ORIGINAL ARTICLE

Evaluating the Role of Serum Beta-D-glucan Testing in Safely Reducing Antifungal Therapy in Critically Ill Patients: A Retrospective Study

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Abstract

Background and aims: The role of (1→3)-β-D-glucan (BDG) testing in guiding antifungal therapy (AFT) in critically ill patients remains unclear. While BDG has a high negative predictive value (NPV), is it safe to withhold AFT in critically ill BDG-negative patients has not been well studied.

Patients and methods: This retrospective cohort study analyzed BDG-negative intensive care unit (ICU) patients (<60 pg/mL) at a tertiary care hospital from March 2024 to January 2025. The ICU survival was compared between those who received AFT and those who did not. Propensity score matching (PSM) adjusted for illness severity, and logistic regression identified independent predictors of survival.

Results: Among 100 BDG-tested patients, 53 (53%) were BDG-negative. Of these, 22 (41.5%) received AFT, while 31 (58.5%) did not. Unadjusted ICU survival was lower in the AFT group (45.5%) vs no AFT (80.6%) ($p = 0.008$). Antifungal therapy recipients had higher sequential organ failure assessment (SOFA) scores (9.7 ± 3.46 vs 7.4 ± 3.15, $p = 0.014$), indicating greater illness severity. Proven invasive candidiasis was rare (3.77%), with both cases due to Candida auris ($p = 0.168$). After PSM, survival differences were no longer significant ($p = 0.246$). Logistic regression confirmed AFT was not an independent predictor of survival [odds ratio (OR): 0.363, $p = 0.156$].

Conclusions: Withholding AFT in BDG-negative critically ill patients did not impact ICU survival, supporting BDG's role in antifungal stewardship. However, its limitations in detecting Candida auris warrant further prospective studies.

Keywords: Antifungal stewardship, Antifungal therapy, Beta-D-glucan, Chart review, ICU survival, Invasive candidiasis retrospective cohort.

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Highlights

No survival difference was observed between those who received and who did not receive antifungal therapy (AFT) in a cohort of (1→3)-β-D-glucan (BDG)-negative critically ill patients. Findings support BDG-guided antifungal stewardship to minimize AFT.

Introduction

The management of invasive candidiasis (IC) in critically ill patients remains a complex challenge, particularly in the context of diagnostic uncertainty. Blood cultures, the gold standard for diagnosis of IC, suffer from poor sensitivity and prolonged turnaround times.[1] The BDG assay has emerged as a valuable adjunctive tool for diagnosing IC, however, its low specificity and high false positivity limit its usefulness in a mixed intensive care population. Studies focusing on AFT based on positive BDG results in this population have reported increased inappropriate antifungal use with no improvement in patient outcomes.[2] Despite these limitations, the negative predictive value (NPV) of BDG remains high in carefully selected ICU patients at high risk of IC, including those colonized with Candida species, those with prolonged antibiotic use, those with abdominal sepsis, or those on immunosuppressants like steroids.[3] Unfortunately, few studies have directly addressed the question: "Can a negative BDG test rule out invasive fungal infection in critically ill patients at risk?" The answer to this question may contribute to antifungal stewardship efforts by identifying patients in whom AFT may not be necessary thus mitigating the growing burden of antifungal resistance.

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This study aimed to evaluate whether AFT could be safely withheld in ICU patients with negative BDG results, providing a real-world perspective in a heterogeneous, mixed ICU population. The primary objective of this study was to compare survival outcomes between BDG-negative (<60 pg/mL) critically ill patients who

received AFT and those who did not receive AFT. The primary endpoint was survival to ICU discharge. Secondary objective was to assess the incidence of proven IC in BDG-negative patients.

Patients and Methods

This was a retrospective cohort study conducted at Amrita Institute of Medical Sciences and Research Centre, Faridabad, a tertiary care teaching hospital in North India. Data were collected from electronic medical records (EMR) (Hospital Information System, HIS). To ensure the appropriateness of chart review for addressing the study objectives, preliminary assessments were conducted to confirm the availability of relevant data in EMR. Data collection was performed by two independent investigators, with cross-checking of 10% of data, to ensure accuracy. Data collection was performed using standardized abstraction forms with clear variable definitions. Institutional review board approval (AIMS-IEC-BAS-01-25-003) was obtained prior to data collection, and a waiver of patient consent was granted.

All adult critically ill patients who underwent serum beta-D-glucan (BDG) testing in the mixed medical-surgical ICU between March 2024 and January 2025 were screened for inclusion. Each BDG test conducted during a single ICU admission for a new sepsis episode was treated as a separate event (data point). If a patient was readmitted after discharge and underwent BDG testing again, it was recorded as a new data point. However, repeat BDG testing during the same ICU admission in patients whose initial BDG was positive—typically performed to assess trends after initiating antifungal treatment—was not included in the analysis. Conversely, if BDG testing was repeated after an initial negative result during the same admission, it was considered a separate event and included as a new data point. Instances where the required data for the study was missing were also excluded. Patients already on antifungals for more than 1 day before BDG testing were also excluded.

Data were collected on patient demographics, severity of illness, including sequential organ failure assessment (SOFA) scores and shock at the time of BDG testing, Candida colonization, presence of abdominal sepsis, and antimicrobial treatments received. Additional variables included risk factors for IC, and Candida species isolated when applicable. Candida colonization was defined as the isolation of Candida species from nonsterile sites such as endotracheal aspirates, urine, wound swabs, or gastrointestinal secretions, excluding rectal swabs present at the time of BDG testing. The Candida score (CS) and the Ostrosky-Zeichner (OZ) clinical prediction rule for IC were calculated for each BDG testing time point. Candida score is based on presence of sepsis, colonization, surgery, or total parenteral nutrition (TPN).[4] A score of ≥3 was considered positive. The OZ clinical prediction rule defines high-risk patients as those on any systemic antibiotic or presence of a central venous catheter and at least two of minor risk factors including TPN, any dialysis, major surgery, pancreatitis, use of steroids, or use of other immunosuppressive agents.[5] Proven IC was defined as Candidemia or isolation of Candida species from normally sterile sites, such as ascitic or pleural fluid.[3] Antifungal therapy constituted systemic administration of any antifungal agent for more than a day with intent to treat rather than prophylaxis. Primary outcome was patient discharged alive from ICU.

Blood and other cultures and BDG assays were ordered at the discretion of the ICU consultant. FungiXpert® BDG assay by Genobio Pharmaceutical Co. Ltd. (Tianjin, China), based on chemiluminescent method, was used to quantitate serum BDG.[6,7] Test results of <60 pg/mL were interpreted as negative results. For the current study, a test result of 60 pg/mL or higher was considered positive. Microbiologically documented infections were defined based on blood cultures and other relevant cultures obtained within the closest timeframe to BDG testing, ensuring they were part of the same sepsis episode. Instances with missing essential data for key study variables were excluded from the analysis to ensure data completeness and validity. No imputation methods were applied.

We represented categorical variables as frequencies and percentages and compared them using Fisher's exact test or the Chi-square (χ^2) test according to their characteristics. Shapiro–Wilk test was performed to verify the normal distribution of continuous variables. Normally distributed variables were expressed as means ± standard deviations (SD) and compared using the independent Student's *t*-test. Whereas variables that were not distributed normally were reported as medians and Inter-quartile range (IQR) and compared using the Mann–Whitney *U*-test.

To adjust for the baseline difference in illness severity between patients who did and did not receive AFT, propensity score matching (PSM) was used. The following variables were utilized in matching: Sequential organ failure assessment (SOFA) score, day of BDG testing with shock, Candida colonization, and abdominal sepsis. KNIME Analytics Platform (Zurich, Switzerland) was used for PSM with a nearest-neighbor matching algorithm.[8]

A multiple logistic regression analysis was conducted in the matched cohort to identify independent predictors of ICU survival, including the use of AFT. The model also included SOFA score, the presence of shock, and Candida colonization as independent variables, identified by an initial univariate analysis. The model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test. A *p*-value less than 0.05 was deemed statistically significant. All statistical analyses were performed using JASP software (JASP Team, Amsterdam, The Netherlands) for univariate and multivariate analyses.[9]

A formal sample size calculation was not performed prior to data collection due to the retrospective nature of this study. Nevertheless, a *post hoc* estimate suggests that approximately 90 BDG-negative patients would have been required to detect a 30% difference in ICU survival between groups (80% power, $\alpha = 0.05$). Given our final sample size of 53 BDG-negative patients, the study may be underpowered to detect smaller survival differences.

The reporting of this study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies.[10] Due to ethical and institutional regulations, the dataset is not publicly available. No funding was received for this study.

Results

Serum BDG testing was performed for 117 times on critically ill patients admitted to ICU during the study period. A total of 17 of these instances were excluded as the patients were on antifungals for more than 1 day (7 instances), BDG was repeated in same ICU admission despite previous positive BDG (4 instances), patient was already diagnosed with confirmed candidiasis (1 instance) or missing essential data (5 instances). Although BDG testing was ordered at the discretion of the treating physician, our selection criteria aimed to include only cases where BDG was performed for a new sepsis episode with suspected IC. Of the remaining 100 BDG-tested patients, 53 (53%) had BDG-negative results (<60 pg/mL) and were included in the primary analysis. The remaining 47 patients

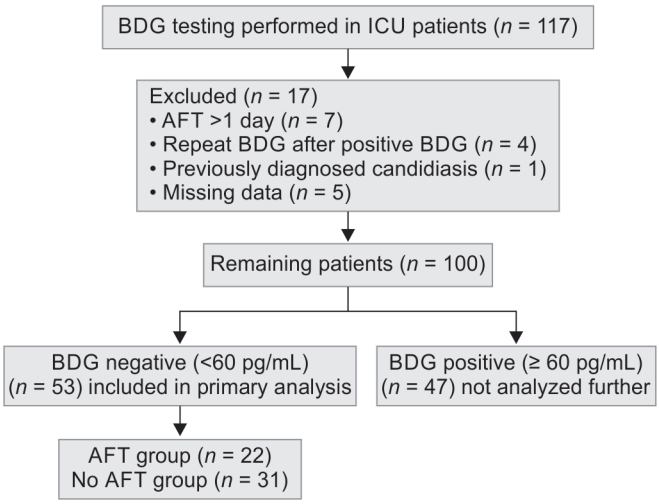

Fig. 1: Flowchart depicting case selection

had BDG-positive results (≥60 pg/mL) and were not analyzed further. Among BDG-negative patients, 22 (41.5%) received AFT, while 31 (58.5%) did not receive AFT (Fig. 1).

The median age of BDG-negative patients was 59 years (IQR: 50–69) and 36 (67%) were male. The study patients were severely ill: Mean SOFA was 8.4 ± 3.45. Shock was present in 37 of 53 patients (69.8%), with similar rates between those who received AFT and those who did not ($p = 0.376$). Out of the 53 patients, 10 (18.8%) had at least one site (other than rectal swabs) colonized with a Candida species. Nine (16.9%) of them had abdominal sepsis, but there were no significant differences between the groups ($p = 0.724$ and $p = 1.000$, respectively). Patients were receiving antibiotics for a median of 8 days (IQR: 1–14) before candidiasis was suspected, and BDG testing performed. The median candida score was 2 (IQR: 1–3). Candida score and OZ clinical prediction rule were positive in 17 (32.0%) and 11 (27%) of patients, respectively (Table 1). Among the 22 BDG-negative patients who received AFT, 15 (68.2%) received azoles, 6 (27.3%) received echinocandins, and 1 (4.5%) received amphotericin B.

The ICU survival was significantly lower in the AFT group (45.5%) compared to the no AFT group (80.6%, $p = 0.008$) (Table 2). Patients in the AFT group had significantly higher SOFA scores compared to those who did not receive antifungals (9.7 ± 3.46 vs 7.4 ± 3.15, $p = 0.014$), suggesting greater illness severity among those who were treated. Proven IC was rare ($n = 2$, 3.77%), and both cases (100%) were Candida auris infections in patients who received AFT ($p = 0.168$). Microbiologically proven infections other than candidiasis were diagnosed in 12 (54.5%) episodes in the AFT group and 14 (45.1%) episodes in the no AFT group, with no significant difference between the groups ($p = 0.501$).

Given the significant baseline differences between patients who received AFT and those who did not, PSM was performed to adjust for confounding factors. Patients were matched based on SOFA score, presence of shock on the day of BDG testing, Candida colonization, and abdominal sepsis status as these factors might have influenced the treating physician's decision to start AFT. This resulted in 31 matched pairs ($n = 62$) of those who received AFT and those who did not. After PSM, ICU survival rates in the matched groups (AFT and no AFT) were no longer significantly different. Ten (32.3%) survived in AFT group and 11 (35.5%) survived in no AFT group ($p = 0.246$, Table 2). This suggests that the initial survival difference was likely due to illness severity rather than antifungal use.

A multiple logistic regression analysis was performed in the matched cohort with survival at ICU discharge as dependent variable and AFT use, SOFA score, presence of shock, and Candida colonization as independent variables. The regression model demonstrated moderate explanatory power (Nagelkerke $R^2 = 0.326$). Antifungal therapy use was not significantly associated with survival [odds ratio (OR: 0.363, $p = 0.156$), suggesting that AFT did not independently influence mortality. Shock was the strongest predictor of mortality, with an OR of 0.195 ($p = 0.097$) for ICU survival, indicating that patients with shock had a higher likelihood of dying, though this result did not reach statistical significance. Higher SOFA scores were associated with lower survival (OR: 0.810, $p = 0.108$), with a trend toward significance. Candida colonization did not significantly affect survival (OR: 1.217, $p = 0.882$) (Table 3).

Discussion

Our study revealed several important insights. First, among BDG-negative patients, those who received empiric AFT had significantly higher illness severity, as evidenced by higher SOFA scores and lower ICU survival rates compared to those who did not receive AFT. However, after PSM, the survival differences disappeared, indicating that the observed mortality disparity was probably caused by illness severity rather than the use of antifungals. Logistic regression analysis further confirmed that AFT use was not an independent predictor of survival, while shock and higher SOFA score showed trends toward predicting worse outcomes. These findings suggest that withholding AFT in BDG-negative patients does not negatively impact survival. Our sample included mixed surgical and medical patients including those with liver failure, renal failure (some on renal replacement therapy), patients suffering from solid/hematological cancers and patients on immunosuppressants for various reasons. This case mix reflects real world ICU population enhancing the generalizability of our findings to routine ICU practice, particularly in resource-limited settings. Our selection criteria were designed to include only instances where BDG testing was performed for a new sepsis episode with suspected IC. Most of the cohort was moderately to severely ill, with nearly three-quarters experiencing shock at the time of BDG testing. Most had one or more risk factors for IC including prolonged antibiotic use or Candida colonization. Of note, in our cohort, two (3.7%) patients were subsequently diagnosed with confirmed IC despite negative BDG. Candida auris was isolated in both these cases. This aligns with previous reports of low sensitivity of BDG testing in Candida auris infections.[11] The findings indicate that BDG testing should be employed with caution to exclude candidiasis in units with a high incidence of Candida auris.[12]

Several previous studies have suggested that a protocolized use of BDG testing can reduce the duration of AFT and thus positively impacts antifungal stewardship.[13] The randomized clinical trial (RCT): Empirical Antifungal Treatment in ICUS (EMPIRICUS) provided a subgroup analysis based on BDG levels which suggests that empirical micafungin treatment, compared to placebo, did not significantly improve invasive fungal infection-free survival at day 28 in patients with lower BDG levels (≤80 pg/mL).[14] An Indian study describing patients with candidemia, however, suggested that 15.6% of patients had a negative BDG value despite having proven IC.[15] To our knowledge, no study has specifically examined

Table 1: Baseline characteristics and proven microbiological infection in BDG-negative patients

Parameter	*All patients (n = 53)*	*AFT group (n = 22)*	*No AFT group (n = 31)*	*p-value*
Age (years), median (IQR)	59 (50–69)	61 (54–67)	58 (49–69)	0.545[d]
Sex				0.528[a]
Male, *n* (%)	36 (67.9%)	16 (72.7%)	20 (64.5%)	
Female, *n* (%)	17 (32.0%)	6 (27.2%)	11 (35.4%)	
SOFA score, mean ± SD	8.4 ± 3.45	9.7 ± 3.46	7.4 ± 3.15	0.014[c]*
Days on antibiotics, median (IQR)	8 (1–14)	6 (0–9)	10 (2–14)	0.097[d]
Shock				0.376[b]
Present, *n* (%)	37 (69.8%)	17 (77.2%)	20 (64.5%)	
Absent, *n* (%)	16 (30.1%)	5 (22.7%)	11 (35.5%)	
Candida colonization				0.724[b]
Present, *n* (%)	10 (18.8%)	5 (22.7%)	5 (16.1%)	
Absent, *n* (%)	43 (81.1%)	17 (77.2%)	26 (83.9%)	
Candida score, median (IQR)	2 (2–3)	2 (2–3)	2 (2–3)	
Candida score (CS)				0.573[a]
Positive (≥3), *n* (%)	17 (32.0%)	8 (36.3%)	9 (29.0%)	
Negative, *n* (%)	36 (67.9%)	14 (63.6%)	22 (71.0%)	
OZ clinical prediction rule:				1.000[b]
Positive, *n* (%)	11 (27%)	5 (22.7%)	6 (19.3%)	
Negative, *n* (%)	42 (79.2%)	17 (77.2%)	15 (48.3%)	
Abdominal sepsis				1.000[b]
Yes, *n* (%)	9 (16.9%)	4 (18.1%)	5 (16.1%)	
No, *n* (%)	44 (83.0%)	18 (81.8%)	26 (83.8%)	
Microbiologically documented infection				0.501[a]
Absent, *n* (%)	27 (50.9%)	10 (45.5%)	17 (54.8%)	
Present, *n* (%)	26 (49.0%)	12 (54.5%)	14 (45.1%)	
Proven invasive candidiasis, *n* (%)	2 (3.77%)	2 (9.0%)	0 (0%)	0.168[b]

[a]Chi-square test; [b]Fisher's exact test; [c]*t*-test; [d]Mann–Whitney *U* test; *($p < 0.05$)

Table 2: ICU survival before and after propensity score matching

Outcome	*Before PSM (all patients, n = 53)*	*AFT group (n = 22)*	*No AFT group (n = 31)*	*p-value*	*After PSM (matched patients, n = 62)*	*AFT group (n = 31)*	*No AFT group (n = 31)*	*p-value*
ICU survival, *n* (%)	35 (66.0%)	10 (45.5%)	25 (80.6%)	0.008[a]	21 (33.9%)	10 (32.3%)	11 (35.5%)	0.246[a]

[a]Chi-square test

Table 3: Multiple logistic regression analysis for ICU survival after matching

Variable	*Estimate*	*Standard error*	*Odds ratio*	*95% CI (lower - upper)*	*Wald statistic*	*p-value*
AFT (received)	–1.013	0.714	0.363	0.085–1.467	2.016	0.156
Candida colonization	0.196	1.327	1.217	0.090–2.796	0.022	0.882
SOFA score	–0.211	0.131	0.810	0.627–1.048	2.588	0.108
Shock (present)	–1.634	0.986	0.195	0.028–1.350	2.747	0.097

the impact of withholding AFT in critically ill patients with negative BDG results. Conducting a prospective randomized trial to answer this question would pose ethical challenges, as withholding AFT from critically ill patients suspected of IC carries potential risks. A retrospective cohort study conducted on EMR datasets such as ours provides a pragmatic approach to assessing the real-world impact of BDG-guided decision-making. The use of PSM and multivariate logistic regression strengthens the validity of our conclusions, addressing potential confounding factors and isolating the effect of AFT on outcomes. Beyond its clinical impact, BDG-guided AFT can reduce unnecessary AFT use, lowering costs in resource-constrained ICUs, particularly in middle-income countries.

There are potential limitations to our study. Its retrospective design introduces potential biases, including selection bias and unmeasured confounders, despite the use of propensity score matching to minimize these effects. The small sample size, particularly in the matched cohort, may have reduced statistical power. This might have led to limiting the ability to detect significant effects. For instance, our research suggested decreased odds of survival with AFT (though not statistically significant), even after PSM, likely due to residual confounding. Additionally, our findings, while relevant to critically ill patients in a mixed ICU, may not be generalizable to noncritically ill or specialized populations like transplant patients. Last, the study focuses on ICU survival, without assessing long-term outcomes such as post-ICU-discharge mortality or recurrent fungal infections.

Conclusion

Our study suggests that withholding AFT in BDG-negative-critically ill patients does not negatively impact ICU survival, reinforcing the role of BDG as a stewardship tool to minimize unnecessary antifungal use, given the limitations of our study and the detection failures in certain Candida species, this approach requires further validation in larger, prospective studies before being widely adopted in clinical practice.

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