ORIGINAL ARTICLE

The (1,3)-β-D-glucan use for invasive candidiasis diagnosis in non-neutropenic critically ill patients: A prospective cohort study

Le (1,3)-β-D-glucane pour le diagnostic de la candidose invasive chez les patients non neutropéniques en réanimation: Etude de cohorte prospective

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Abstract

Introduction: Invasive candidiasis (IC) is a widespread infection in intensive care. As culture-based diagnostic techniques take several days before positivity and leaks of sensitivity. (1,3)-β-D-glucan (BDG) was proposed as a mycological criterion for IC diagnosis in selected patients.
Aim: To determine the performance of BDG assay in the early diagnosis of IC in non-neutropenic critically ill patients
Methods: We conducted a prospective evaluative study. All adults who were hospitalized in La Rabta Tertiary Hospital intensive care unit from January to June 2023 and at risk of IC were screened on a weekly basis. A true positive status corresponded to confirmed or highly probable IC and a positive BDG test (>80 pg/mL).
Results: A total of 123 BDG tests were performed on 85 patients with a median age of 58 years [41.5-67.5] and a median SOFA score=3 [2-5.5]. The median colonization index was 0.16 [0-0.33], and Candida albicans was the most common species isolated (71%). The median Candida score was 0.9 [0-2.9]. IC was retained in 30 cases. The median BDG level was 98 pg/mL [24-275]. Sixty-one patients had a positive BDG test, in whom only 21 had an IC. The performance of the BDG test in the diagnosis of IC was moderate (AUC/ROC=0.68 [0.575-0.788], p=0.003). The discriminatory power was better with the negative prediction (PNV=85.5%).
Conclusion: The major benefit of BDG test in intensive care seems to lie in its NPV allowing to roll out the invasive candidiasis diagnosis then withhold or interrupt antifungal therapy.

Key words: Beta-Glucans, Invasive Candidiasis, Intensive Care, Diagnosis, Performance.

Résumé

Introduction: La candidose invasive (CI) est une infection répandue en soins intensifs. Les techniques de diagnostic basées sur la culture mettent plusieurs jours avant la positivité et manque de sensibilité. Le (1,3)-β-D-glucane (BDG) a été proposé comme critère diagnostic de la CI chez des patients sélectionnés.
Objectif: Étudier les performances diagnostiques du BDG chez les patients non neutropéniques en réanimation.
Méthodes: Nous avons mené une étude prospective évaluative. Les adultes hospitalisés au service de réanimation l'hôpital La Rabta de janvier à juin 2023, à risque de CI, ont eu un dépistage hebdomadaire. Un vrai positif correspondait à une CI confirmée ou fort probable avec un test BDG positif (>80 pg/mL).
Résultats: Au total, 123 tests BDG étaient réalisés chez 85 patients. L'âge médian était 58 ans [41,5-67,5] et le score SOFA médian 3 [2-5,5]. L'index de colonisation médian était 0,16 [0-0,33], et Candida albicans était l'espèce la plus isolée (71%). Le Candida score médian était 0,9 [0-2,9]. La CI a été retenue dans 30 cas. Le taux du BDG était de 98 pg/ml [24-275]. Soixante et un patients avaient un test BDG positif, parmi lesquels le diagnostic de CI a été retenu chez seulement 21 patients. Les performances du test BDG dans le diagnostic de l'IC étaient modérées (AUC/ROC=0,68 [0,575-0,788], p=0,003). Néanmoins, la prédiction négative était bonne de l'ordre de 85.5%.
Conclusion: L'intérêt du BDG en réanimation réside dans sa valeur prédictive négative permettant d'éliminer une candidose invasive et de s'abstenir voire interrompre le traitement antifongique.

Mots clés: Bêta-Glucanes, Candidose invasive, Soins intensifs, Diagnostic, Performance.

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Introduction

The incidence of invasive candidiasis (IC) has increased over the past decade (1). Even in the absence of traditional hematological risk factors, critically ill patients undergo various invasive organ supply procedures, making them particularly vulnerable to invasive fungal infections (IFIs) (2).
An accurate and timely diagnosis associated to appropriate antifungal therapy is crucial to the vital prognosis. The diagnostic methods used for reference are based on microscopic inspection and culture. However, the latter lose sensitivity and take several days before being positive (3). Consequently, antifungal treatment is often prescribed in an empirical or probabilistic manner, causing the emergence of multidrug-resistant strains (4).
(1,3)-β-D-glucan (BDG) is a polysaccharide, a major and specific component of the cell wall of most fungi except Mucorales and some basidiomycetous yeasts, such as Cryptococcus spp., which can be detected in the patient's serum in cases of invasive fungemia (5).
This serum marker figures among the European Organization for Research and Treatment of Cancer/ Mycoses Study Group (EORTC/MSG) adopted criteria for the diagnosis of probable invasive fungal infection (6).
Its performance has been assessed in several studies among high-risk hematologic cancer patients (7). Clinical data on the effectiveness of this technique and its contribution to the diagnosis and optimization of antifungal prescriptions in heterogeneous nonneutropenic critically ill adult patients are lacking, and its diagnostic accuracy still needs to be proven (8). Hence, we report our experience aiming to determine the performance of BDG assay in the early diagnosis of IC in non-neutropenic critically ill patients.

Methods

Study design and patients

This prospective observational study was conducted from January 1, 2024, to June 30, 2024, in the Department of Intensive Care Medicine, La Rabta Tertiary Hospital, Tunisia.
In addition to routine diagnostic procedures, all adult patients with at least one risk factor were screened for invasive candidiasis once a week (every Wednesday) using a (1,3)-β-D-glucan (BDG) test and a colonization index (CI). In septic patients, blood cultures were also taken for fungal examination.
Patients for whom the dosage was not available due to sampling errors or technical problems were excluded from the statistical analysis.

Definitions

Cases of IC were identified as positive blood cultures or cultures from a specimen obtained by a sterile procedure growing Candida spp. or in cases of sepsis (9) with a significant Candida score > 3 and no bacterial infection.

Microbiological analysis

Patient serum samples were tested for BDG using the Food and Drug Administration (FDA)-approved Fungitell assay (Associates of Cape Cod, Falmouth, MA, USA) according to the protocol supplied by the manufacturer. BDG values were interpreted as follows: positive if > 80 pg/ml, undetermined between 60 and 79 pg/ml and negative if the dosage was less than 60 pg/ml. Blood culture bottles (BD Bactec Mycosis) were inoculated with a venous whole blood sample and incubated according to the manufacturer's recommendations.
Sampling techniques for the analysis of Candida spp. colonization were standardized, and swabs were obtained from six distinct body sites (oral, nasal, ear, rectum, axillary skin, and urine samples).
All the samples were processed by specialized medical parasitologists in the Parasitology/Mycology Laboratory of our hospital.

Data collection

Demographic, clinical, and microbiologic data were prospectively collected. Risk factors for IC were assessed, including age, sex, past medical history, surgery, immunosuppression status, and severity of clinical presentation according to the clinical severity score (Sepsis-related Organ Failure Assessment, Simplified Acute Physiology Score, Acute Physiology and Chronic Health Evaluation). The details of the different invasive procedures including central venous catheter (CVC) placement, invasive ventilation days, renal replacement therapy, the use of broad-spectrum antibiotics, total parenteral nutrition, and the length of ICU stay.
The CI was calculated as the ratio of colonized body sites to the total number of cultured body sites. Candida score components (assigned points) were severe sepsis (2 points), total parenteral nutrition (1 point), abdominal surgery (1 point), and multifocal Candida colonization or CI > 0.5 (1 point) according to the protocol proposed by Leon et al. (10).

Statistical analysis

The data were analyzed using the SPSS Base 20 statistical software package. Quantitative data were expressed as the mean ± standard deviation (SD) or median [IQR 25-75] depending on whether the variables were normal or not. The qualitative variables were expressed as percentages. The performance of the BDG test was evaluated using receiver operating characteristic (ROC) curves and contingency tables to calculate the specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV). A true positive status corresponded to a patient in whom the diagnosis of IC was retained and a positive BDG test. A p value less than 0.05 was considered to indicate statistical significance.

Results

Flow patients and clinical characteristics

During the study period, 123 tests were performed in 85 critically ill patients at high risk of invasive candidiasis, as shown in Figure 1.

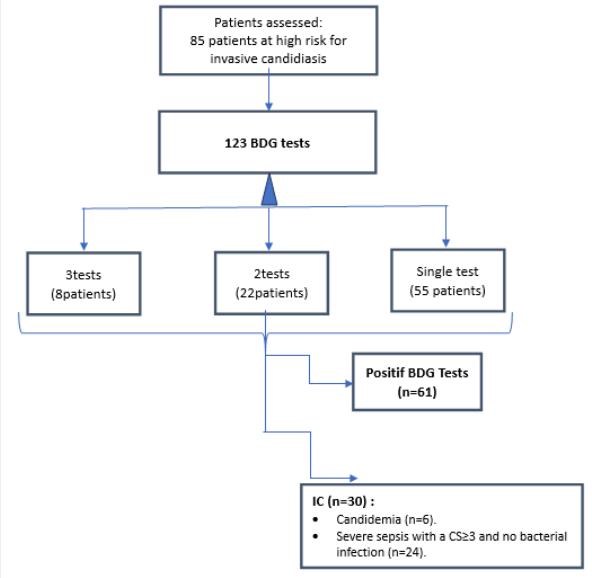

Figure 1. Study flow chart

BDG:(1,3)-β-D-glucan; **CS**: Candida score; **IC**: invasive candidiasis.

The 85 included patients had a median age of 58 years [41.5-67.5] and were predominantly male (57/28 with sex ratio=2.03). All patients were admitted to the medical ward for respiratory or neurological reasons before admission to the ICU (34% and 28%, respectively); and four patients had a postabdominal surgical status. Invasive candidiasis was diagnosed in two cases (isolation of *candida* in blood cultures (n=6) and very likely IC in front of a severe sepsis, a *Candida* score ≥ 3 without documented bacterial infection (n=24)). The clinical features of the patients are shown in Table 1.

Fungal data

During the study period, 123 CIs and 32 fungal blood cultures were collected from 85 patients. *Candida albicans* was the most isolated *Candida* species, with 92 swabs and all 6 cases of candidaemia. All fungal data are shown in Table 2.

Performance of the BDG

Upon initial testing, the mean BDG value was 98 pg/mL [24-275]. Sixty-one of the 123 BDG tests were positive. Invasive candidiasis was diagnosed in 21 of them (true positive). In the other 62 cases, invasive candidiasis was ruled out in 53 (true negative). Applying the study cutoff, the BGD test showed a sensitivity of 70% and a specificity of 57%. The positive predictive value (PPV) was 34.4%, and the negative predictive value (NPV) was 85.5%. The receiver operating characteristic (ROC) curve illustrating the diagnostic accuracy of BDG for invasive candidiasis in critically ill patients is included in Figure 2.

Table 1. Clinical characteristics and invasive candidiasis risk factors.

Characteristic	
Age [Years],median [IQR]	58 [41.5-67.5]
Sex, male,no of patients (%)	57 (67)
Comorbidities, no of patients (%)	
• Arterial hypertension	26 (31)
• Diabetes millets	34 (40)
• Chronic respiratory failure	13 (15)
• Chronic kidney disease	3 (4)
• Immune deficiency	3 (4)
• Solid Tumor	6 (7)
Gravity score, median [IQR]	
• SAPS II	27 [19-43]
• APACHE	12 [7-20]
• SOFA	3 [2-5.5]
Duration of ICU stay, median [IQR]	9 [5-15]
Invasive candidiasis risk factors, no of study cases (%):	
• Central venous catheter	89 (72)
• Parenteral nutrition	68 (55)
• Invasive ventilation	62 (50)
• Board spectrum antibiotics	56 (46)
• Sepsis	49 (40)
• Post operative context	13 (11)
• Hemodialysis	7 (6)

APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II; **SAPS II**: Simplified Acute Physiology Score; **SOFA**: Sepsis Related Organ Failure Assessment.

Table 2. Fungal data.

Characteristic	
Positive colonization index, number of study cases (%)	69/123 (56)
• One site, n (%)	36/69 (52)
• Two sites, n (%)	14/69 (20)
• Three sites, n (%)	12/69 (17)
• Four sites, n (%)	6/69 (9)
• Five sites, n (%)	1/69 (1)
Colonized sites, number of study cases (%)	129/738 (17.5)
• Oral cavity swab, n (%)	60/129 (46)
• Urine culture, n (%)	20/129 (16)
• Axilla skin surface, n (%)	15/129 (12)
• Nasal swab, n (%)	14/129 (11)
• Rectal swab, n (%)	12/129 (9)
• Ear swab, n (%)	8/129 (6)
Candida isolated species, number of study cases (%)	129/738 (17.5)
• C. albicans, n (%)	92/129 (71)
• C. glabrata, n (%)	18/129 (14)
• C. tropicalis, n (%)	15/129 (12)
• C. krusei, n (%)	4/129 (3)
Candidemia, number of study cases (%)	6/32 (19)
Colonization index, median [IQR]	0.16[0-0.33]
Candida score, median [IQR]	0,9 [0-2.9]
Candida score ≥3, number of study cases (%)	24/123 (19.5)

Discussion

The (1,3)-β-D-glucan test has been proposed as a new alternative that offers a rapid and reliable diagnosis of invasive fungal infections compared to the gold standard of culture-based techniques. This hypothesis was not fulfilled in our study. Nevertheless, it had a satisfactory NPV.

We prospectively analyzed 123 BDG tests in a cohort of 85 non neutropenic, critically ill adult patients with various high-risk factors for invasive candidiasis (2) using the

Fungitell Assey (Associates of Cape Cod, Falmouth, MA, USA) according to the protocol and cutoff values provided by the manufacturer. This approach was justified by the aim of the study: to evaluate the diagnostic accuracy of the test and by the limited number of patients with serial screening (30 patients).

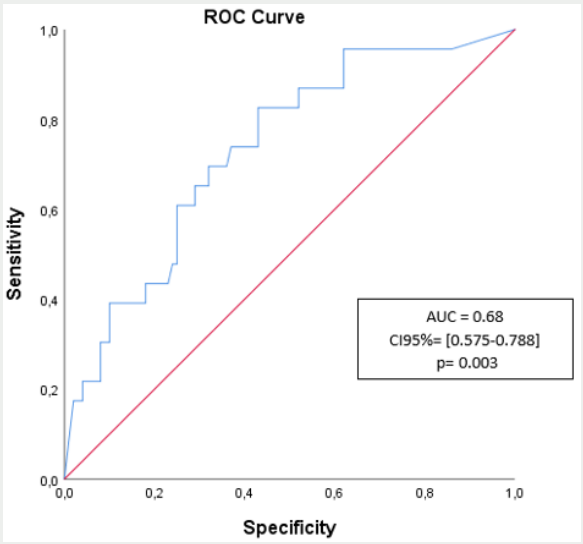

Figure 2. Performance of the BDG in invasive candidiasis diagnosis.
AUC: area under the curve; **BDG**: (1,3)-β-D-glucan; **CI**: confidence interval; **NPP**: negative predictive value; **PPV**: positive predictive value.

The BDG test leaked specificity and showed a low positive predictive value of 34.4%. The same findings have been reported in other studies and meta-analyses, leading to uncertainties regarding its diagnostic accuracy (5). Haydour et al. analyzed 10 studies, eight of which used the Fungitell kit with a cutoff value of 80 pg/ml, and showed that the BDG assay has a sensitivity of 0.81 (95% CI, 0.74–0.86) and a specificity of 0.60 (95% CI, 0.49–0.71) in ICU patients at risk of IC or candidaemia (11).
Several confounding factors responsible for false-positive results have been reported, including Candida colonization and the use of multiple common antimicrobials, two of the most commonly reported risk factors for invasive candidiasis infections in our study (12,13). While the EORTC/MSG has proposed BDG testing as a mycological criterion in conjunction with at least one host factor and clinical criterion for the diagnosis of probable invasive fungal infection since 2008 (6), the FUNDIC study panel experts concluded that, based on current evidence, serum BDG positivity may not achieve sufficient specificity as a mycological criterion to define probable deep-seated candidiasis (8). Serial testing and higher cutoff values have been proposed to optimize the diagnostic value of the BDG test. But large meta-analyses are lacking, probably due to the heterogeneity of the population studied (14,15).
In our analysis, we reported a negative predictive value of 85.5%. In non neutropenic as well as immunocompromised critically ill adult patients, the (1,3)-β-D-glucan test appears to be more suitable for its excellent negative predictive value of more than 90% in several studies allowing withholding or interrupting antifungal therapy decisions among ICU patients at risk for IC when interpreted in conjunction with other microbiological results and clinical signs/severity of infection (5,16,17).
Our study has several limitations. First, the small cohort population and the limited number of patients with proven invasive candidiasis, second, the single test analysis according to the manufacturer's instructions without consideration of kinetics and different cutoff values. However, we consider that we have evaluated the performance of the test independently of other confounding parameters.

Conclusion

BDG testing with the recommended cutoff values has limited value for the diagnosis of invasive candidiasis infection in nonneutropenic critically ill patients at high risk due to its low specificity and positive predictive value. It can be used as a guide for withholding or discontinuing antifungal treatment in defined patient groups due to its excellent negative predictive value.

List of abbreviations:
IC: Invasive candidiasis
BDG: (1,3)-β-D-glucan
IFIs: Invasive fungal infections
CI: Colonization index
CS: Candida score
ICU: Intensive care unit
EORTC/MSG: European Organization for Research and Treatment of Cancer/Mycoses Study Group)
SOFA: Sepsis-related Organ Failure Assessment
SAPS: Simplified Acute Physiology Score
APACHE: Acute Physiology and Chronic Health Evaluation
CVC: Central venous catheter
ROC: Receiver operating characteristic
AUC: area under the curve
PPV: Positive predictive value
NPV: Negative predictive value
CI: confidence interval

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