CRITICAL CARE

COMMENTARY

Is (1→3)-β-D-glucan the missing link from bedside assessment to pre-emptive therapy of invasive candidiasis?

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See related research by Posteraro *et al.*, http://ccforum.com/content/15/5/R249

Abstract

Invasive candidiasis is a frequent life-threatening complication in critically ill patients. Early diagnosis followed by prompt treatment aimed at improving outcome by minimizing unnecessary antifungal use remains a major challenge in the ICU setting. Timely patient selection thus plays a key role for clinically efficient and cost-effective management. Approaches combining clinical risk factors and *Candida* colonization data have improved our ability to identify such patients early. While the negative predictive value of scores and predicting rules is up to 95 to 99%, the positive predictive value is much lower, ranging between 10 and 60%. Accordingly, if a positive score or rule is used to guide the start of antifungal therapy, many patients may be treated unnecessarily. *Candida* biomarkers display higher positive predictive values; however, they lack sensitivity and are thus not able to identify all cases of invasive candidiasis. The (1→3)-β-D-glucan (BG) assay, a panfungal antigen test, is recommended as a complementary tool for the diagnosis of invasive mycoses in high-risk hemato-oncological patients. Its role in the more heterogeneous ICU population remains to be defined. More efficient clinical selection strategies combined with performant laboratory tools are needed in order to treat the right patients at the right time by keeping costs of screening and therapy as low as possible. The new approach proposed by Posteraro and colleagues in the previous issue of *Critical Care* meets these requirements. A single positive BG value in medical patients admitted to the ICU with sepsis and expected to stay for more than 5 days preceded the documentation of candidemia by 1 to 3 days with an unprecedented diagnostic accuracy. Applying this one-point fungal screening on a selected subset of ICU patients with an estimated 15 to 20% risk of developing candidemia is an appealing and potentially cost-effective approach. If confirmed by multicenter investigations, and extended to surgical patients at high risk of invasive candidiasis after abdominal surgery, this Bayesian-based risk stratification approach aimed at maximizing clinical efficiency by minimizing health care resource utilization may substantially simplify the management of critically ill patients at risk of invasive candidiasis.

Clinical and epidemiological investigations over the past 25 years have significantly expanded our knowledge on invasive candidiasis in critically ill patients [1-4]. Prolonged exposure to multiple risk factors progressively increases the risk of developing invasive candidiasis from less than 5% to more than 15%. While early antifungal treatment has been suggested to improve clinical outcome of this life-threatening complication, timely prospective identification of patients who need pre-emptive therapy aimed at minimizing both mortality and unnecessary prophylactic or empirical use of antifungals remains a major challenge for ICU physicians [5].

In contrast to positive *Aspergillus* cultures, which are highly predictive of invasive aspergillosis in profoundly immunocompromised patients, only a minority of critically ill patients with documented *Candida* colonization will develop invasive infections [1-4]. Multiple approaches, including *Candida* colonization index [2], *Candida* scores and clinical prediction rules based on a combination of risk factors and colonization data [6,7], as well as molecular [8] and antigen/antibody blood assays, have been proposed for the early identification of ICU patients who are developing invasive candidiasis.

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Colonization and clinical risk assessments are highly sensitive; however, their specificity is poor and positive predictive values ranging from 10 to 60% would imply that most patients with positive results would be treated in the absence of candidiasis. This would unnecessarily expose them to drug side effects, select resistant *Candida* species and result in substantial health care resource utilization due to the high costs of antifungal agents [9]. Whereas biomarkers are more specific, they would miss a high number of infections due to limited sensitivity [10,11]. Negative predictive values of up to 95 to 99% obtained with these clinical and laboratory tools in unselected groups of ICU patients at low risk of invasive candidiasis (less than 5%) do not thus allow efficient identification of those who do not need antifungal therapy. Accordingly, none of these scores, rules or biomarkers is currently used for clinical decision-making at the bedside [5]. More efficient clinical selection strategies combined with laboratory tools are thus needed in order to treat the right patients at the right time while keeping costs of screening and therapy as low as possible.

β-D-glucan (BG) is a panfungal cell wall component circulating in blood during invasive fungal infection. In recent meta-analyses its detection has been associated with variable diagnostic sensitivity and specificity, ranging between 50 and 85% and 80 and 99%, respectively [12]. Based on its accuracy, experts recommend using BG for diagnosis to early detect invasive mycoses, both in clinical research and daily management in high-risk hemato-oncological patients [13]. Moreover, when compared with clinical, radiological and culture-based assessment, a study in acute leukemic patients has suggested that BG may anticipate diagnosis of invasive mycoses [10]. Due to a lack of clinical data, experts agree that its diagnostic role in the more heterogeneous ICU patient population remains to be defined.

In this context, the study by Posteraro and colleagues [14] is an important step forward on the way to early identification of critically ill patients with invasive candidiasis. The diagnostic performance of BG antigenemia measured by the Fungitell® assay in medical ICU patients with sepsis was compared with that of Leon's *Candida* score and Pittet's colonization index. During a 6-month period, 377 out of 450 (83.7%) consecutive ICU patients presented signs of sepsis and 95 of them (25%) were enrolled based on a length of ICU stay exceeding 5 days and the absence of documented invasive fungal infection at time of screening and of any systemic antifungal treatment. Out of the 95 included patients, 16 (16.8%) developed an invasive fungal infection: 14 (87.5%) were due to *Candida,* including 13 with candidemia.

The diagnostic accuracy was highest for a single positive BG value >80 pg/ml (receiver operating characteristic (ROC) area under the curve (AUC) 0.98), the cutoff recommended by the manufacturer, when compared with *Candida* score (0.80) and colonization index (0.63), respectively. The sensitivity of BG was 93.7%, specificity 93.6%, positive predictive value 75%, and negative predictive value 98.6%. Moreover, BG detection preceded microbiological documentation of fungemia by 1 to 3 days. This impressive diagnostic performance, the best ever reported for a fungal biomarker in ICU patients, does probably reflect its use in strictly selected patients at high risk of candidemia. While a combination of BG and *Candida* score increased sensitivity and negative predictive value (both to 100%), specificity and positive predictive value decreased (to 83.5% and 51.8%, respectively).

In addition, Posteraro and colleagues [14] provide important information for the routine use of BG. As environmental contamination resulting in false-positive results is a major issue, specific precautions, including the use of BG-free materials, are recommended for blood sampling and processing. In the present study, BG measurements were compared in blood simultaneously drawn from peripheral venipuncture and via indwelling arterial catheters. The correlation between BG values measured in the two types of samples was excellent. This observation has important practical implications as it simplifies the bedside procedures without impacting on the accuracy of BG measurement.

Some limitations of this single-center study in candidemic medical ICU patients need to be addressed. The study does not provide data for surgical patients at high risk of deep-seated *Candida* infections without candidemia, mainly peritonitis after gastrointestinal tract surgery complicated by anastomotic leakage [1,4]. This well-defined patient subgroup represents a substantial proportion of cases of invasive candidiasis in the ICU and might significantly benefit from early non-invasive diagnosis. In this setting, *Candida* colonization of multiple body sites, absence of fungemia, and surgical gauze dressings as well as other multiple potential sources of environmental BG may all influence the circulation of BG and thus impact on the diagnostic performance of the recommended test's cutoff value. The low local incidence of bacterial bloodstream infections when compared with the high incidence of fungemia suggests that the results obtained in the study setting might not apply to ICUs with different epidemiological backgrounds. Last but not least, this observational study does not provide any information on the impact on patient outcome of integrating BG in real-time clinical management decisions.

In conclusion, this proof-of-concept study in invasive candidiasis opens the way to a new sequential approach for risk stratification in critically ill patients. With a Bayesian approach based on straightforward clinical

criteria for identification of medical ICU patients at high risk of developing candidemia, the intrinsic specificity of BG results in high diagnostic accuracy of a single positive test [15]. Provided that the hospital lab is able to provide results to clinicans within 12 to 24 hours, BG antigenemia would prompt the start of pre-emptive antifungal therapy. Alternatively, empirical antifungal therapy may be discontinued as soon as negative BG and blood culture results are available. However, demonstration of the reproducibility of this sound and appealing unprecedented observation in different hospitals and patient settings is needed. In particular, the utility of BG in patients at high risk of invasive candidiasis after complicated abdominal surgery needs to be investigated, as it might have a significant impact on therapeutic decisions and outcomes. Should these results be confirmed, this very attractive, simple and inexpensive approach may represent a major advance in the management of critically ill patients at risk of invasive candidiasis.

Abbreviations
BG, β-D-glucan.

Competing interests
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