Topic:

Non-invasive fungal infection (IFI) factors contributing to serum (1→3)-β-D-Glucan positivity.

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Discussion:

Invasive fungal disease is a widespread problem in a number of clinical contexts, including immunosuppression, gastrointestinal surgery with complications, long term intensive care, and parenteral feeding[1,2]. Improved methods to assist with diagnosis have been sought and Fungitell® a (1→3)-β-D-Glucan (BG) measurement kit, was introduced by Associates of Cape Cod, Inc. to address this need. The appropriate interpretation of serum BG data in patient management requires an understanding of potential sources of BG that are unrelated to invasive fungal infection.

Serum BG tests have been cleared for clinical use in Japan since 1995, in the US since 2004, and in Europe since 2008. As experience with BG testing has been gained, a variety of factors other than invasive fungal infection (IFI) that might be associated with positive serum BG levels have been reported[3,4,5]. It is important for physicians to be aware of these factors and use this knowledge in clinical case management. A major non-IFI factor that is worthy of consideration is iatrogenic introduction of BG. A list of potentially BG-contributing factors that have been discussed in various publications is presented in Table 1. These are also listed in the instructions for use for Fungitell. Another reported possible source of non-IFI BG is paracellular translocation from the gut lumen following injury to the mucosal barrier. Ellis *et al.*[6] have suggested that severe mucositis or enterocolitis is a potential cause of elevated serum beta-glucan in patients lacking other evidence of fungal infection. In addition, the possibility of that bacterial infection might lead to elevated serum BG has been raised as a potential contributor, but data are limited and often contradictory[7]. One published report suggests that 20% of *Ps. aeruginosa* strains produce (1→3)-β-D-Glucan[8]. This report also described a strain of *Strep pneumoniae* that produced (1→3)-β-D-Glucan. Studies by Metan and coworkers investigated the possibility of bacterial infection contribution of BG without finding an association[9,10].

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Table 1. Possible Non-IFI Sources of (1→3)-β-D-Glucan

Potential Source of Beta-Glucan	Detailed Description	Literature Reference
Recent infusion of blood fractionation products.	Use of glucan-leaching cellulosic depth filters in their manufacturing.	Koo, S. *et al.* Clin. Microbiol. Infect. 2012; 18:E122-7 Parenteral Drug Assoc. Filtration of liquids using cellulose-based depth filters. Technical Report 45 v. 62 S. 2 Held, J. and Wagner D. β-glucan kinetics for the assessment of treatment response in *Pneumocystis jirovecii* pneumonia. Clin. Microbiol. Infect. 2011; 17:1118-22.
Recent surgery with use of surgical sponges and/or gauze.	Elevated serum BG levels have been shown to decline to below cutoff 3-4 days after surgery.	Mohr, J.F. *et al.* Prospective survey of (1→3)-β-D-Glucan and its relationship to invasive candidiasis in the surgical intensive care setting. 2011; JCM 49:58-61. Kanamori, H. *et al.* Measurment of (1→3)-β-D-Glucan from different gauze types. Tohoku J. Exp. Med. 2009; 217: 117-121.
Hemodialysis	Regenerated cellulose filter membranes may leach (1→3)-β-D-Glucan. Seldom used in recent years.	Kanda, H. *et al.* Influence of various hemodialysis membranes on the plasma (1→3)-β-D-Glucan level. Kidney International. 2001; 60:219-23.
Blood collection by heel- or finger-stick.	Isopropyl alcohol soaked gauze used to prepare stick site deposits beta-glucan on skin	Finkelman, M.A. and Lempitski, S. (1→3)-β-D-Glucan (BG) testing in invasive fungal infection (IFI): Sources of potential contamination. International Society of Human and Animal Mycology Meeting, Paris, 2006. Poster P-0381.

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10. Metan, G. *et al.* Does ampicillin-sulbactam cause false positivity of (1,3)-beta-D-glucan assay? A prospective evaluation of 15 patients without invasive fungal infections. Mycoses 2011 Nov 1. doi: 10.1111/j.1439-0507.2011.02131.x. [Epub ahead of print]

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Recent Publications on Serum BG and Related Matters:

Issa, N.C., *et al.* Serum galactomannan and (1→3)-β-D-Glucan assays for patients with multiple myeloma and Waldenstrom's macroglobulinemia. J. Clin. Micro. 2012; 50: 1054-1056. This study addressed a phenomenon observed in the testing of serum samples; that of sample precipitation upon the addition of the Fungitell reagent. Samples from hematological malignancy patients which contained high levels of IgG (>2,000 mg/dL) are reported to have a greater likelihood of precipitation and uninterpretable results. The authors speculated that optical artifacts may be associated with IgG class antibody elevation due to the isolelectric point being closer to the pH of the Fungitell reaction mixture than those of IgM or IgA. The study concluded that BG was not falsely elevated in cases of Multiple Myeloma or Waldenstrom's Macroglobulinemia, although plasma cell disorders with IgG>2,000 mg/dL may cause results to be uninterpretable.

Eggimann, P. and Marchetti, O. Is (1→3)-β-D-Glucan the missing link from bedside assessment to pre-emptive therapy of invasive candidiasis? Critical Care 2011; 15: 1017-1019. In this editorial, the authors discuss the utility of serum BG in the ICU setting, particularly in the role of identifying patients who would benefit from pre-emptive antifungal therapy. The authors opined that data serum BG data, returned within a 12-24 hour time period, would allow the start of pre-emptive therapy or, conversely, allow the discontinuation of empirical therapy.

Gutierrez, S., *et al.* *Pneumocystis jirovecii* colonization in chronic pulmonary disease. Parasite 2011; 18: 121-126. This review describes a series of chronic pulmonary conditions in which significant colonization with *Pneumocystis jirovecii* was observed. These include chronic obstructive pulmonary disease (COPD), interstitial lung diseases, cystic fibrosis, and lung cancer. The authors point put that while there is a sound theoretical basis for the potential contribution of *P. jirovecii* colonization to the exacerbation of airway symptoms and inflammatory processes, sound data are limited to chronic obstructive pulmonary disease.

Yoshida, K., *et al.* Clinical viability of Fungitell, a new (1→3)-β-D-Glucan measurement kit, for diagnosis of invasive fungal infection, and comparison with other kits available in Japan. J. Infect. Chemother. 2011; 17: 473-477. This study is an evaluation of all of the existing serum beta-glucan detection kits that are currently in use. These include the Fungitell kit (Associates of Cape Cod, Inc., East Falmouth, MA); Fungitec-G, (Seikagaku Corporation, Tokyo, Japan); β-glucan test Wako (Wako, Osaka, Japan); β-glucan test Maruha (Maruha Nichiro, Tokyo, Japan). Plasma samples from 121 patients were tested and the diagnostic performance values were determined for each of the kits. For Fungitell, the sensitivity, specificity, and positive and negative predictive value were 83.3, 92.6, 58.8, and 97.8 percent respectively. The sensitivity of Fungitell is the highest reported, followed by Fungitec at 75% and the Wako and Maruha tests at 41.7% each.

Ginnochio, F. *et al.* Reliability of (1→3)-β-D-Glucan monitoring during treatment of peritoneal candidiasis in a child in continuous peritoneal dialysis: A case report. Clin. Vaccine Immunol. doi:10.1128/CVI.00008-12. This case report describes the use of serum BG measurement in the diagnosis of candidal peritonitis in a four year old male child. The serum and peritoneal fluid was assessed for BG titer through the course of treatment. The authors noted that rising and declining BG titers reflected the impact of the therapeutic measures and clinical resolution of the infection. *C. parapsilosis* was identified as the causative organism. While not cited by the authors, fungi are estimated to be responsible for about 2-10% of peritoneal dialysis-related peritonitis with most species being from the genus *Candida* (Chavada et al. PLoS One 2011; 6: e28247).

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