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Claire Dupuis, Clément Le Bihan, Daniele Maubon, Laure Calvet, Stéphane Ruckly, et al.. Performance of Repeated Measures of (1–3)-β-D-Glucan, Mannan Antigen, and Antimannan Antibodies for the Diagnosis of Invasive Candidiasis in ICU Patients: A Preplanned Ancillary Analysis of the EMPIRICUS Randomized Clinical Trial. Open Forum Infectious Diseases, 2021, 8 (3), 10.1093/ofid/ofab080 . hal-03190667

HAL Id: hal-03190667
https://hal.science/hal-03190667v1

Submitted on 6 Apr 2021

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Open Forum Infectious Diseases

MAJOR ARTICLE

Performance of Repeated Measures of (1–3)-β-D-Glucan, Mannan Antigen, and Antimannan Antibodies for the Diagnosis of Invasive Candidiasis in ICU Patients: A Preplanned Ancillary Analysis of the EMPIRICUS Randomized Clinical Trial

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Background. We aimed to assess the prognostic value of repeated measurements of serum (1–3)-β-D-glucan (BDG), mannan-antigen (mannan-Ag), and antimannan antibodies (antimannan-Ab) for the occurrence of invasive candidiasis (IC) in a high-risk nonimmunocompromised population.

Methods. This was a preplanned ancillary analysis of the EMPIRICUS Randomized Clinical Trial, including nonimmunocompromised critically ill patients with intensive care unit–acquired sepsis, multiple *Candida* colonization, and multiple organ failure who were exposed to broad-spectrum antibacterial agents. BDG (>80 and >250 pg/mL), mannan-Ag (>125 pg/mL), and antimannan-Ab (>10 AU) were collected repeatedly. We used cause-specific hazard models. Biomarkers were assessed at baseline in the whole cohort (cohort 1). Baseline covariates and/or repeated measurements and/or increased biomarkers were then studied in the subgroup of patients who were still alive at day 3 and free of IC (cohort 2).

Results. Two hundred thirty-four patients were included, and 215 were still alive and free of IC at day 3. IC developed in 27 patients (11.5%), and day 28 mortality was 29.1%. Finally, BDG >80 pg/mL at inclusion was associated with an increased risk of IC (CSHR[IC], 4.67; 95% CI, 1.61–13.5) but not death (CSHR[death], 1.20; 95% CI, 0.71–2.02).

Conclusions. Among high-risk patients, a first measurement of BDG >80 pg/mL was strongly associated with the occurrence of IC. Neither a cutoff of 250 pg/mL nor repeated measurements of fungal biomarkers seemed to be useful to predict the occurrence of IC. The cumulative risk of IC in the placebo group if BDG >80 pg/mL was 25.39%, which calls into question the efficacy of empirical therapy in this subgroup.

Keywords. (1,3)-β-D-glucan; competing risk models; invasive candidiasis.

Invasive candidiasis (IC), including deep-seated candidiasis and candidemia, is found in 15%–20% of critically ill patients and is associated with high intensive care unit (ICU) mortality rates of up to 30%–40% [1–5].

Its management is still challenging, mainly because of the difficulty in establishing a final diagnosis. Most of the time, fungal sepsis is very similar in presentation to sepsis of other origins, blood culture results are often negative, and puncture or surgery of a normally sterile site for histopathological confirmation is not always feasible.

In this context, because delayed appropriate treatment can increase the risk of death, empirical antifungal treatment (AFT) could be initiated to treat suspected IC as soon as possible. However, such treatment entails significant costs and results in an epidemiological shift toward more resistant *Candida* species [6, 7].

Several strategies have been proposed to identify high-risk ICU patients for targeted empirical AFT. Most are based on known risk factors of IC such as sepsis, parenteral nutrition, central vein catheters, broad-spectrum antimicrobial exposure, and surgery, which are common occurrences in ICU patients.

Received 19 November 2020; editorial decision 9 February 2021; accepted 26 February 2021.

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DOI: 10.1093/ofid/ofab080

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As a result, the indication for empirical AFT now depends mainly on clinical signs including sepsis, persistence of organ failure after broad-spectrum antibiotics, and other risks of invasive fungal infections (IFIs) such as the *Candida* colonization index, which are not at all sensitive or specific [8]. Biomarkers could improve early diagnosis of IC and help guide the decision to start empirical AFT. Serum mannan-antigen (mannan-Ag), antimannan antibody (antimannan-Ab), and 1,3 beta-D-glucan (BDG) are among the biomarkers commercially available for the detection of IC. Their accuracy in the prediction of the occurrence of IFIs [8–13] has already been assessed in several studies (Supplementary Table 1).

BDG, in particular, owing to early positivity in ICU patients, has quite good sensitivity and negative predictive value [14–18]. The BDG test has also been proposed to rule out the diagnosis of IC in adult patients at risk of infection [11, 19], and its accuracy is considered to be greater than that of the colonization index in predicting IC [20]. However, very few studies have been performed in ICU patients, for whom the probability of IC is the highest. Furthermore, the most recent recommendations suggested not relying solely on results of serum BDG testing alone for diagnostic decision-making. Unfortunately this recommendation was based on low-quality evidence and must therefore be considered with caution [21]. The positive predictive value of mannan-Ag and antimannan-Ab in IC has also been reported, but with varying results [5, 22]. Most of these studies were retrospective, involved heterogeneous populations (both ICU and hematologic patients), and used different cutoff values and diagnostic criteria. In addition, none assessed the added value of their repeated measurements, and hence no definitive conclusions can be drawn concerning the real accuracy of repeated measurements of BDG, mannan-Ag, and antimannan-Ab in the diagnosis of IC.

EMPIRICUS is a randomized controlled trial (RCT) that compares early therapy with micafungin and placebo to prevent proven IFI or death at day 28 in a highly selected ICU population of *Candida* multicolonized nonimmunocompromised ICU patients with nosocomial sepsis and multiple organ failure [23].

The aim of this preplanned analysis of EMPIRICUS data [24] was to assess the performance of repeated measurements of BDG, mannan-Ag, and antimannan-Ab in predicting the occurrence of IC and death in ICU patients.

METHODS

This was a preplanned analysis of the EMPIRICUS randomized clinical trial [24] (clinicaltrials.gov identifier: NCT01773876).

Patient Consent Statement

The EMPIRICUS randomized clinical trial was approved by an authorized ethics committee (Comité de Protection des Personnes CPP Sud Est V; December 7, 2011) and the French Health Authorities (AFSSAPS; December 2, 2011). Written informed consent was obtained from all participants or their proxies (in cases of impaired decision-making capacity) at the time of enrollment.

Study Population

Briefly, EMPIRICUS compared the benefits of 14-day AFT with micafungin and those of placebo in terms of 28-day survival without IFI in adult patients with suspected invasive candidiasis. Patients were included if they met the following criteria: (1) mechanically ventilated for at least 5 days; (2) at least 1 colonization site (other than rectal swab or stool) positive for *Candida* species by standard culture methods; (3) at least 1 additional organ dysfunction; (4) previous treatment for more than 4 days with broad-spectrum antibacterial agents within the last 7 days; (5) 1 arterial or central vein catheter; and (6) 1 new finding of ICU-acquired sepsis of unknown origin. The exclusion criteria were (1) neutrophil count <500/mm^3; (2) previous bone marrow or solid organ transplantation; (3) ongoing systemic immunosuppressant agent therapy other than corticosteroids at doses <2 mg/kg/d of prednisolone or equivalent; and (4) antifungal treatment with an echinocandin agent for >1 day or with any other antifungal agent for >72 hours during the week before inclusion.

Data Collection

The main characteristics recorded during this trial were age, sex, principal comorbidities, SAPS II, admission category, duration of ICU stay before inclusion, and SOFA score at inclusion. BDG, mannan-Ag, and antimannan-Ab were measured on day 0, day 3, day 7, day 14, and day 28 after inclusion.

BDG Testing

Patients' sera were stored in Pyroclear Pyrotube glucan-free tubes (Associates of Cape Cod Inc., Falmouth, MA, USA) and frozen at −20°C. The Fungitell BDG assay (Associates of Cape Cod Inc.) was performed according to the manufacturer's instructions. We used the positive cutoff ≥80 pg/mL suggested by the manufacturer and tested the cutoff ≥250 pg/mL already assessed in several studies dealing with critically ill patients [16, 25, 26]. Samples with BDG levels >500 pg/mL were diluted and retested. As recommended, each sample was tested in duplicate, taking the mean as the result. When a 20% difference was observed between duplicates, the assay was repeated.

Mannan-Ag and Antimannan-Ab Testing

Patient sera were stored in cryotubes at −80°C. Mannan-Ag and antimannan-Ab were measured with the Platelia Candida Ag Plus and Platelia Candida Ab Plus on an automated EVOLIS system (BioRad, Marnes-la-Coquette, France), as recommended by the manufacturer. We used the cutoff ≥125 ng/mL for positivity and ≥10 AU for mannan-Ag

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and antimannan-Ab, respectively, as indicated by the manufacturer.

All biomarkers were measured blindly by the attending physicians in a centralized laboratory.

Outcomes and Subgroup Analyses

The outcomes considered were death at day 28 and the occurrence of IC before day 28, as defined according to the modified criteria of Tissot et al. [12].

Biomarkers at inclusion were studied in the whole cohort (cohort 1). Biomarkers recorded after inclusion (days 3, 7, 14, and 28) were studied only in patients free of IC and still alive at day 3 (cohort 2).

The serum biomarkers and their threshold values assessed were BDG (>80 and >250 pg/mL), mannan-Ag (>125 pg/mL), antimannan-Ab (>10 AU), and the combination of mannan-Ag and antimannan-Ab. A biomarker was positive if its value was above its threshold value.

Statistical Analysis

The data were expressed as number and percentage for categorical variables and median and interquartile range (IQR) for continuous variables. Comparisons were made with the Fisher exact test for categorical data and Wilcoxon test for continuous data. A P value of <.05 was considered statistically significant.

Death and IC were considered mutually exclusive events. Cause-specific hazard models were built to assess the association between fungal biomarkers and the probability of IC in the ICU or death at day 28. In these models, the occurrence of IC before day 28 was the variable of interest, while death was considered a competing event for IC rather than a censored variable. Discharge alive from the ICU without IC was considered a censored variable. In such models, cause-specific hazards of both events should be interpreted jointly [27].

Because of the low number of events, only univariate analyses could be performed. Several models were performed: in cohort 1, only biomarkers at inclusion were assessed in the model; in cohort 2, model A assessed biomarkers at inclusion and during ICU stay as time-dependent variables; model B assessed biomarkers at inclusion and an increase of >25% (margin of error) of a serum biomarker value compared with the previous measurement. Results were expressed as cause-specific hazard ratios (CS HRs) with their 95% CIs. The missing data for the biomarkers were imputed via linear interpolation. All analyses were performed with SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Characteristics of the Cohort

A total of 234 patients were included, of whom 118 received micafungin (Table 1, Figure 1), and 215 were still alive without IC at day 3. Their median age (IQR) was 64.2 (53.4–73.7) years. They mainly had respiratory (22.6%) or cardiac (25.3%) chronic disease. Their median SAPS II on ICU admission (IQR) was 48 (38–57). The main reasons for admission were medical (75.6%), including acute respiratory failure (39.3%) and septic shock (35%). Cardiac surgery was the main reason for surgery (75.9%). The median duration of ICU stay before inclusion (IQR) was 10 (7–16) days. At inclusion, the median SOFA score (IQR) was 8 (6–11) days; all the patients were mechanically ventilated, 56.8% were treated with vasopressors, and 32.1% were treated with renal replacement therapy (RRT).

Occurrence of IC

In the main cohort (cohort 1, n = 234), 27 (11.5%) patients developed an IC and 68 (29.1%) died before day 28. There were no differences in the IC rate between patients treated with micafungin and patients in the placebo group, 8.5% vs 14.7% (P = .14), nor in 28-day mortality, 30.2% and 28% (P = .71), respectively. IC was diagnosed at inclusion in 11 (4.7%) patients, and during the ICU follow-up after a median duration (IQR) of 14 (11–20) days following inclusion in 16 (6.8%) others. Compared with patients with no IC during ICU stay (n = 207), those with IC (n = 27) had a higher colonization index (P = .05) at inclusion and were more often under parenteral nutrition (P = .05). They had higher median BDG serum values (IQR): 88.7 (39.5–197.2) pg/mL vs 163.1 (95.1–262.6) pg/mL (P = .02), but no difference in 28-day mortality (n = 58 [28%] and n = 10 [37%], respectively; P = .33). Compared with patients with IC at inclusion (n = 11), those with IC during ICU stay (n = 16) were more often in the placebo subgroup (n = 13 [81.3%] vs n = 4 [36.4%], respectively; P = .02) and were less severely ill at ICU admission (SAPS II: median [IQR], 47.5 [35–55.5] and 60 [56–75], respectively; P < .01). All the patients with IC at inclusion had BDG serum values >80 pg/dL (Table 2).

Association Between BDG, Mannan-Ag, Antimannan-Ab, and the Risks of IC and Mortality

The main results are reported in Table 3. In cohort 1 (n = 234), a BDG serum value >80 pg/mL at inclusion was associated with an increased risk of IC (CSHR(IC), 4.67; 95% CI, 1.61–13.5), but not with an increased risk of day 28 mortality (CSHR(death), 1.20; 95% CI, 0.71–2.02). The cumulative risk of IC (IQR) was 19.8% (19.5%–20.0%) in patients with a BDG serum value >80 pg/mL and 5.24% (5.1%–5.37%) in patients with BDG serum values <80 pg/mL (Figure 2). In cohort 2 (n = 215), a BDG serum value at inclusion >80 pg/mL tended to be associated with an increased risk of IC (CSHR(IC), 3.32; 95% CI, 0.9–12.2), but not with an increased risk of day 28 mortality (CSHR(death), 1.34; 95% CI, 0.7–2.57), while BDG serum values >80 pg/mL recorded at any time later (at days 3, 7, 14, and 28) were not associated with an increased risk of IC (CSHR(IC), 0.67; 95% CI, 0.21–2.09) or with an increased risk of day 28 mortality (CSHR(death), 0.92; 95% CI,

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Table 1. Characteristics of the Patients (All) and of the Patients in the Placebo or Micafungin Subgroups

	All	Placebo	Mica	
Patient Characteristics	n = 234	n = 116	n = 118	*P*
Age, y	64.2 [53.4–73.7]	64.6 [55.8–73.6]	63 [52.2–73.7]	.57
Women	80 (34.2)	39 (33.6)	41 (34.7)	.86
Chronic disease categories				
Respiratory	53 (22.6)	20 (17.2)	33 (28)	.05
Cardiac	59 (25.2)	28 (24.1)	31 (26.3)	.71
Hepatic	24 (10.3)	10 (8.6)	14 (11.9)	.41
Renal	19 (8.1)	13 (11.2)	6 (5.1)	.09
Immunosuppression[a]	9 (3.8)	4 (3.4)	5 (4.2)	.75
Diabetes	63 (26.9)	39 (33.6)	24 (20.3)	.02
SAPS II score at admission	48 [38–57]	49 [37–57]	47 [41–58]	.78
Admission category				
Medical	177 (75.6)	89 (76.7)	88 (74.6)	.88
Emergency surgery	52 (22.2)	25 (21.6)	27 (22.9)	.
Scheduled surgery	5 (2.1)	2 (1.7)	3 (2.5)	.
Main surgical procedures				
Abdominal	12 (21)	5 (18.5)	7 (23.3)	.80
Cardiac	44 (75.9)	22 (81.5)	22 (71)	.35
Main reason for ICU admission				
Acute respiratory failure	92 (39.3)	44 (37.9)	48 (40.7)	.67
Septic shock	82 (35)	35 (30.2)	47 (39.8)	.12
Cardiogenic shock	36 (15.4)	21 (18.1)	15 (12.7)	.25
Acute renal failure	24 (10.3)	11 (9.5)	13 (11)	.70
Duration of ICU stay before inclusion	10 [7–16]	11 [7–17]	10 [7–15]	.22
Variables assessed at inclusion				
SOFA score	8 [6–11]	8 [5–11.5]	8 [6–11]	.28
Candida score >2/5	171 (73.1)	81 (69.8)	90 (76.3)	.27
Dialysis or hemofiltration	75 (32.1)	39 (33.6)	36 (30.5)	.61
Adre/noradrenaline	133 (56.8)	64 (55.2)	69 (58.5)	.61
Parenteral nutrition	62 (26.5)	29 (25)	33 (28)	.61
Biomarkers at inclusion				
1–3 B-D-glucan	95.6 [41.9–200.7]	100.8 [42.3–210.2]	95 [41.1–197.2]	.93
1–3 B-D-glucan >80 pg/mL	135 (57.7)	66 (56.9)	69 (58.5)	.81
1–3 B-D-glucan >250 pg/mL	47 (20.1)	25 (21.6)	22 (18.6)	.58
Antimannan-Ab	4.6 [1.4–11.7]	4.3 [1.2–12.4]	5.4 [1.5–11.6]	.72
Antimannan-Ab >10 UA/mL	63 (26.9)	31 (26.7)	32 (27.1)	.95
Mannan-Ag	5 [0–41.4]	4.8 [0–28.9]	5.2 [0–47.1]	.69
Mannan-Ag >125 pg/mL	28 (12)	10 (8.6)	18 (15.3)	.12
Mannan-Ag >125 pg/mL and antimannan-Ab >10 UA/mL	9 (3.8)	2 (1.7)	7 (5.9)	.09
Main outcomes				
IC at inclusion	11 (4.7)	4 (3.4)	7 (5.9)	.37
IC at day 28	27 (11.5)	17 (14.7)	10 (8.5)	.14
Death at day 28	68 (29.1)	35 (30.2)	33 (28)	.71
Death at day 90	104 (44.4)	53 (45.7)	51 (43.2)	.70
Death or IC at day 28	85 (36.3)	47 (40.5)	38 (32.2)	.19

Data are presented as No. (%) or median [interquartile range].

Abbreviations: IC, invasive candidiasis; ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score; SOFA, Sepsis-related Organ Failure Assessment.

[a]Source of immunosuppression not included in the exclusion criteria (mainly AIDS).

0.47–1.8). A BDG serum value >250 pg/mL or an increased value over time, a positive or an increased mannan-Ag, and a positive or an increased antimannan-Ab over time were not predictive for IC or day 28 mortality. All the results from the placebo and micafungin subgroups are given in Supplementary Tables 2 and 3.

The sensitivity, specificity, and accuracy of serum BDG to predict IC were 0.85, 0.46, and 0.5 at a cutoff value of 80 pg/mL and 0.3, 0.81, and 0.75 at a cutoff value of 250 pg/mL, respectively. All the fungal biomarkers at baseline in both cohorts had high negative predictive values to predict IC, ranging

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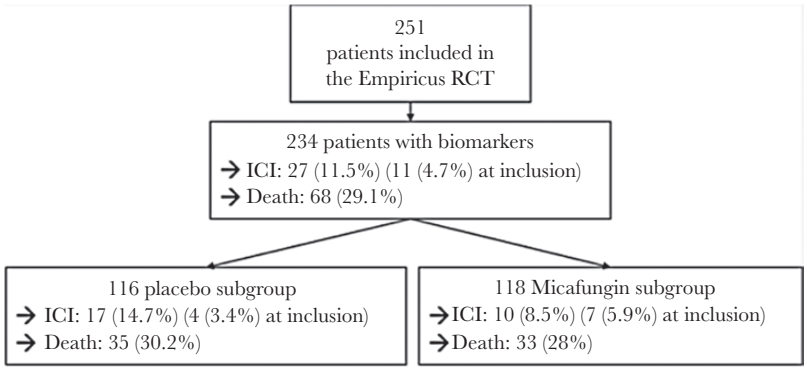

Figure 1. Flowchart. Abbreviations: IC, invasive candidiasis; RCT, randomized controlled trial.

from 0.88 to 0.96 (Supplementary Table 4; Supplementary Figure 1).

DISCUSSION

We show that in a nonimmunocompromised ICU population at very high risk of IC, BDG serum values >80 pg/dL measured on the day when patients fulfilled the criteria for high-risk IC, but had neither serum values >250 pg/mL nor an increase in serum values over time, were associated with the occurrence of IC. Serum values of mannan-Ag, antimannan-Ab, or the combination of mannan-Ag–anti-mannan-Ab measured at any time were not predictive of IC. None of these fungal biomarkers were associated with risk of death.

These results must be interpreted in the light of the current literature.

Most data on the diagnostic performance of serum mannan-Ag and antimannan-Ab to predict the occurrence of IC come from studies in onco-hematology. For instance, Mikulska et al. [22], in a systematic review, reported a sensitivity and specificity of mannan-Ag and antimannan-Ab of 58% and 93% and 59% and 83%, respectively, and a higher performance of the combination of the tests, with a sensitivity of 83% and a specificity of 86%. In our study, performed in a mixed medical surgical ICU population, neither serum mannan-Ag and antimannan-Ab nor their combination was predictive of IC. Our results are in agreement with those of Leon et al. [25], who reported a poorer accuracy of these biomarkers, alone or in combination, than BDG in diagnosing invasive candidiasis in ICU patients with severe abdominal conditions.

The accuracy of serum BDG for predicting IC varies widely across studies. Several of them were performed in onco-hematological patients. Several systematic reviews have been published [18, 28]. For instance, a Cochrane systematic review [29] involving 4316 patients in 36 studies found an overall sensitivity ranging from 27% to 100% and a specificity ranging from 0% to 100%. The high level of heterogeneity across the studies could be explained by the study design, differences in patient populations, the timing and mode of sampling (single or repeated measurements), and the thresholds used for positivity.

Studies on the diagnostic performance of serum BDG in nonimmunocompromised critically ill patients were also achieved [12–14, 25, 30], and their results were heterogeneous. Most were conducted in surgical patients at risk of candidemia or intraabdominal candidiasis and showed a sensitivity and specificity ranging between 51% and 100% and 59% and 98.4%, respectively [13]. They reported different diagnostic cutoffs, between 80 and 350 pg/mL [12, 16, 25, 26, 31, 32]. Positive results of 2 consecutive serum BDG measurements have also been tested, with sensitivity and specificity from 65% to 80% and 75% to 78%, respectively [12, 15, 33]. Combining serum BDG results with results of other serum fungal biomarkers was reported to improve the diagnostic accuracy of serum BDG alone [33]. Also, some of these studies found good negative predictive values and poor positive predictive values for BDG [14, 26, 34]. The results of these studies suggest that focusing on the use of these fungal biomarkers in subgroups of ICU populations at very high risk of developing IC could improve their diagnostic performance. Our study is one of the first studies performed in a nonimmunocompromised ICU population with as many risk factors for IC.

We found that only the measurement of serum BDG with a threshold of 80 pg/mL performed on the day when patients fulfilled all the following criteria for IC, that is, ICU-acquired sepsis, multiple *Candida* colonization, multiple organ failure, and prior exposure to broad-spectrum antibacterial agents, was associated with an increased risk of IC. Subsequent measurements of BDG did not improve the prediction of IC. In addition, we found that only 5.4% of patients with criteria for high risk of IC but with a serum BDG <80 pg/mL developed IC. Of note, we showed that all the fungal biomarkers assessed in the study had good negative predictive values at baseline.

Such results could be explained by our inclusion criteria, namely ICU patients with acquired sepsis, under broad-spectrum antibiotics, with fungal colonization and other risk factors of fungal infections. Consequently, the tests were

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Table 2. Comparison of the Patients With and Without IC During ICU Stay and of the Patients With IC at Inclusion vs Those Developing IC During ICU Stay

	No IC	IC		IC After Admission	IC on Admission	
Patient Characteristics	n = 207	n = 27	*P*	n = 16	n = 11	*P*
Micafungin	108 (52.2)	10 (37)	.14	3 (18.8)	7 (63.6)	.02
Age, y	64.4 [53.3–73.7]	63.8 [54.4–75.7]	.94	58.7 [53.1–66.6]	72.9 [55.5–87.9]	.14
Chronic disease categories						
Respiratory	48 (23.2)	5 (18.5)	.59	5 (31.3)	0 (0)	.04
Cardiac	51 (24.6)	8 (29.6)	.57	4 (25)	4 (36.4)	.53
Hepatic	21 (10.1)	3 (11.1)	.88	2 (12.5)	1 (9.1)	.78
Renal	16 (7.7)	3 (11.1)	.55	2 (12.5)	1 (9.1)	.78
Immunosuppression[a]	9 (4.3)	0 (0)	.27			
Diabetes	53 (25.6)	10 (37)	.21	8 (50)	2 (18.2)	.09
SAPS II	47 [38–57]	55 [37–59]	.18	47.5 [35–55.5]	60 [56–75]	<.01
Admission category						
Medical	159 (76.8)	18 (66.7)	.26	9 (56.3)	9 (81.8)	.17
Emergency surgery	43 (20.8)	9 (33.3)	.	7 (43.8)	2 (18.2)	
Scheduled surgery	5 (2.4)	0 (0)	.			
Main surgical procedures						
Abdominal	8 (16.7)	4 (44.4)	.32	4 (57.2)	0 (0)	.39
Cardiac	39 (79.6)	5 (55.6)	.12	3 (42.9)	2 (100)	.15
Main reason for ICU admission						
Acute respiratory failure	83 (40.1)	9 (33.3)	.50	8 (50)	1 (9.1)	.03
Septic shock	72 (34.8)	10 (37)	.82	5 (31.3)	5 (45.5)	.45
Cardiogenic shock	33 (15.9)	3 (11.1)	.51	0 (0)	3 (27.3)	.03
Acute renal failure	20 (9.7)	4 (14.8)	.41	2 (12.5)	2 (18.2)	.68
Duration of ICU stay before inclusion, d	10 [7–16]	9 [7–17]	.53	10 [7–16.5]	9 [5–17]	.57
Variables assessed at inclusion						
SOFA score	8 [6–11]	9 [7–14]	.14	7.5 [5–12.5]	13 [7–15]	.12
Candida score >2/5	147 (71)	24 (88.9)	.05	14 (87.5)	10 (90.9)	.78
Dialysis or hemofiltration	64 (30.9)	11 (40.7)	.30	6 (37.5)	5 (45.5)	.68
Adre/noradrenaline	118 (57)	15 (55.6)	.89	7 (43.8)	8 (72.7)	.14
Parenteral nutrition	51 (24.6)	11 (40.7)	.07	6 (37.5)	5 (45.5)	.68
Biomarkers at inclusion						
1–3 B-D-glucan	88.7 [39.5–197.2]	163.1 [95.1–262.6]	.02	108.4 [76.9–188.5]	217.3 [135.8–329.1]	.03
1–3 B-D-glucan >80 pg/mL	112 (54.1)	23 (85.2)	<.01	12 (75)	11 (100)	.07
1–3 B-D-glucan >250 pg/mL	39 (18.8)	8 (29.6)	.19	3 (18.8)	5 (45.5)	.45
Antimannan-Ab	4.5 [1.3–11.9]	7 [1.6–10.8]	.40	3.1 [1.6–11.8]	7.4 [3.9–10.1]	.87
Antimannan-Ab >10 UA/mL	55 (26.6)	8 (29.6)	.74	5 (31.3)	3 (27.3)	.82
Mannan-Ag	4.2 [0–38.6]	8.8 [0–93.8]	.10	6.5 [0–30.7]	65.2 [3.8–398]	.19
Mannan-Ag >125 pg/mL	24 (11.6)	4 (14.8)	.63	1 (6.3)	3 (27.3)	.13
Antimannan-Ab >10 UA/mL and mannan-Ag >125 pg/mL	8 (3.9)	1 (3.7)	.97	0 (0)	1 (9.1)	.22
Main outcomes						
IC at inclusion	0 (0)	11 (40.7)	<.01			
IC at day 28		27 (100)	.	16 (100)	11 (100)	
Death at day 28	58 (28)	10 (37)	.33	4 (25)	6 (54.5)	.12
Death at day 90	89 (43)	15 (55.6)	.22	8 (50)	7 (63.6)	.48
Death or IC at day 28	58 (28)	27 (100)	<.01	16 (100)	11 (100)	

Data are presented as No. (%) or median [interquartile range].

Abbreviations: AC, antimannan antibodies; AG, mannan antigen; IC, invasive candidiasis; ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score; SOFA, Sepsis-related Organ Failure Assessment.

[a]Source of immunosuppression not included in the exclusion criteria (mainly AIDS).

performed when the patients were the most at risk of IC, around 10 days after ICU admission, something never done before, as most of the other studies began monitoring BDG immediately after admission. The added values of repeated measurements in previous studies could be explained by the increasing risk of IC over time, which might not have been the case for our patients after their inclusion in the EMPIRICUS trial.

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Table 3. Association of BDG, Mannan-Ag, Antimannan-Ab, and the Occurrence of IC and Death, Cause-Specific Survival Models[a]

Variable	Cause-Specific HR Invasive Candidasis	95% CI IC	*P*	Cause-Specific HR Death	95% CI IC Death	*P*
Cohort 1 (n = 234 patients)[b]						
BDG >80 pg/mL at inclusion	4.67	1.61–13.5	<.01	1.20	0.71–2.02	.49
BDG >250 pg/mL at inclusion	1.65	0.72–3.77	.23	0.92	0.48–1.77	.80
Mannan-Ag >125 pg/mL	1.29	0.44–3.72	.64	0.87	0.37–2.03	.75
Antimannan-Ab >10 UA/mL	1.10	0.48–2.51	.83	0.74	0.4–1.37	.34
Antimannan-Ab >10 UA/mL and mannan-Ag >125 pg/mL	0.99	0.13–7.28	.99	0.96	0.23–3.93	.95
Cohort 2 (n = 215 patients)[b]						
Model A						
BDG >80 pg/mL at inclusion	3.32	0.9–12.24	.07	1.34	0.7–2.57	.37
BDG >80 pg/mL[c]	0.67	0.21–2.09	.49	0.92	0.47–1.8	.81
BDG >250 pg/mL at inclusion	1.46	0.37–5.77	.59	0.90	0.41–1.97	.80
BDG >250 pg/mL[c]	0.27	0.03–2.48	.25	1.18	0.51–2.78	.70
Antimannan-Ab >10 UA/mL at inclusion	3.47	0.75–16.16	.11	0.71	0.31–1.6	.41
Antimannan-Ab >10 UA/mL[c]	0.28	0.05–1.43	.13	0.99	0.46–2.12	.98
Mannan-Ag >125 pg/mL at inclusion	-	-	-	-	-	-
Mannan-Ag >125 pg/mL[c]	-	-	-	-	-	-
Model B						
BDG >80 pg/mL at inclusion	2.66	0.85–8.31	.09	1.35	0.79–2.33	.27
↗ BDG[d]	1.16	0.33–4.13	.82	1.71	0.92–3.2	.09
BDG >250 pg/mL at inclusion	0.90	0.25–3.15	.86	1.01	0.52–1.97	.97
↗ BDG[d]	0.99	0.28–3.5	.99	1.64	0.88–3.05	.12
Antimannan-Ab >10 UA/mL at inclusion	1.16	0.4–3.35	.78	0.71	0.38–1.36	.30
↗ Antimannan-Ab[d]	1.27	0.45–3.57	.65	1.18	0.65–2.15	.59
Mannan-Ag >125 pg/mL at inclusion	0.52	0.07–3.93	.53	0.93	0.4–2.18	.87
↗Mannan-Ag[d]	1.99	0.72–5.49	.18	1.09	0.57–2.09	.80

Model A: The impact of the value of the biomarker at inclusion and of the biomarkers considered time-dependent covariates on the occurrence of IC or death in cohort 2 was tested in the same model. Model B: The impact of the value of the biomarker at inclusion and of an increase of the biomarker over time on the occurrence of IC or death in cohort 2 was tested in the same model.

Abbreviations: BDG, 1–3 β-D-glucan; IC, invasive candidiasis; ICU, intensive care unit.

[a]Cause-specific models with occurrence of invasive candidiasis as the main outcome and death as competing risk. Patients who left the ICU before day 28 or at day 28 were censored. Because of the lack of events, only univariate or bivariate analyses were performed. All the models are independent.

[b]Cohort 1: whole cohort; cohort 2: subgroup, the patients still alive without IC at day 3.

[c]Time-dependent covariates without considering the value at inclusion.

[d]The increase is defined by an increase of at least 25% compared with the previous measurement. This variable is considered a time-dependent covariate.

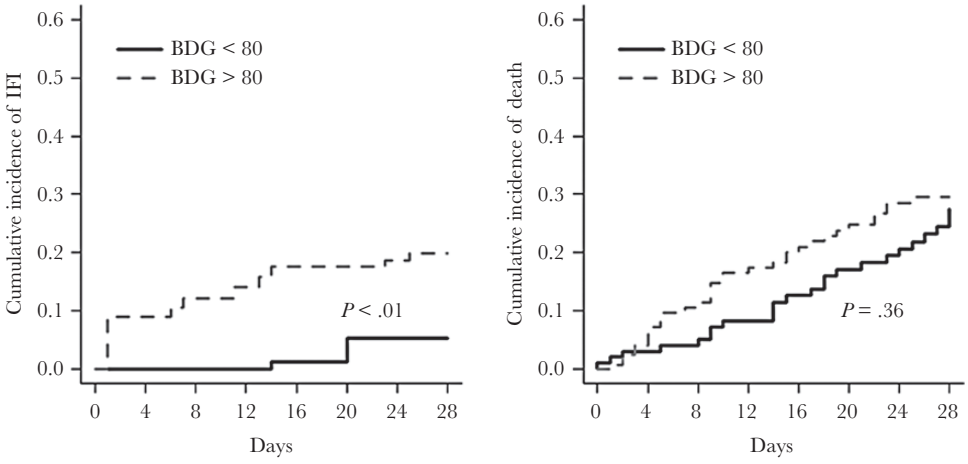

Figure 2. Cumulative incidence of IC and death depending on the levels of BDG (+/- 80 pg/mL) on inclusion. Abbreviations: BDG, serum (1–3)-β-D-glucan; IC, invasive candidiasis.

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The increase in BDG in patients with documented IAI has been associated with a worse outcome in surgical ICU patients with intestinal anastomotic leakage and acute pancreatitis [12]. Our results suggest that serial BDG in a more general population for whom empirical antifungal therapy is indicated is not related to patients' risk of death.

In the light of our results and because of the high negative predictive value of BDG, we believe that serum BDG could be used in combination with our inclusion criteria to avoid or reduce time exposure to empirical antifungal treatment.

Data supporting the role of serum BDG results in halting empirical treatment or in adopting a preemptive strategy to initiate ATF in clinical practice are scarce. In a recent study [35], the positive predictive value of BDG was questionable because most patients with a positive BDG (88%) had no IC. However, in a subgroup of a preselected population at risk of IC, the predictive positive value of the test increased. Two studies involving patients with sepsis and fungal colonization reported that a negative BDG could avoid the initiation of an antifungal treatment without increasing the risk of IFI and death [36, 37].

Continuous efforts are warranted to implement BDG testing algorithms to help guide antifungal drug prescriptions in the ICU. In this context, Rouzé et al. [38] proposed an algorithm based on BDG, mannan-Ag, and antimannan-Ab measured at days 0 and 4 to stop empiric treatment. They reported a reduction in the number of patients and the time on treatment in the interventional arm, thereby showing that, if their rules were applied, empirical AFT could be safely stopped without increasing the risk of subsequent IFI or death while achieving a significant reduction in treatment duration.

Advantage of the Study

The main advantages of our study were the high quality of the data, which were prospectively recorded, and our statistical analysis, which took into consideration competing risk factors.

Limits of the Study

Not all the fungal biomarkers and combinations were assessed in our study, for example, *Candida* species germ tube antibody (CAGTA) and T2C panel [39], and we did not investigate innovative polymerase chain reaction techniques and miniaturized magnetic resonance–based technology [33]. However, these biomarkers have already shown poor performance or require validation in large patient cohorts. Then, the cause of death of our patients was not reported, mostly because the causal relationship between death and IC is very difficult to ascertain, especially in ICU patients, where possible causes of death are numerous. Finally, the main limit of BDG is its turnaround time, which can drastically differ from 1 center to another due to the need to batch the samples in series and hence alter the feasibility of BDG-driven antifungal strategies. The recent development of single-sample assays may fill this gap, as they allow a time-to-result in <2 hours [40, 41].

CONCLUSIONS

Our results confirm the good negative predictive value and good performance of BDG >80 pg/mL in predicting the risk of IC in those critically ill nonimmunocompromised patients at greatest risk of IC.

BDG monitoring could thus be useful in identifying nonimmunocompromised ICU patients at the highest risk of developing an IC and used to rule out the diagnosis of IC in this population. Consequently, BDG monitoring should be used to decide not to start preemptive treatment or to stop empiric treatment. Preemptive strategies based on clinical criteria, fungal colonization indices, and BDG warrant further studies.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Financial support. Astellas provided a research grant to the Grenoble Alpes University Hospital based on the final study protocol. The study was sponsored by the University of Grenoble 1/Albert Michallon University Hospital. The University of Grenoble provided compensation to the participating hospitals and universities for extra costs associated with the study. Dr Timsit reports receipt of lecture fees from Gilead, Pfizer, Merck, Astellas; research grants to his university and research organization from Astellas, Gilead, Merck and Pfizer companies; a consultancy honorarium from Bayer; personal fees from Abbott for scientific board participation; and participation on a scientific committee of epidemiological studies organized by Astellas and Merck companies outside the submitted work. Dr Azoulay reports receipt of personal fees from Gilead, Astellas, and Alexion and grants from Cubist and Alexion during the conduct of the study. Dr Cornet reports receipt of research grants from Pfizer.

Potential conflicts of interest. J.F.T. declares no conflicts of interest related to the submitted work. Outside the submitted work, J.F.T. declares participation in advisory boards for Merck, Pfizer, Gilead, Nabriva, and Paratek; having received lecture fees from Biomerieux, Pfizer, and Merck; and having received research grants to his research unit from Merck, 3M, Astelas, and Thermofisher. 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.

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