Topic:

Beta-Glucan (BG) Kinetics as a Biomarker

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Introduction:

The effective medical treatment of patients suffering from invasive fungal disease (IFD) has been shown to require timely administration of appropriate anti-fungal therapy. Fungitell®, an *in vitro* diagnostic test for (1→3)-β-D-glucan is used to provide laboratory evidence of the presence or absence of invasive fungal infection. Early diagnosis and treatment of IFD is associated with improved outcomes.

Fungitell® is cleared for marketing as an adjunct to the diagnosis of invasive fungal disease (IFD). It is not cleared for monitoring the efficacy of antifungal treatment. However, since the introduction of serum (1→3)-β-D-glucan (BG) testing in 2004, clinical researchers have also been interested in evaluating whether BG can be used as a bio-marker for the evaluation of antifungal therapy efficacy. A number of studies have looked at this with decidedly mixed results. Some studies have observed reductions in serum BG levels that corresponded with clinical resolution of fungal disease[1,2] and others have noted persistently elevated BG levels in spite of apparent clinical resolution[3,4]. Work with animal models is suggestive of a relationship between disease organism burden, therapy success, and BG levels, but the data is limited[5,6,7]. The factors that may affect BG clearance are briefly reviewed by Marty and Koo (2009)[3]. These include pathogen-associated factors such as type of organism, angioinvasiveness, the characteristics of the BG and host factors such as fungal burden, affected organs, and clearance efficiency (hepatic and renal). While rising serum BG levels during antifungal therapy is generally considered a poor prognostic indicator, there is, as yet, no consensus as to the meaning of persistently elevated BG levels in the context of apparent clinical resolution. The most significant concern is that elevated BG levels might mean residual infection and a high risk of disease recurrence. Additional data should be available this year on candidemia outcome and BG levels.

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Recent Publication:

Karageorgopoulos, D. E. *et al.* β-Glucan assay for the diagnosis of fungal infections: A meta-analysis. Clin Infect. Dis. 2011; 52: 750-770.
The authors analyzed a total of 16 studies that assessed (1→3)-β-D-glucan (BDG) testing in the diagnosis of invasive fungal infection. A total of 2979 patients were examined in these studies and 594 had proven or probable invasive fungal infections. The analysis determined that the overall sensitivity and specificity were 76.8% and 85.3%, respectively and that there was high statistical heterogeneity among the included studies. The area under the receiver-operator curve (ROC) was 0.89. The authors concluded that "serum BDG measurement has good diagnostic accuracy for IFIs diagnosed in accordance with EORTC/MSG or similar criteria."

Mikulska, M. *et al.* Persistence of positive (1→3)-β-D-glucan test after clearance of candidemia in HSCT recipients. Clin. Vacc. Immunol. 2011; 18:518-519.
This study addressed the diagnostic utility of BG testing in human stem cell transplant patients. They found that their patients developed BG positivity after culture positivity in 5/6 cases. They also observed that BG remained positive for a median 48 days after blood sterility was achieved. One consideration that they noted was that most of their patients retained their catheters, despite being diagnosed with candidemia. Catheter biofilms have been observed to produce elevated levels of (1→3)-β-D-glucan. This adds to the complexity of determining the source of positive beta-glucan levels where resolution of disease is indicated by clinical assessment.

Swain, S. D. *et al. Pneumocystis* infection in an immunocompetent host can promote collateral sensitization to respiratory antigens. Infect. And Immun. 2011; doi:10.1128/IAI.01273-1.
This study evaluated a sensitization response to the presence of *Pneumocystis murinii*, in the lungs of mice. The authors observed that at day 14 post-inoculation, the pulmonary inflammatory response peaked. They also observed that at this point a secondary exposure with a different antigen resulted in a hyper-sensitization to that antigen. This hyper-responsiveness to the secondary antigen did not occur in that absence of *P. murinii* infection. The ability of *Pneumocystis* to facilitate airway sensitization was deemed, by the authors, to represent a mechanism for worsening of obstructive airway disease.

Heyland, D. *et al.* Serum β-D-glucan of critically ill patients with suspected ventilator-associated pneumonia: Preliminary observations. J. Crit. Care. 2011; Mar. 2, epub ahead of print.
This study examined the association between elevated serum BG and pulmonary *Candida* and risk of death in patients with suspected ventilator-associated pneumonia (VAP). The findings demonstrated BG positivity of 66.7%, 50%, and 26.3% for the *Candida*-only (12/57), culture negative (26/57), and bacteria-only (19/57) groups, respectively. Another observation was that serum BG-positive and *Candida* positive (in lung secretions) patients were 4.2-fold more likely to die than BG-negative patients (p=0.03). The authors concluded that this preliminary study indicated that serum "BG positivity in suspected VAP may be a marker for *Candida* in the lung and worse outcomes," and "that further validation of this postulate was warranted."

Duffner, U. *et al.* Serum (1→3)-β-D-glucan levels (Fungitell assay) is not useful as a screening test for recipients of an allogeneic HSCT while on immunoglobulin replacement. Bone Marrow Transplant. 2011; 28 February 2011; doi:10.1038/bmt.2011.24.
This case report series established that the observations of serum BG elevation in two Human Stem Cell Transplant (HSCT) recipients that were inconsistent with their clinical status with respect to invasive fungal infection. After eliminating other sources of iatrogenic contamination, they measured the BG levels of the intravenous immunoglobulin (IVIG) preparation which at least one patient was receiving and found it to be contaminated. They demonstrated an association between the receipt of IVIG infusion and serum BG level elevation. Levels trended lower as the period after infusion lengthened with one patient approaching negative or equivocal after two weeks and in the second, BG levels were undetectable after 3 weeks. These observations underscore the potential of BG contamination in blood fractionation products to generate elevated serum BG levels in patients, in the absence of IFI.

References

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