Topic:

Role of ingested (1→3)-β-D-Glucan in the stimulation of innate immune responses and potential for translocation.

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Discussion:

In addition to a variety of disease states, modern medical care can place patients into a state of immunosuppression, rendering them susceptible to invasive fungal disease. Fungal infection leading to fungal disease is associated with high morbidity and mortality, and much higher cost of care. Earlier diagnosis and appropriate antifungal care has been shown to result in better outcomes. Fungitell®, which measures surem levels of (1→3)-β-D-Glucan (BG), a fungal cell wall component, assists patient management as an adjunct to the diagnosis of invasive fungal disease.

BG has also been developed as a health supplement whose ingestion has been widely observed to stimulate innate immune responses, conferring enhanced resistance to infection and stimulating erythropoiesis[1,2,3]. A rich literature has developed documenting the molecular and cellular circuitry associated with BG effects upon immune response and this has supported its development as a commonly utilized dietary supplement[4,5,6]. One of the concerns that arises in the utilization of serum BG measurement as an adjunct to the diagnosis of IFD is whether ingested BG can result in false positive results. The data developed to date show that for humans with a normal intestinal mucosal permeability barrier, ingestion of very large levels of either soluble or particulate BG has no effect upon serum BG levels[7]. Conversely, for patients with mucosal permeability barrier injury (MBI), translocation of BG from the gut is a potential cause of elevated serum levels[8,9]. A variety of factors can cause MBI. These include infection, chemotherapy, and gut hypoxia[10]. It must also be appreciated that MBI is a risk factor for the translocation commensal *Candida* from the gut to the circulation, placing affected patients at higher risk of IFD. In addition, risk may be elevated with certain antibiotics that eliminate gut anaerobic bacteria and potentiate multi-log increases in gut *Candida* populations[11]. This is underscored by recent data demonstrating that exposure to high levels of ciprofloxacin is associated with significantly higher rates of invasive candidiasis than low levels[12]. The above-described observations reinforce the need for assessing the full spectrum of host, clinical, and laboratory findings in the diagnosis of invasive fungal disease.

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Recent Publications:

Acosta J., *et al.* (2011) Prospective study in critically ill non-neutropenic patients: diagnostic potential of (1→3)-β-D-glucan assay and circulating galactomannan for the diagnosis of invasive fungal disease. Eur J Clin Microbiol Infect Dis. [Epub ahead of print] Acosta *et al* prospectively compared serum beta-glucan and galactomannan results in the diagnosis of invasive fungal disease (IFD) in the intensive care setting. This study analyzed the results of 98 patients. Proven IFD cases comprised 4 invasive aspergillosis (IA), 9 invasive candidiasis (IC), 1 zygomycosis, 1 mixed proven IC and probable IA, and I proven mycelial. Probable cases included 7 IA. In IA, the area under the curve (AUC) for receiver-operator curves (ROC) were not significantly different for GM (0.873) or BG (0.856). The AUC for IC and other IFD were 0.605 and 0.768, respectively. Positive serum BG predated other diagnostic indicators of IFD. NPV was reported as 94.5%.

Lu, Y., *et al.* (2011) Diagnosis of invasive fungal disease using serum (1→3)-β-D-glucan: A bivariate meta-analysis. Internal Medicine 50: 2783 – 2791. The purpose of the study was to determine the overall accuracy of the BG assay for the diagnosis of IFD. The authors examined 12 reports comprising 15 studies. They reported aggregate sensitivity, specificity, and positive and negative likelihood ratio (PLR & NLR) values of 0.76, 0.85, 5.05, and 0.28, respectively. Of 13 reports listed, 9 (69.2%) utilized Fungitell® (Associates of Cape Cod, Inc.), 2 (15.4%) utilized Fungitec G (Seikagaku Corporation), and 2 (15.4%) utilized β-Glucan Test (Wako). The authors concluded that serum BG is clinically useful for diagnosing IFD in at-risk patients and in particular hematology patients. They noted that BG results should be interpreted in parallel with clinical findings.

Montagna, M.T., *et al.* (2011) Diagnostic performance of (1→3)-β-D-glucan in neonatal and pediatric patients with candidemia. Int. J. Mol. Sci. 12: 5871 – 5877. This study compared the performance of serum BG and *Candida* mannan (CM) detection in a case series of 10 pre-term neonates and 5 onco-hematological pediatric patients, all with proven candidemia. It was observed that all patients had a positive serum BG level greater than 80 pg/mL on the same day as a positive blood culture was obtained while CM was negative (0.25 ng/mL) in the 5 patients with *C. parapsilosis* infection. Additionally, one patient with a *C. albicans* candidemia was negative on the CM test. For negative controls, 10 pre-term infants and 5 pediatric hematological oncology patients were selected. All were negative for both BG and CM.

Del Bono, V. *et al.* (2011) Clinical performance of (1→3)-β-D-glucan assay in early diagnosis of nosocomial *Candida* blood stream infection. Clin. Vacc. Immunol. 18: 2113-2117. The authors performed a prospective study of the clinical utility of serum BG in the early diagnosis of candidemia. 152 subjects were enrolled, 53 with proven candidemia, 47 possible candidemia, and 52 in whom candidemia was excluded. Positive serum BG values were observed in 41/53 (77.3%) of the provens, 38/47 (80.8%) of the possible, and in 9/52 (17.3%) of the candidemia negatives. The overall sensitivity and specificity were 77%, and 83% respectively. The authors also noted that in 24 patients, 23/24 consecutive paired tests, repeated within a 72 hour interval, were fully concordant. They concluded that a single time point could be used for diagnostic purposes.

Posteraro, B. *et al.* (2011) Early diagnosis of candidemia in intensive care unit patients with sepsis: A prospective comparison of (1→3)-β-D-glucan assay, *Candida* score, and colonization index. Crit. Care 15: R249 (22 October). This was an intensive care unit study enrolling 95 patients with sepsis and a > 5 day stay. The proven IFD rate was 16.8%. For the 12 candidemic patients, a positive BG result was observed 24 – 72 hours prior to culture based diagnosis of invasive candidiasis. The relative values for negative and positive predictive values for the BG, *Candida* Score, and Colonization Index were, respectively: 72.2%, 57.1%, and 27.3%; 98.7%, 97.2%, and 91.7%. The authors also observed that there were no significant differences between the arterial and venous specimens using 70 simultaneously obtained paired specimens from 35 patients. The authors concluded that a single BG result drawn at the onset of sepsis can guide antifungal administration decision-making.

Discussion References

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