Topic:

Effect of fungal colonization upon serum (1→3)-β-D-glucan titer

April, 2015

the Fungitell® Bulletin

volume 5, issue 3

Discussion:

Serum (1→3)-β-D-glucan (BG) titer has been demonstrated to be a useful adjunct to the diagnosis of invasive fungal disease (IFD)[1,2]. In addition to high sensitivity, serum BG has been consistently shown to provide very high Negative Predictive Value scores[3,4], providing laboratory result support for the sparing of therapy with systemic anti-fungals[5]. One frequently asked question is whether fungal colonization has an impact upon serum BG titer. Studies have addressed this question with mixed results. Takesue, *et al.* (2004) observed that increasing, multiple site colonization was associated with elevation of serum BG titers. Similar observations were made by Del Bono *et al.* (2012) who noted that 12 % of patients without *Candida* colonization were BG positive while 29% of patients with multi-focal colonization were BG positive[6]. Pazos *et al.* (2005)[7], in a study of patients with invasive aspergillosis, observed that *Candida* colonized patients, negative for serum BG, were also negative for *Candida albicans* anti-germ tube antibodies (anti-CAGT), a marker of invasive disease. In a follow-up study of patients with invasive candidiasis (IC), similar observations were made; only when both serum BG and anti-CAGT were positive did the patients have either proven or probable IC[8]. The serum BG specificities were 75.3% and 89.6% at cutoffs of 80 and 120 pg/mL, respectively. In separate analyses of patients with either *Pneumocystis* pneumonia or colonized by *Pneumocystis*, Damiani *et al.* (2011) reported median values for PCP and colonized patients of 1768.5 and 69.5 pg/mL, respectively[9]. The second study (Damiani *et al.,* 2013) reported median values for PCP and colonized patients of 1945 and 40 pg/mL, respectively, while controls registered a median of 28 pg/mL[10]. Thus, in the context of fungal colonization, serum BG titers are routinely shown to be much lower than those observed in the case of invasive fungal disease. The potential mechanisms responsible for increased serum BG in the circumstance of severe *Candida* colonization include greatly increased intestinal *Candida* populations in patients exposed to broad spectrum gut-active antibacterials, translocation of BG, and breakdown of tissue barriers in colonized tissue.[11,12]

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Recent Publications on Serum BG and Related Matters:

Lyons, J.L. *et al.,* Utility of measuring (1,3)-β-D-glucan in cerebrospinal fluid for diagnosis of fungal central nervous system infection J Clin Microbiol. 2015;53:319-22. This study examined the relationship of serum and cerebrospinal fluid (1→3)-β-Dglucan titers in the diagnosis of invasive fungal disease. The authors observed that CSF BG titer was 2-fold lower than serum levels in patients without invasive fungal disease, but was 25-fold higher in patients with non-cryptococcal CNS mycosis. Measurable CSF BG was observed in all non-CNS proven, probable, or possible fungal infection, but the median serum/CSF BG ratio was 14.9. CSF BG diagnostic performance using a cutoff of 110 pg/mL demonstrated the following; sensitivity, 100%; specificity, 96%; Receiver-Operator Curve Area Under Curve, 0.982.

Damiani, C., *et al.* Usefulness of (1,3)-β-D-glucan detection in bronchoalveolar lavage samples in *Pneumocystis* pneumonia and *Pneumocystis* pulmonary colonization. J. Mycol. Med. 2015;25:36-43. This study evaluated the utility of (1→3)-β-D-Glucan titer measurement in broncho-alveolar lavage (BAL) specimens obtained from patients either colonized with *Pneumocystis jirovecii*, diagnosed with *Pneumocystis* pneumonia, or uninfected. Although BAL is not a validated matrix for Fungitell®, fungal antigen detection in BAL fluid has generated interest in the mycotic diseases community in recent years. The BAL BG titer analysis revealed that the *Pneumocystis* pneumonia, *Pneumocystis* colonized, and uninfected had BG means of 20,588, 105, and 74 pg/mL, respectively. The authors concluded that BAL BG titers may facilitate the differential diagnosis of *Pneumocystis* pneumonia and colonization.

He, S., *et al.* A systematic review and meta-analysis of diagnostic accuracy of serum 1,3-β-D-glucan for invasive fungal infection: Focus on cutoff levels. J Microbiol Immunol Infect. 2014 Jul 28. pii: S1684-1182(14)00120-0. doi: 10.1016/j.jmii.2014.06.009. [Epub ahead of print]. This paper reviews the diagnostic performance of multiple (1→3)-β-D-glucan *in vitro* diagnostic kits from several manufacturers. Included in the analysis are kits from Associates of Cape Cod, Inc. (Fungitell®, East Falmouth, USA), WAKO Pure Chemical Industries (β-D-Glucan Test, Tokyo, Japan), and Seikagaku Corporation (Fungitec G, Tokyo, Japan). The meta-analysis utilized 28 studies of which 27 were evaluated as meeting the quality requirements for the meta-analysis. This is the largest number of studies reviewed to date in a meta-analysis of serum (1→3)-β-D-glucan diagnostic performance. Using the 28 study data, the sensitivity, specificity, diagnostic odds ratio, and area under the summary receiver operating characteristic (AUC-SROC) curve were 0.78 [95% confidence interval (CI), 0.75-0.81], 0.81 (95% CI, 0.80-0.83), 21.88 (95% CI, 12.62-37.93), and 0.8855, respectively.

Tasaka, S., *et al.* Serum (1→3)-β-D-glucan assay for discrimination between *Pneumocystis jirovecii* pneumonia and colonization. J. Infect. Chemotherapy. 2014; 20:678-681. This study examined the utility of PCR and BG analysis of BAL samples for the purpose of distinguishing colonization from pneumonia. The authors found that the BAL BG titers in *Pneumocystis* pneumonia (PCP) patients were statistically significantly higher than those in non-PCP ($p<0.001$) and that they could be used to differentiate PCP from non-PCP. They also noted that the positive predictive value of BAL BG for PCP was 92.5%. They further concluded that PCR's very high sensitivity created a risk for false positives and the addition of BAL BG titer determination could offer clinically significant utility.

Sanada, Y. *et al.,* Impact of β-D glucan during liver transplantation. Hepato-Gastroenterology. 2014; 61:1368-1373. The authors analyzed the utility of serum (1→3)-β-D-glucan as an indicator of hepatic function during liver transplantation. The liver has a critical role in the removal of BG from the blood . This study compared the BG titer in the portal vein blood to peripheral blood. As the portal vein drains the intestinal circulation, comparison with the post-hepatic BG titer (in peripheral venous blood) was used to generate a clearance index. The authors reported that there was a significant positive correlation between preoperative BG levels in peripheral/portal vein blood and the post-operative length of stay in hospital.

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Clancy, C.J. and Nguyen, M.H. Undiagnosed invasive candidiasis: Incorporating non-culture diagnostics into rational prophylactic and preemptive antifungal strategies. Expert Rev. Anti. Infect. Ther. 2014; 12: 731-734. This review describes the diagnostic conditions driving the extensive use of anti-fungal prophylaxis and empirical therapy. The inadequacy of blood culture sensitivity is discussed (sensitivity of culture is ~ 50% and becomes positive late in disease). The authors propose that a rational management approach be adopted in which the negative predictive value of beta-glucan, a non-culture-based test, is used to discontinue antifungal prophylaxis in low- to moderate-risk patients. They propose, for high-risk patients, a positive beta-glucan test be used to trigger pre-emptive therapy. In the setting of extremely high-risk patients, the authors call for universal prophylaxis.

Discussion References:

1. Karageorgopoulos, D.E., *et al.* β-D-Glucan assay for the diagnosis of invasive fungal infections: a meta-analysis. Clin. Inf. Dis. 2011; 52:750-770.
2. Karageorgopoulos, D.E., *et al.* Accuracy of β-D-Glucan for the diagnosis of *Pneumocystis jirovecii* pneumonia: A meta-analysis. Clin. Microbiol. Infect. 2013; 19: 39-49.
3. Hammarstrom, H., *et al.* How to interpret serum levels of beta-glucan for the diagnosis of invasive fungal infections in adult high-risk hematology patients: optimal cut-off levels and confounding factors. Eur. J. Microbiol. Infect. Dis. DOI 10.1007/s10096-014-2302-9.
4. Held, J. *et al.* Comparison of (1→3)-β-D-glucan, mannan/anti-mannan antibodies, and Cand-Tec *Candida* antigen as serum biomarkers for candidemia. J. Clin. Micro. 2013; 51:1158-1164.
5. Prattes, J., *et al.* Serum 1,3-beta-glucan for antifungal stratification at the intensive care unit and the influence of surgery. Mycoses DOI: 10.1111/myc.12221.
6. Del Bono, V. *et al.,* Clinical performance of the (1→3)-β-D-glucan assay in early diagnosis of nosocomial *Candida* bloodstream infections. Clin Vaccine Immunol. 2011;18:2113-2117.
7. Pazos, C. *et al.* Contribution of (1→3)-β-D-glucan chromogenic assay to diagnosis and therapeutic monitoring of invasive Aspergillosis in neutropenic adult patients: a comparison with serial screening for circulating galactomannan. J. Clin. Micro. 2005; 43:299-305.
8. Pazos, C. *et al.* Diagnostic potential of (1→3)-β-D-glucan and anti-Candida germ tube antibodies for the diagnosis and therapeutic monitoring of invasive candidiasis in neutropenic adult patients. Rev. Iberoam. Micol. 2006; 23:209-215.
9. Damiani, C. *et al.,* Serum (1→3)-β-D-glucan levels in primary infection and pulmonary colonization with *Pneumocystis jirovecii*. J. Clin. Micro. 2011; 49: 2000-2002.
10. Damiani, C. *et al.* Combined quantification of pulmonary *Pneumocystis jirovecii* DNA and serum (1→3)-β-D-glucan for differential diagnosis of *Pneumocystis* pneumonia and *Pneumocystis* colonization.
11. Samonis, G. *et al.* Fluoroquinolones elevate gut *Candida* populations 1-2 logs. AAC. 2005; 49:5189.
12. Clemons, K.V. and Stevens, D.A. Orogastrointestinal model of mucosal and disseminated candidiasis. Methods Mol Biol. 2012; 845: 557-567.

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