

A Randomized, Placebo-controlled Trial of Preemptive Antifungal Therapy for the Prevention of Invasive Candidiasis Following Gastrointestinal Surgery for Intra-abdominal Infections

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Background. Patients undergoing emergency gastrointestinal surgery for intra-abdominal infection are at risk of invasive candidiasis (IC) and candidates for preemptive antifungal therapy.

Methods. This exploratory, randomized, double-blind, placebo-controlled trial assessed a preemptive antifungal approach with micafungin (100 mg/d) in intensive care unit patients requiring surgery for intra-abdominal infection. Coprimary efficacy variables were the incidence of IC and the time from baseline to first IC in the full analysis set; an independent data review board confirmed IC. An exploratory biomarker analysis was performed using logistic regression.

Results. The full analysis set comprised 124 placebo- and 117 micafungin-treated patients. The incidence of IC was 8.9% for placebo and 11.1% for micafungin (difference, 2.24%; [95% confidence interval, -5.52 to 10.20]). There was no difference between the arms in median time to IC. The estimated odds ratio showed that patients with a positive (1,3)- β -D-glucan (β DG) result were 3.66 (95% confidence interval, 1.01–13.29) times more likely to have confirmed IC than those with a negative result.

Conclusions. This study was unable to provide evidence that preemptive administration of an echinocandin was effective in preventing IC in high-risk surgical intensive care unit patients with intra-abdominal infections. This may have been because the drug was administered too late to prevent IC coupled with an overall low number of IC events. It does provide some support for using β DG to identify patients at high risk of IC.

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Candida species are the most common fungal pathogens in the intensive care unit (ICU) [1], and invasive candidiasis (IC) is associated with considerable morbidity and mortality in critically ill patients [2, 3]. Early antifungal treatment reduces mortality rates in patients with documented IC [4, 5], but a swift definitive diagnosis is difficult [6, 7]. Although prophylaxis or preemptive treatment strategies should be used in patients at high risk for IC [6, 8], their identification is clinically challenging, because preemptive intervention markers have not been fully defined.

Risk factors for IC in critically ill patients include broad-spectrum antibiotic exposure, cancer chemotherapy, fungal colonization, indwelling vascular catheters, total parenteral nutrition, surgery, renal failure, hemodialysis, and prolonged ICU stay [9, 10]. Although these factors can be present in patients who do not have IC and individually are not sufficiently discriminatory, together they can still be used to identify high-risk patients. Risk identification strategies, such as *Candida* colonization index [11], clinical predictive rules [12, 13] and a *Candida* score [14, 15] have been proposed to aid in deciding when to initiate early antifungal therapy [7].

Antifungal prophylaxis in patients at high risk for IC has been investigated in several randomized, controlled trials. Trials in homogenous populations, such as surgical patients with recurrent gastrointestinal perforations or anastomotic leakages [16] and severe acute pancreatitis [17], showed prophylaxis to be an effective strategy, because infection rates were high with placebo and significantly lower with active antifungal therapy. Studies with heterogeneous ICU patients, however had low incidences of infections in the placebo arms, and treatment differences between placebo and active therapy were not shown [18–24]. Therefore, antifungal prophylaxis should be used only in specific subgroups where there is clear evidence of benefit [7, 8, 25]. For the majority of ICU patients at high IC risk, a preemptive antifungal strategy, based on clinical risk factors and microbiologic evidence of substantial colonization, is proposed [7, 8, 25].

Patients requiring ICU management after emergency surgery for intra-abdominal infection have a high IC risk [26]. As a commensal of the digestive tract, *Candida* may leak into the peritoneal cavity after perforation or during surgical resection of the intestine. Peritoneal seeding can result in intra-abdominal *Candida* infection with risk of dissemination to the bloodstream and extra-abdominal tissue and organs [27]. The INTENSE (Invasive Candidiasis – Pre-emptive Treatment in High Risk Surgical Subjects) study assessed the strategy of preemptive antifungal therapy versus placebo in hospitalized patients requiring surgery for intra-abdominal infection. Micafungin was used as the active therapy, and the efficacy and safety of its use in that setting was assessed.

METHODS

Patients and Study Design

INTENSE (Clinicaltrials.gov identifier NCT01122368) was an exploratory, multicenter, randomized, double-blind, placebo-controlled trial of preemptive antifungal therapy in adults (aged ≥ 18 years), who presented with a generalized or localized intra-abdominal infection requiring surgery and an ICU stay. Patients were included if they had a community-acquired (CAI) or nosocomially acquired (NAI) intra-abdominal infection. Patients with CAI were those who presented with intra-abdominal infection before or within 48 hours after hospital admission. Patients with NAI were those who developed intra-abdominal infection >48 hours after hospital admission and were hospitalized for reasons other than infection. Key exclusion criteria were acute pancreatitis, infected intra-peritoneal dialysis, solid organ transplantation, severe liver disease, or neutropenia at randomization. Exclusion criteria included receipt of a systemic antifungal within 14 days before study drug, documented IC at randomization, or expected survival <48 hours. The study was conducted from 13 July 2010 to 15 December 2011.

Eligible patients were randomized 1:1 to intravenous micafungin (100 mg/d) or saline solution as a placebo. Patients were included within 48 hours (NAI) or 72–120 hours (CAI) after surgery providing they had an expected minimum ICU stay of 48 hours. Patients were treated for 6 weeks unless they experienced an end of treatment (EOT) event: confirmed IC, improvement in surgical condition (as indicated by recovery of gastrointestinal function allowing enteral feeding of up to 50% of daily calorie requirement), alternative antifungal treatment, or death. If IC was confirmed, study medication was discontinued and alternative antifungal medication was given. The type of surgery and antibiotic required for the treatment of the intra-abdominal infection were prescribed according to center policy. The study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki. Written or witnessed informed consent was obtained for all patients.

Outcome Measures and Assessments

Evaluation for IC

Patients were evaluated (Supplementary Appendix 1) for IC at baseline, during treatment, at EOT assessment, and at the end of study (EOS). The EOT assessment visit occurred within 1–3 days after the last dose of study medication, and the EOS visit occurred 28 days after the last dose. Blinded assessments and confirmation of IC were made by an independent data review board (IDRB) (P. E., C. L., and P. M.), as well as the investigators, based on histologic evidence at biopsy or positive culture from blood, from a freshly placed peritoneal drain or biliary catheter or intra-abdominal abscess.

The coprimary efficacy variables were the incidence of IDRB-confirmed IC diagnosed between baseline and EOT assessment and the time from baseline to first IDRB-confirmed IC. The start date of a confirmed case was provided by the IDRB, and the time to IC was calculated relative to the date of first dose of study drug. The incidence of IC according to the investigator was also calculated. Post hoc analysis of the incidence of IC confirmed by the IDRB or an investigator (hereafter “any-confirmed” IC) was conducted for all patients and subgroups, as described in [Supplementary Appendix 2](#).

Biomarkers

The fungal biomarkers (1,3)- β -D-glucan (β DG), *Candida* antibody, mannan antigen, and *Candida* were measured in blood samples at baseline, during treatment and at the EOT assessment; *Candida* antibody and mannan antigen were measured with enzyme-linked immunosorbent assay, and *Candida* was detected by polymerase chain reaction.

Safety

Treatment-emergent adverse events (AEs) and serious AEs, including death, were recorded up to 90 days after EOT. Routine laboratory assessments, including biochemistry, hematology, and urinalysis, were performed at baseline and up to the EOS.

Statistical Methods

Power Calculation

A formal power calculation was not performed for this exploratory study, owing to a lack of suitable data on preventive therapy studies at time of study design and therefore the use of potentially poor estimates of parameters for sample size

calculations. It was considered that randomization of 125 patients per arm might allow observation of clinically important differences in the incidence of IC, even with a 20% dropout rate.

Analysis Sets

Baseline characteristics, incidence and time to IDRB-confirmed IC, and biomarker data are reported for the full analysis set (FAS), which comprised all randomized patients who received ≥ 1 dose of study medication and did not have an IDRB-confirmed IC at baseline. For the investigator-confirmed IC, a modified FAS was used, which took into account investigator-confirmed IC at baseline. Similarly for any-confirmed IC (confirmed by the IDRB or investigator), a modified FAS was used, which took into account the any-confirmed IC at baseline. The incidence and time to IDRB-confirmed IC were further assessed in the per-protocol set (PPS), defined as all FAS patients (1) who had an assessment of IC, as confirmed by the IDRB at EOT; (2) received ≥ 3 days of study medication; (3) had no confirmed IC before baseline, according to the IDRB; and (4) had no major protocol violations. Prior and concomitant medication use and safety assessments are described for the safety analysis set, which included all randomized patients who received study medication at least once.

Statistical Analysis

Unless otherwise stated, data are summarized using descriptive statistics of mean (standard deviation [SD]) and median (where not normally distributed) values for continuous variables, and frequency and percentage for categorical data. The differences in IC incidence between micafungin- and placebo-treated patients and the corresponding 95% confidence intervals (CIs)

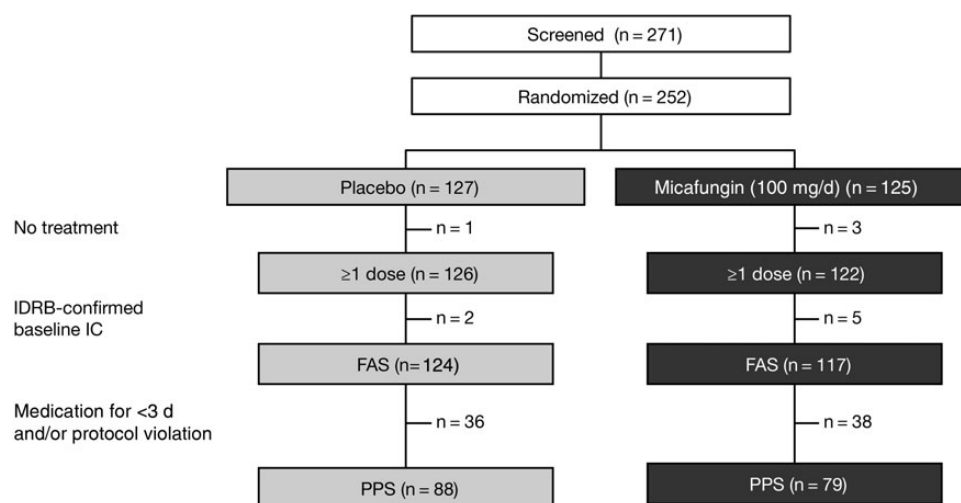


Figure 1. Patient flow through the study. In the full analysis set (FAS), 30.7% of patients had either violated the protocol (10.4% had received concurrent antifungal agents and 12.9% were outside the drug study window) or had received treatment for <3 days (11.6%). Abbreviations: IC, invasive candidiasis; IDRB, independent data review board; PPS, per-protocol set.

Table 1. Baseline Demographic and Clinical Characteristics (Full Analysis Set)

Characteristic	Patients, No. (%) ^a		
	Placebo (n = 124)	Micafungin (n = 117) ^b	Total (n = 241)
Sex			
Male	41 (33.1)	50 (42.7)	91 (37.8)
Female	83 (66.9)	67 (57.3)	150 (62.2)
Age, mean (SD), y	63.0 (15.8)	61.6 (14.8)	62.3 (15.3)
Age group			
18–65 y	63 (50.8)	66 (56.4)	129 (53.5)
>65 y	61 (49.2)	51 (43.6)	112 (46.5)
Type of intra-abdominal infection			
CAI	45 (36.3)	41 (35.0)	86 (35.7)
NAI	79 (63.7)	76 (65.0)	155 (64.3)

Abbreviations: CAI, community-acquired infection; NAI, nosocomially acquired infection; SD, standard deviation.

^a Data represent No. (%) except where otherwise indicated.

^b Micafungin 100 mg/d.

were derived using the Newcombe–Wilson method without continuity correction. The time to IDRB-confirmed IC was modeled using the accelerated failure time model, a general model for time-to-event data. The time to IDRB-confirmed IC was presented graphically by nonparametric Kaplan–Meier curves, with patients without IDRB-confirmed IC during the treatment period censored either on the day of the EOT event or at the EOT assessment. Statistical comparisons were performed using log-rank tests.

Logistic regression was used to evaluate the impact of biomarkers on the binary response for IDRB-confirmed IC. All 4 biomarkers were included in the model: β DG (≥ 62.5 pg/mL for positive response vs < 62.5 pg/mL for negative), *Candida* polymerase chain reaction (positive vs negative after > 30 cycles), *Candida*

antibody (5.0–10.0 or > 10.0 antibody units [AU]/mL for intermediate or positive, respectively, vs 5.0 AU/mL for negative), and mannan antigen (62.5–125 or > 125 pg/mL for intermediate or positive vs < 62.5 pg/mL for negative). Other covariates (continuous and categorical) included in the model were age, sex, study drug, CAI or NAI, and time from ICU admission to first study drug dose. Data analyses were performed using SAS software for Windows (version 9.2 [2011]; SAS Institute).

RESULTS

Study Population

The study was conducted at 53 centers across 17 countries. Participant flow is shown in Figure 1. The FAS comprised 241 patients, 124 randomized to placebo and 117 to micafungin (100 mg/d); baseline characteristics are provided in Table 1.

Study Drug Exposure

The mean (SD) duration of study drug exposure was 8.3 (6.9) days for placebo and 7.7 (6.8) days for micafungin (median, 6 days for both arms). In the placebo and micafungin arms, the percentages of patients who received the study drug for < 3 days (protocol deviations) were 9.7% and 13.7%, respectively; for 3–14 days, 79.0% and 75.2%; and for > 14 days, 11.2% and 11.1%.

Efficacy

In the FAS, the IDRB-confirmed IC incidence at EOT was 8.9% (n = 11) for placebo and 11.1% (n = 13) for micafungin, for an estimated difference of 2.24% (95% CI, -5.52 to 10.20) (Table 2). The *Candida* species are listed in Table 3. Most infections occurred in NAI patients; 9 of 11 in the placebo arm and 11 of 13 in the micafungin arm. There was no difference between treatment groups in the median time to IDRB-confirmed IC; the time ratio of micafungin relative to placebo was 0.69 (95% CI, $.34$ – 1.38). The Kaplan–Meier failure curves are displayed in Figure 2. For patients

Table 2. Incidence of Invasive Candidiasis in the Full Analysis Set and Per-Protocol Set for All Patients

IC Incidence	Patient With IC/Total Patients, No. (%)		
	Placebo	Micafungin ^b	Treatment Difference (Micafungin – Placebo), % (95% CI)
All patients (FAS)			
IDRB-confirmed IC	11/124 (8.9)	13/117 (11.1)	2.24 (–5.52 to 10.20)
Investigator-confirmed IC ^a	20/121 (16.5)	16/116 (13.8)	–2.74 (–11.92 to 6.56)
Any-confirmed IC ^a	20/120 (16.7)	17/115 (14.8)	–1.88 (–11.24 to 7.58)
All patients (PPS)			
IDRB-confirmed IC	5/88 (5.7)	5/79 (6.3)	0.65 (–7.17 to 8.95)

Abbreviations: CI, confidence interval; FAS, full analysis set; IC, invasive candidiasis; IDRB, independent data review board; PPS, per-protocol set.

^a FAS was modified according to who assessed for IC at baseline. Any-confirmed IC includes IC confirmed by IDRB and/or investigator.

^b Micafungin 100 mg/d.

Table 3. Type and Frequency of *Candida* Species Confirmed by Independent Data Review Board at the End of Treatment

<i>Candida</i> Species	Cultures Positive for <i>Candida</i> Species, No. ^a			
	Placebo		Micafungin	
	Blood Culture	Other Culture ^b	Blood Culture	Other Culture ^b
<i>C. albicans</i>	1	6	2	7
<i>C. glabrata</i>	1	3	1	0
<i>C. parapsilosis</i>	1	1	0	1
<i>C. tropicalis</i>	0	2	0	0
<i>C. dubliniensis</i>	0	2	0	0
Not identified to species level	2	2	2	3

^a Some patients were infected with >1 *Candida* species.

^b Other culture sites included freshly placed peritoneal drain or biliary catheter and intra-abdominal abscess.

Table 4. End of Treatment Events (Full Analysis Set)

Reason for EOT	EOT Events, No. (%)	
	Placebo (n = 124)	Micafungin (n = 117) ^b
IDRB-confirmed IC	11 (8.9)	13 (11.1)
No IDRB-confirmed IC,	113 (91.1)	104 (88.9)
Sufficient improvement	78 (62.9)	75 (64.1)
Alternative antifungal therapy	8 (6.5)	5 (4.3)
Death	1 (0.8)	5 (4.3)
Other reasons for EOT ^a	25 (20.2)	18 (15.4)
Maximum 6-wk treatment	1 (0.8)	1 (0.9)

Abbreviations: EOT, end of treatment; IC, invasive candidiasis; IDRB, independent data review board.

^a Other reasons include investigator-confirmed IC, adverse events, lack of efficacy, and protocol violation.

^b Micafungin 100 mg/d.

without an IDRB-confirmed IC, the most common EOT event was sufficient improvement in surgical condition (Table 4). The results obtained in the PPS for incidence (Table 2) and time to IDRB-confirmed IC (time ratio of micafungin relative to placebo, 0.80, 95% CI, .26–2.50) were consistent with those in the FAS.

In the FAS, the investigators diagnosed IC in 20 patients (16.5%) in the placebo arm and 16 (13.8%) in the micafungin arm (Table 2). The incidence of any-confirmed IC was also lower for micafungin than for placebo for all patients (Table 2), as well as for all post hoc subgroups considered to have a higher risk of IC, although the CIs included 0 (Figure 3).

Biomarkers

Biomarker results are reported for β DG data, which were available for 41% of the FAS population. The mean (SD)

change from baseline at the EOT assessment for β DG was +53 (356) pg/mL in the placebo arm (n = 54) and –35 (207) pg/mL in the micafungin arm (n = 44). Logistic regression modeling used to evaluate the impact of biomarkers on the binary response for IDRB-confirmed IC showed only β DG to be related to the response, with an odds ratio of 3.66 (95% CI, 1.01–13.29).

Safety

AEs and deaths are reported in [Supplementary Appendix 3](#). There were no clinically significant differences between study arms in the mean biochemical, hematologic, and urinalysis parameters analyzed between baseline and either EOT or EOS. Alanine aminotransferase levels were similar between treatment groups ([Supplementary Appendix 3; Figure 1](#)).

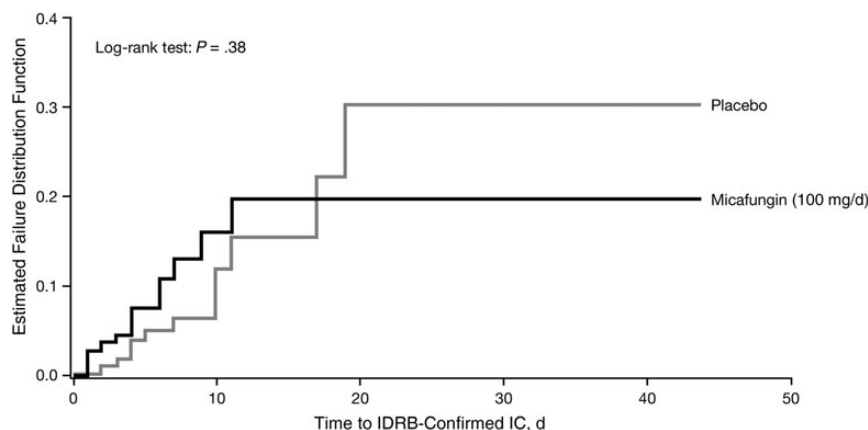


Figure 2. Kaplan–Meier failure curves of time to independent data review board (IDRB)-confirmed invasive candidiasis (IC) (full analysis set).

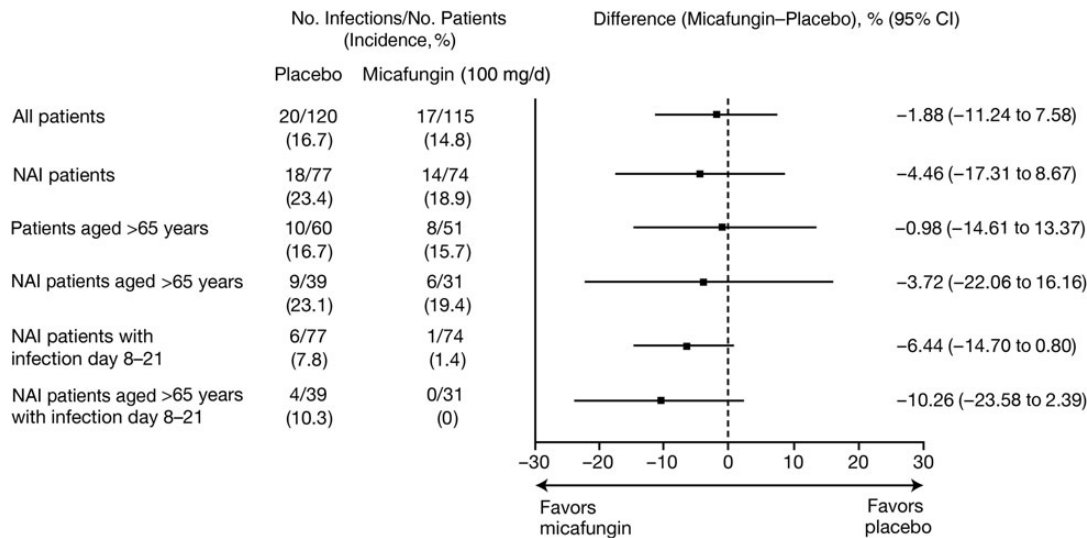


Figure 3. Incidence of confirmed cases of invasive candidiasis (IC) by higher-risk subgroups (full analysis set, modified according to who assessed for IC at baseline; cases were confirmed by independent data review board and/or investigator). Abbreviations: CI, confidence interval; NAI, nosocomially acquired infection.

DISCUSSION

The INTENSE study did not provide evidence to support the use of a preemptive antifungal strategy in high-risk surgical patients with intra-abdominal infections. In the FAS, the patient selection criteria successfully identified an IDR-confirmed incidence rate of 8.9% in the placebo arm. However, the incidence of 11.1% in the miconazole arm was unexpected. Because miconazole is an effective treatment for candidemia and IC, this suggests that IC might have been established in these patients and preemptive therapy was administered too late. This supposition is supported by the relatively high number of baseline IC cases (Figure 1), with the majority of emergent IC cases within the first few study days (Figure 2).

A similar lack of evidence for a prophylaxis antifungal strategy in at-risk ICU patients was found in a randomized, placebo-controlled study of caspofungin [24]. A lower-than-expected IC incidence resulted in a lack of difference between placebo (16.7%) and caspofungin (9.8%). A comparison between preemptive and empiric antifungal therapy with anidulafungin also showed no difference between strategies in the incidence of IC in ICU patients [28]. Antifungal treatment administered in the absence of a proven IC diagnosis was found to have no effect on mortality rates or IC occurrence compared with no treatment in critically ill patients receiving mechanical ventilation, possibly owing to the absence of actual IC [29]. These studies, together with ours, highlight the challenge of demonstrating the benefit of antifungals in the absence of proven IC, even in ICU patient populations with multiple risk factors for IC.

The challenge of early IC identification in the surgical setting is widely recognized [26], and for this reason we used blinded assessment and confirmation of IC by an independent panel of experts. The incidence was higher with investigator-diagnosed IC (16.5% for placebo in the FAS), and only some diagnosed infections overlapped with those assessed by the IDR. The disparity between the IDR and investigators in the incidence of confirmed IC, a phenomenon observed in other studies [30, 31], again illustrates the difficulty in early identification of IC.

Preliminary studies investigating β DG in ICU patients found higher β DG levels in those with IC than in those without IC [24, 28, 32], and its detection has been shown to precede a microbiologic diagnosis by several days [33, 34]. In our study, β DG was the only biomarker correlating with confirmed IC, although β DG measurements were not available for all patients.

Miconazole was well tolerated in these patients, with one-half the incidence of pyrexia, wound infection, vomiting, and pleural effusion compared with placebo. The incidence of anemia was slightly higher in miconazole-treated patients than in those receiving placebo. No hepatobiliary AEs were related to miconazole. There was no clinically relevant difference in mortality rates between miconazole and placebo.

Statistical powering of prophylaxis and preemptive trials in ICU patients is difficult, and for this reason INTENSE was designed to be an exploratory study and was not formally powered. We recognize this as a limitation of our study. Any *P* values are considered nominal and only hypothesis generating rather than conclusive. Other limitations include the possible

inclusion of patients who already had established IC and difficulty on the part of the investigators in deciding which patients should be enrolled in this study, as highlighted by the fact that 31% of patients in the FAS were excluded from the PPS.

Several key findings from the INTENSE study should be considered in future studies of preventive antifungal strategies in critically ill patients. The type of treatment strategy needs to be classified by current definitions as prophylactic, preemptive, or empiric [7], because this classification determines the timing of treatment. These definitions have evolved from when the INTENSE study was designed, and with hindsight it could be considered a prophylaxis study. Identification of ICU patients at high risk for IC is challenging and requires careful selection of patients. In our study for example, the overall incidence of IC (any-confirmed cases) in the NAI subgroup was 21%, confirming that this might be a population worth focusing on in future studies, whereas the infection rate in the CAI group was very low. We echo a point made by Montravers et al [27], that additional tools and prediction rules to identify patient populations with the highest risk are required. Our data add to the evidence that, in conjunction with risk factors, β 2D-G has potential use as a marker to help physicians select high-risk patients who might benefit from early antifungal treatment. Our findings support the need for further investigations on these measures as criteria in prediction rules.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Author contributions. All authors had access to the data, participated in the preparation of the manuscript, agreed to submit the manuscript, and vouch for the accuracy of the data and analyses.

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Potential conflicts of interest. W. K. reports serving as a consultant for Astellas Pharma, Gilead, Merck Sharp & Dohme, Novartis, and Pfizer. B. F. reports being a member of advisory boards for Cubist, KentaBiotech, and Medimmune and serving as a consultant for Asahi-Kasei, GlaxoSmithKline, Lascco, Sanofi, and Tigenix. J. C. V. is a member of the speakers' bureaus for Astellas Pharma, Merck Sharp & Dohme, Novartis, Orion, and Pfizer. P. E. has received research grants, educational grants, speaker honoraria, and/or consultant honoraria from Astellas Pharma, Merck Sharp & Dohme-Chibret, and Pfizer. C. L. has received research grants and/or consultant honoraria from Astellas Pharma. P. M. reports acting as a consultant for Astellas Pharma, AstraZeneca, Cubist, Merck Sharp & Dohme, Pfizer, and The

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* **2009**; 302:2323–9.
2. Calandra T, Marchetti O. Clinical trials of antifungal prophylaxis among patients undergoing surgery. *Clin Infect Dis* **2004**; 39(suppl 4): S185–92.
3. Schelenz S. Management of candidiasis in the intensive care unit. *J Antimicrob Chemother* **2008**; 61(suppl 1):i31–4.
4. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of *Candida* bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. *Antimicrob Agents Chemother* **2005**; 49:3640–5.
5. 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.
6. Eggimann P, Ostrosky-Zeichner L. Early antifungal intervention strategies in ICU patients. *Curr Opin Crit Care* **2010**; 16:465–9.
7. Eggimann P, Bille J, Marchetti O. Diagnosis of invasive candidiasis in the ICU. *Ann Intensive Care* **2011**; 1:37.
8. Cornely OA, Bassetti M, Calandra T, et al. ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients. *Clin Microbiol Infect* **2012**; 18(suppl 7):19–37.
9. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Risk factors for hospital-acquired candidemia: a matched case-control study. *Arch Intern Med* **1989**; 149:2349–53.
10. Eggimann P, Garbino J, Pittet D. Epidemiology of *Candida* species infections in critically ill non-immunosuppressed patients. *Lancet Infect Dis* **2003**; 3:685–702.
11. Pittet D, Monod M, Suter PM, Frenk E, Auckenthaler R. *Candida* colonization and subsequent infections in critically ill surgical patients. *Ann Surg* **1994**; 220:751–8.
12. Paphitou NI, Ostrosky-Zeichner L, Rex JH. Rules for identifying patients at increased risk for candidal infections in the surgical intensive care unit: approach to developing practical criteria for systematic use in antifungal prophylaxis trials. *Med Mycol* **2005**; 43:235–43.
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. Leon C, Ruiz-Santana S, Saavedra P, et al. A bedside scoring system (“*Candida* score”) for early antifungal treatment in nonneutropenic critically ill patients with *Candida* colonization. *Crit Care Med* **2006**; 34:730–7.
15. Leon C, Ruiz-Santana S, Saavedra P, et al. Usefulness of the “*Candida* score” for discriminating between *Candida* colonization and invasive

- candidiasis in non-neutropenic critically ill patients: a prospective multicenter study. *Crit Care Med* **2009**; 37:1624–33.
16. 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.
 17. He YM, Lv XS, Ai ZL, et al. Prevention and therapy of fungal infection in severe acute pancreatitis: a prospective clinical study. *World J Gastroenterol* **2003**; 9:2619–21.
 18. Slotman GJ, Burchard KW. Ketoconazole prevents *Candida* sepsis in critically ill surgical patients. *Arch Surg* **1987**; 122:147–51.
 19. Savino JA, Agarwal N, Wry P, Policastro A, Cerabona T, Austria L. Routine prophylactic antifungal agents (clotrimazole, ketoconazole, and nystatin) in nontransplant/nonburned critically ill surgical and trauma patients. *J Trauma* **1994**; 36:20–5.
 20. Ables AZ, Blumer NA, Valainis GT, Godernick MT, Kajdasz DK, Palesch YY. Fluconazole prophylaxis of severe *Candida* infection in trauma and postsurgical patients: a prospective double-blind, randomized, placebo-controlled trial. *Infect Dis Clin Pract* **2000**; 9:169–75.
 21. 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.
 22. 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.
 23. Schuster MG, Edwards JE Jr, Sobel JD, et al. Empirical fluconazole versus placebo for intensive care unit patients: a randomized trial. *Ann Intern Med* **2008**; 149:83–90.
 24. Ostrosky-Zeichner L, Shoham S, Vazquez J, et al. 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. *Clin Infect Dis* **2014**; 58:1219–26.
 25. Eggimann P, Garbino J, Pittet D. Management of *Candida* species infections in critically ill patients. *Lancet Infect Dis* **2003**; 3:772–85.
 26. Bassetti M, Marchetti M, Chakrabarti A, et al. A research agenda on the management of intra-abdominal candidiasis: results from a consensus of multinational experts. *Intensive Care Med* **2013**; 39:2092–106.
 27. Montravers P, Dupont H, Eggimann P. Intra-abdominal candidiasis: the guidelines-forgotten non-candidemic invasive candidiasis. *Intensive Care Med* **2013**; 39:2226–30.
 28. Hanson KE, Pfeiffer CD, Lease ED, et al. β -D-glucan surveillance with preemptive anidulafungin for invasive candidiasis in intensive care unit patients: a randomized pilot study. *PLoS One* **2012**; 7:e42282.
 29. Bailly S, Bouadma L, Azoulay E, et al. Failure of empirical systemic antifungal therapy in mechanically-ventilated critically ill patients. *Am J Respir Crit Care Med* **2015**; 191:1139–46.
 30. Cornely OA, Maertens J, Bresnik M, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). *Clin Infect Dis* **2007**; 44:1289–97.
 31. Pappas PG, Rotstein CM, Betts RF, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. *Clin Infect Dis* **2007**; 45:883–93.
 32. Mohr JF, Sims C, Paetznick V, et al. Prospective survey of (1 \rightarrow 3)- β -D-glucan and its relationship to invasive candidiasis in the surgical intensive care unit setting. *J Clin Microbiol* **2011**; 49:58–61.
 33. Posteraro B, De Pascale G, Tumbarello M, et al. Early diagnosis of candidemia in intensive care unit patients with sepsis: a prospective comparison of (1 \rightarrow 3)- β -D-glucan assay, *Candida* score, and colonization index. *Crit Care* **2011**; 15:R249.
 34. Tissot F, Lamoth F, Hauser PM, et al. β -glucan antigenemia anticipates diagnosis of blood culture-negative intraabdominal candidiasis. *Am J Respir Crit Care Med* **2013**; 188:1100–9.