69.80)	100 (65.79)	
Black	23 (17.04)	17 (11.41)	27 (17.76)	
Hispanic	2 (1.48)	1 (0.67)	4 (2.63)	0.58
Asian	17 (12.59)	23 (15.44)	18 (11.84)	
Mestizo	4 (2.96)	4 (2.68)	2 (1.32)	
Other	2 (1.48)	0 (0.00)	1 (0.66)	
Weight	77.0 (±21.1)	69.3 (±18.6)	76.2 (±22.7)	0.002
Hematological malignancy	11 (8.15)	20 (13.42)	20 (13.16%)	0.30
Neutropenia at baseline	5 (3.70)	10 (6.71)	7 (4.61%)	0.49
Solid tumor	26 (19.26)	29 (19.46)	29 (19.08%)	1.00
Median apache II score at baseline and range	13 (8, 18)	14 (10, 19)	14 (10, 19)	0.30
Corticosteroid use within 2 weeks	36 (26.67)	50 (33.56)	48 (31.58)	0.44
Antineoplastic chemotherapy within 30 days	12 (8.89)	28 (18.79)	22 (14.47)	0.06
Radiotherapy within 2 weeks	0 (0.00)	3 (2.01)	2 (1.32)	0.27
Surgery within 2 weeks	52 (38.52)	39 (26.17)	41 (26.97)	0.04
Solid organ transplantation	3 (2.22)	4 (2.68)	7 (4.61)	0.47
HSCT*	4 (2.96)	6 (4.03)	2 (1.32)	0.35
GVHD^{+}	1 (0.74)	1 (0.67)	1 (0.66)	1.00
Hemodialysis	21 (15.56)	12 (8.05)	17 (11.18)	0.14
Diabetes	42 (31.11)	49 (32.89)	55 (36.18)	0.65
Catheter removal	117 (92.86)	126 (94.74)	136 (93.15)	0.80
Catheter removal (Among Catheter removal "Yes")				0.66
Late catheter removal	39 (33.33)	41 (32.54)	51 (37.50)	
Early catheter removal	78 (66.67)	85 (67.46)	85 (62.50)	
Organism				
Other	103 (76.30)	121 (81.21)	136 (89.47)	0.01
Candida parapsilosis	32 (23.70)	28 (18.79)	16 (10.53)	
Type of infection				
IFI§	6 (4.44)	15 (10.07)	11 (7.24)	0.19
Fungemia only	129 (95.56)	134 (89.93)	141 (92.76)	
Liver disease	63 (46.67)	59 (39.60)	64 (42.11)	0.48
Lung disorder	48 (35.56)	44 (29.53)	56 (36.84)	0.36
Kidney disease	32 (23.70)	53 (35.57)	35 (23.03)	0.03
Concomitant bacterial infection				
Bacteremia	31 (23.13)	32 (21.48)	52 (34.21)	0.02

Table 1. Contd.

Non-bacteremic infection	98 (73.13)	107 (71.81)	93 (61.18)	0.06
AUC:MIC 1500				
< 1500	134 (99.26)	56 (37.58)	32 (21.05)	< 0.001
≥1500	1 (0.74)	93 (62.42)	120 (78.95)	

*HSCT: Hematopoietic stem cell transplantation; [+]GVHD: graft versus host disease; § IFI: invasive fungal infection; **AUC:MIC: ratio of area under the concentration curve:minimum inhibitory concentration; [¶]invasive fungal infection; [‡‡]Area under the inhibitory curve.

mycological eradication.

Also, using a univariate logistic regression model, there was a statistically significant difference in the mycological eradication for all *Candida* spp. versus *C. parapsilosis*, in the DRP assessment (ORE 0.39, p=0.004). An ORE of < 1.00 indicated that the odds of pathogen eradication for patients with *C. parapsilosis* were less than the odds for patients with other *Candida* spp. Adding catheter removal into the model showed that catheter removal had no impact on mycological eradication.

Multivariate logistic regression analysis was used to model the effect of other risk factors on mycological eradication per treatment group with an AUC:MIC threshold of 3000. The antifungal treatment used proved to have a significant impact on *Candida* eradication, but the M150 group had a lower chance of eradication compared to the caspofungin group (p=0.02). Other risk factors having a significant impact on the ORE included: race (others vs. white) (ORE 0.30, CI 0.14-0.64, p=0.002); diabetes (ORE 2.73, CI 1.24-6.02, p=0.01); *C. parapsilosis* (ORE 0.33, CI 0.14-0.79, p=0.01); and liver disease (ORE 0.47, CI 0.25-0.88, p=0.02) with either of the assessments.

Although univariate logistic regression showed that catheter removal had no direct correlation with mycological eradication, we further explored the impact of catheter removal by incorporating it as a variable in multivariate models for mycological eradication. According to the DRP outcome adjudication, when catheter removal was included in the multivariate modelling, the treatment arm was again significant with M150 having a 68% lower odds of eradication compared to the caspofungin arm (p=0.04).

Univariate logistic regression was also used to examine the interrelationship of treatment and correlated risk factors with clinical response and no differences were found. Clinical outcomes generated by the DRP evaluation were also assessed. The treatment arm was significant; the M150 arm had 58% lower odds of clinical response compared to the caspofungin arm. Race (others vs. white) (ORS 0.37, CI 0.19-0.71, p=0.003), APACHE II score at baseline (ORS 0.96, CI 0.93-1.00, p=0.05), type of infection (ORS 3.01, CI 1.34-6.77, p=0.01), and lung disorder (ORS 0.36, CI 0.22-0.59, p < 0.001) were significant correlated risk factors. When catheter removal was included in the model, treatment (M150 vs. caspofungin) (ORS 0.35, CI 0.15-0.81, p=0.01), race (ORS 0.39, CI 0.20-0.78, p=0.01) along with liver disease (ORS 0.35, CI 0.21-0.59, p < 0.001) were significant.

Univariate generalized linear Poisson regression was used to model the effect of treatment on average DTE. Per the DRP assessment, treatment was a significant factor: the M150 arm required 0.15 and 0.14 more DTE, respectively than the caspofungin and M100 arms (CI 0.02-0.28, p=0.02, and CI 0.01-0.26, p=0.03). Early catheter removal (<2 days) also produced fewer DTE than those patients with later catheter removal (p<0.001 for both). The following correlated risk factors also had a significant effect on the number of DTE: race (black vs. white) (0.31 fewer DTE, p<0.001) and others vs. white (0.32 more DTE, p<0.001); neutropenia (0.59 more DTE, p<0.001); type of infection, candidemia vs. IFI with candidemia (0.30 fewer DTE, p=0.02); *C. parapsilosis* (0.27 fewer DTE, p=0.002); AUIC (≥ 3000 vs. < 3000) (0.37 fewer DTE, p<0.001); radiation within 2 weeks (0.85 more DTE, p<0.001); surgery within 2 weeks (0.28 more DTE, p < 0.001); and kidney disease (0.15 more DTE, p=0.02).

Catheter removal was also included as a risk factor in the DTE analysis. Using the DRP review, treatment arm was once again significant. The M100 arm required 0.26 more DTE (CI 0.10-0.42, p=0.001) than the caspofungin arm, while the M150 arm required 0.39 more DTE than the caspofungin arm (CI 0.21-0.56, p < 0.001). As earlier stated, type of infection (0.53 fewer DTE for candidemia, p < 0.001), *C. parapsilosis* (0.36 fewer DTE, p<0.001) and AUIC (≥ 3000 vs. < 3000) (0.48 days fewer DTE, p < 0.001) were again significant correlated risk factors.

Univariate logistic regression was used to examine the effect of treatment on recurrence and emergent fungal infection. With multivariate model evaluations, the DRP data for recurrence employed an AUC:MIC threshold of 3000 and yielded a multivariate model result where weight (every 1 kg increase) was a significant risk factor producing an odds ratio of recurrence (ORR) of 1.03 (CI 1.02-1.06, p=0.02). For emergent infections, with the DRP outcomes, significant correlated risk factors were: race (black vs. white) (odds ratio of emergent infection [OREI 0.08, p=0.03); solid organ transplant (OREI 8.09,

Table 2. *In vitro* susceptibilities of Candida isolates per treatment group.

Candida species	M100					M150					Caspofungin				
	N	MIC 50	MIC 90	min MIC	max MIC	N	MIC 50	MIC 90	min MIC	max MIC	N	MIC 50	MIC 90	min MIC	max MIC
C. albicans	61	0.03	0.03	0.03	0.03	72	0.03	0.03	0.03	0.50	57	0.50	0.50	0.03	2.00
C. tropicalis	24	0.03	0.03	0.03	0.25	28	0.03	0.03	0.03	0.03	22	0.50	1.00	0.25	2.00
C. parapsilosis	28	0.50	0.50	0.13	1.00	16	0.50	1.00	0.03	1.00	32	1.00	2.00	0.50	2.00
C. glabrata	22	0.03	0.03	0.03	0.03	25	0.03	0.03	0.03	0.03	17	0.50	1.00	0.25	2.00
C. krusei	7	0.03	0.13	0.06	0.13	7	0.13	0.25	0.06	0.25	1	1.00	1.00	1.00	1.00
Other	7	0.06	0.13	0.03	0.13	4	0.13	0.25	0.03	0.25	6	0.75	1.00	0.50	1.00
Total	149	0.03	0.50	0.03	1.00	152	0.03	0.25	0.03	1.00	135	0.50	1.00	0.03	2.00

*Minimum inhibitory concentration to inhibit 50% of isolates. [+]Minimum inhibitory concentration to inhibit 90% of isolates. [‡]Min MIC = minimum MIC. **Max MIC = maximum MIC.

Table 3. Mycological and clinical outcomes for the treatment groups.

Outcome		Treatment groups			Total [n=436 (%)]
		Caspofungin [n=135 (%)]	M100 [n=149 (%)]	M150 [N=152 (%)]	
Mycological response					
DRP	Persistence	11/135 (8.1)	19/149 (12.8)	23 (15.1)	53/436 (12.2)
	Eradication	124/135 (91.9)	130/149 (87.2)	129/152 (84.9)	383/436 (87.8)
EOT response					
DRP	Failure	24/135 (17.8)	32/148[‡] (21.6)	40/152 (26.3)	96/435 (22.1)
	Success	111/135 (82.2)	116/148[‡] (78.4)	112/152 (73.7)	339/435 (77.9)
Recurrence					
DRP[+]	Number of patients (n)	100	109	120	329
	Yes	4/100 (4.0)	6/109 (5.5)	5/120 (4.2)	15/329 (4.6)
Emergent fungal infection					
DRP	Number of patients (n)	118	131	134	383
	Yes	8/118 (6.8)	11/131 (8.4)	13/134 (9.7)	32/383 (8.4)
Days to eradication					
DRP	Number of patients	110	118	110	338
	Median days (min, max)	2 (1, 23)	2 (1, 19)	2 (1, 26)	2 (1, 26)

Table 3. Contd.

Days of therapy	Median (min, max)	14 (1, 37)	14 (1, 47)	14 (1, 56)	14 (1, 56)
Death within 6 weeks of intravenous therapy	Number of deaths	36/135 (26.7)	39/149 (26.2)	46/152 (30.3)	121/436 (27.8)
	Median days to death (min, max)	17.5 (3, 40)	14 (1, 40)	15.5 (2, 42)	16 (1, 42)
Death (total in the dataset)	Number of deaths	37/135 (27.4)	42/149 (28.2)	54/152 (35.5)	133/436 (30.5)
	Median days to death (min, max)	18 (3, 50)	16 (1, 57)	18 (2, 66)	17 (1, 66)

*One patient had a missing value in mycological response (Investigator). [+]Data review panel. [‡]One patient had missing values in clinical response (Investigator & DRP). **Min = minimum days. [++]Max = maximum days.

Table 4. Univariate logistic regression for the effect of AUC:MIC on mycological eradication for micafungin.

AUC:MIC	Number of patients	Mycological eradication (Investigator)		Mycological eradication (DRP)	
		Odds ratio of eradication	P value	Odds ratio of eradication	P value
AUC:MIC (≥150 vs. <150)	374 vs. 62	1.12 (0.13, 9.55)	0.92	1.03 (0.12, 8.76)	0.98
AUC:MIC (≥200 vs. <200)	349 vs. 87	2.64 (0.67, 10.39)	0.17	1.39 (0.29, 6.66)	0.68
AUC:MIC (≥500 vs. <500)	264 vs. 172	2.47 (1.10, 5.54)	0.03	1.87 (0.82, 4.25)	0.14
AUC:MIC (≥1200 vs. <1200)	249 vs. 187	2.05 (0.95, 4.43)	0.07	1.83 (0.85, 3.93)	0.12
AUC:MIC (≥1500 vs. <1500)	245 vs. 191	2.47 (1.18, 5.17)	0.02	2.19 (1.06, 4.55)	0.04
AUC:MIC (≥2000 vs. <2000)	233 vs. 203	2.40 (1.18, 4.88)	0.02	1.85 (0.91, 3.76)	0.09
AUC:MIC (≥2381 vs. <2381)	227 vs. 209	2.38 (1.18, 4.80)	0.02	1.84 (0.92, 3.69)	0.08
AUC:MIC (≥3000 vs. <3000)	214 vs. 222	2.34 (1.18, 4.65)	0.02	1.80 (0.92, 3.53)	0.09
AUC:MIC (≥3500 vs. <3500)	197 vs. 239	2.18 (1.11, 4.30)	0.03	1.86 (0.96, 3.60)	0.07
AUC:MIC (≥3800 vs. <3800)	185 vs. 251	1.78 (0.91, 3.50)	0.10	1.52 (0.79, 2.93)	0.21
AUC:MIC (≥4000 vs. <4000)	179 vs. 257	1.61 (0.82, 3.17)	0.16	1.38 (0.72, 2.65)	0.34
AU:MICC (≥5000 vs. <5000)	146 vs. 290	1.56 (0.78, 3.12)	0.20	1.44 (0.74, 2.79)	0.28
AUC:MIC (≥5200 vs. <5200)	139 vs. 297	1.40 (0.70, 2.80)	0.33	1.29 (0.66, 2.50)	0.45
AUC:MIC (≥5500 vs. <5500)	123 vs. 313	1.11 (0.56, 2.22)	0.76	1.43 (0.72, 2.84)	0.31
AUC:MIC (≥6000 vs. <6000)	102 vs. 334	1.16 (0.56, 2.41)	0.68	1.50 (0.72, 3.13)	0.28
AUC:MIC (≥6500 vs. <6500)	91 vs. 345	1.10 (0.52, 2.33)	0.79	1.43 (0.67, 3.05)	0.36
AUC:MIC (≥7000 vs. <7000)	82 vs. 354	0.93 (0.44, 1.97)	0.86	1.21 (0.56, 2.59)	0.63
AUC:MIC (≥7500 vs. <7500)	69 vs. 367	0.83 (0.38, 1.80)	0.64	0.92 (0.43, 1.99)	0.84
AUC:MIC (≥8000 vs. <8000)	55 vs. 381	0.60 (0.27, 1.33)	0.21	0.79 (0.35, 1.77)	0.57
AUC:MIC (≥8500 vs. <8500)	44 vs. 392	0.76 (0.31, 1.84)	0.54	0.83 (0.34, 2.02)	0.69
AUIC (≥9000 vs. <9000)	42 vs. 394	0.71 (0.29, 1.73)	0.45	0.78 (0.32, 1.90)	0.59
AUIC (≥9500 vs. <9500)	37 vs. 399	0.59 (0.24, 1.46)	0.26	0.66 (0.27, 1.61)	0.36

Table 4. Contd.

AUIC (≥10000 vs. <10000)	33 vs. 403	0.82 (0.30, 2.26)	0.70	0.70 (0.27, 1.81)	0.46
AUIC (≥12500 vs. <12500)	12 vs. 424	0.43 (0.11, 1.66)	0.22	0.30 (0.09, 1.05)	0.06
AUIC (≥15000 vs. <15000)	5 vs. 431	0.59 (0.06, 5.43)	0.64	0.64 (0.07, 5.9)	0.70

p=0.01); and chemotherapy within 30 days (odds ratio 3.78, p=0.01).

DISCUSSION

This retrospective analysis of the previously published first head-to-head clinical trial comparison of echinocandins for invasive candidiasis (Pappas et al., 2007) was undertaken to evaluate PD parameters of caspofungin, M100, and M150 for the treatment of candidemia alone. The original double blind trial used two independent evaluations from the Investigators and DRP. The DRP assessments were utilized only for the purpose of this study for three treatment arms with regards to five study outcomes: mycological eradication, clinical success at the end of the study drug IV therapy, DTE, recurrence, and emergent fungal infections. With regards to mycological eradication, univariate logistic regression of the DRP outcomes showed that the AUC:MIC threshold of 1500 was a significant factor. Patients with AUC:MICs equal to or above this level exhibited a higher ORE of eradication as compared to patients with AUC:MICs below this threshold. This was only true for the two micafungin arms, as the caspofungin arm had only one patient who attained an AUIC ≥1500.

Thus, higher doses of micafungin lead to better eradication for susceptible organisms as noted by the shorter DTEs. Although, one might then have anticipated that higher doses of the study drug would always correlate with improved *Candida* eradication, the exploratory analyses noted a reversal of the ORE at AUC:MICs >7500. This may indicate a possible paradoxical effect with micafungin. Similarly, an analysis of mycological eradication showed that starting from very high AUC:MIC thresholds of about 7500, M150 was inferior to M100.

The species also impacted mycological eradication. Univariate and multivariate models corroborated the finding that patients with *C. parapsilosis* infections had a decreased chance of eradication compared to patients with infections caused by other species. This was expected, as echinocandins have lower *in vitro* activity and clinical efficacy against *C. parapsilosis* (Pfaller and Diekema, 2007; Walker et al., 2010; Pfaller et al., 2008; Ostrosky-Zeichener et al., 2003; Chen et al., 2011; Barchiesi et al., 2006). Although race was consistently correlated with mycological eradication, the impact of race on the treatment of candidemia is unclear.

Additionally, catheter removal was a significant factor for time to eradication. This was not surprising, as early catheter removal is generally the standard practice for patients with candidemia (Mermel et al., 2009). It is noteworthy that catheter removal had no significant effect on the other outcomes.

The AUC:MIC data analysis support the clinical response results of the original study, whereby M100 was associated with greater success than the M150 arm. This finding is further corroborated by the DTE results in the analysis where the DRP evaluation found treatment arm to be a significant factor affecting DTE: the M150 arm required more DTE than the M100 arm. Finally, APACHE II score was a significant factor in treatment success. For each unit increase in the median score at baseline, there was 3 to 4% less chance of clinical success.

The sole risk factor that correlated with recurrence was weight. With each 1 kg increase in weight, patients had 3% higher odds of recurrent infection per the DRP assessment (ORR 1.03, p=0.02). This may be explained by the following. There is evidence that total body weight may affect volume of distribution (Hanley et al., 2010). Furthermore, there is a statistically significant relationship between weight and drug clearance.

Andes et al. (2011) found that patients with weights over 100 kg had clearance values that were approximately 30% higher than the clearance values for the overall population, while patients with weights under 45 kg had clearance values approximately 30% lower than the overall population (Andes et al., 2011). With faster clearance, the drug is more rapidly removed, rendering it unavailable to produce its pharmacological effect.

Thus, it is plausible that an increase in weight may impact PK/PD factors such as volume of distribution and clearance such that serum levels are diminished, thus reducing the drug's effect. Perhaps larger doses of the drugs may be necessary in patients above 100 kg to prevent recurrence. However, it is unknown why the effect of weight was only observed with regards to

recurrence.

The present study, however, possesses some limitations. The data evaluations were conducted in a retrospective fashion after the publication of the clinical trial. This may have curtailed some of the data collection. Some differences were also noted between the investigator assessment reported in the original study and the DRP assessment. The DRP evaluation was favoured as it was deemed that it would be more robust and less subject to bias. They were also hampered by the use of generalized population pharmacokinetic parameters rather than individualized parameters based on individual antifungal agent serum levels.

In addition, one may question our exclusion of non-candidemic invasive candidiasis. Such cases may have prolonged DTE, but were excluded because the DTE could not be determined with certainty as follow up cultures were not available. Also, the rationale for using a threshold of AUC:MIC 3000 may seem subject to bias. But, this threshold seemed appropriate as caspofungin group did not attain AUC:MIC thresholds above this level. There is however another caveat worth mentioning with regard to the caspofungin MICs that were obtained. It is known that caspofungin MICs to Candida spp. exhibit considerable variability (Espinel-Ingroff et al., 2013).

Thus, the present reported AUC:MIC results for caspofungin may not reflect the true state of affairs for this variable. Furthermore, any pharmacodynamic data on the other echinocandin and anidulafugin was not included. This echinocandin was not part of the data that was assessed nor was there access to data of anidulafungin's pharmacodynamic effects for eradicating candidemia. Precise data on the DTE are not available for anidulafungin (Reboli et al., 2007). These deficiencies notwithstanding were successful in exploring differences between M100 and M150.

Of import, patients treated with micafungin attaining AUC:MICs ≥3000 exhibited less time to eradication than those with AUC:MICs below this threshold. These findings parallel those of Andes et al. (2018). This trend, however, was not consistent at higher AUC:MIC cut points (Table 4). A paradoxical effect with M150 may have been present. Mycological eradication and DTE analyses both showed that M150 was frequently associated with a lower success rates than M100 in the treatment of candidemia.

The present study demonstrated the value of PD analyses in the evaluation of the treatment of candidemia. The clinical response findings were corroborated at the end of therapy as noted by Pappas et al. (2007). The results for pathogen eradication and DTE noted, that M100 was superior to M150. Our multivariate models featuring PD variables also helped to identify correlated risk factors that could serve as predictors of favourable treatment. Finally, AUC:MIC values of ≥3000 but <7000 were associated with optimal outcomes for both micafungin doses. Future PD studies are warranted to explore the optimal dosing for echinocandins with respect to achieving mycological eradication, DTE, and deterring recurrent and emergent infections.

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CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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