Topic:

Antifungals and Beta-Glucan Sensitivity:

1. Lack of evidence for an antifungal drug effect upon Fungitell® diagnostic performance.

2. Beta-glucan's long post-therapy clearance period.

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Discussion:

Understanding the potential impact of confounding factors upon the diagnostic performance of biomarkers is an important consideration in clinical decision-making. This is critical in the area of invasive fungal disease, where biomarker-based diagnostics are increasingly utilized in clinical decision-making. One such confounding factor is the impact of antifungal drugs upon biomarker production from fungal pathogens. For (1→3)-β-D-glucan (BG), the impact of antifungal drugs upon serum titer shows a significant contrast with that of galactomannan. For the latter, the administration of mold-active antifungals is associated with diminished galactomannan signal.[1,2] In contrast, there is an observed lack of effect of administered antifungals upon BG sensitivity.[3,4,5] Odabasi *et al*[3] observed that among 283 high risk patients receiving either caspofungin or itraconazole, all breakthrough invasive fungal infections produced BG positivity at a cutoff of 80 pg/mL. Similarly, Koo *et al*[4] evaluated 871 patients in a single center observational study and did not observe a significant difference in BG sensitivity in patients naive to antifungals versus those receiving them. Azoulay *et al*[5] evaluated 737 consecutive ICU patients, from 17 ICUs, documenting invasive fungal infection in 78. They observed that administration of antifungal therapy at admission had no effect upon BG sensitivity. The AUCROC was 0.74, 0.72, and 0.73 for all patients, patients on antifungals, and patients without antifungals, respectively. Finally, Pini et al observed no difference in the sensitivity of Fungitell® for patients receiving or not receiving azole therapy.[9]

A potential mechanism for the observed maintenance of diagnostic sensitivity of BG may be its slow clearance from the blood. Numerous studies have reported the long period required for BG clearance in a setting of effective antifungal treatment and clinical resolution of the infection.[6,7,8,9,10] This long clearance period, while enhancing BG utility as a diagnostic biomarker, complicates the use of BG titer kinetics for the purposes of evaluating the therapeutic efficacy of antifungal treatment. Nonetheless, studies continue to be performed evaluating this aspect of serum BG monitoring.[7,9] At this point, the sole indicated use for BG testing is as an adjunct to the diagnosis of invasive fungal disease.[11]

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Recent Publications on Serum BG and Related Matters:

Lyons JL, Erkkinen MG, Vodopivec I. Cerebrospinal fluid (1,3)-β-D-glucan in isolated Candida meningitis. Clin Infect Dis. 2015;60:161-2. This case report describes the first demonstration of the use of (1→3)-β-D-Glucan (BG) detection in cerebrospinal fluid in the context of *Candida albicans* meningitis in a 31 year old female i.v. drug user. All microbial markers except BG were negative. Serum and CSF BG were 74 and >500 pg/mL, respectively. Treatment with fluconazole, 400 mg/day, produced clinical improvement. This case underscores the observation that in the context of CNS mycosis, CSF BG levels may be very high with negative or indeterminate serum levels.

Lo Cascio G[1], Koncan R, Stringari G, Russo A, Azzini A, Ugolini A, Ligozzi M, Polati E, Cornaglia G, Concia E, Schweiger V. Interference of confounding factors on the use of (1,3)-beta-D-glucan in the diagnosis of invasive candidiasis in the intensive care unit. Eur J Clin Microbiol Infect Dis. 2015;34:357-65. This ICU-based study (Patients who were serum BG-tested, N=267) evaluated the influence of potential BG contamination in commonly used parenterals in the generation of diagnostic false positives in serum tests. The study evaluated the influence of the following infused materials: Human serum albumin (HSA), azole antifungals, immunoglobulins, red blood cells, concentrated platelets, and frozen plasma. False positives were only significantly associated with HSA administration. Importantly, the authors observed that only the HSA was manufactured using cellulosic filters while the production of the other materials used synthetic filters. Cellulosic depth filters are a well known contributor of BG as it is a minor constituent of plant tissue (callose).

Li WJ, Guo YL, Liu TJ, Wang K, Kong JL. Diagnosis of pneumocystis pneumonia using serum (1-3)-β-D-Glucan: a bivariate meta-analysis and systematic review. J. Thorac. Dis. 2015;7:2214-25. The authors provide a meta-analysis of the diagnostic performance of BG testing in the setting of *Pneumocystis jirovecii* pneumonia (PJP). 13 studies met their inclusion criteria and the serum BG diagnostic performance characteristics in the setting of proven PJP were analyzed and described. Sensitivity and specificity were reported as: Sens: 0.91 (CI; 0.88-0.93); Spec: 0.75 (0.68-0.81). For patients with and without HIV, the Sens. and Spec. were 0.92/0.78 and 0.85/0.73, respectively. The authors concluded that the NPV was sufficient to rule out PJP in HIV cases, while in non-HIV cases, clinical and radiological findings needed to be considered in parallel.

Liss B, Cornely OA, Hoffmann D, Dimitriou V, Wisplinghoff H. 1,3-β-D-glucan concentrations in blood products predict false positive post-transfusion results. Mycoses. 2016 Jan;59(1): 39-42. This study evaluated the potential of blood fractionation products to be contaminated with BG and to produce serum BG diagnostic false positive titers in patients receiving them. Human albumin, fresh frozen plasma, undiluted platelet transfusion, and packed red blood cells were evaluated. In two patients receiving packed red blood cell transfusions, serum BG values were 13 and 17 pg/mL then 183 and 361 pg/mL pre- and post-transfusion, respectively. For human albumin transfusion, serum BG rose from 42 to 58 pg/mL. The authors noted that BG contamination titers in blood fractionation products might be used to predict serum BG diagnostic false positives.

Mutschlechner W, Risslegger B, Willinger B, Hoenigl M, Bucher B, Eschertzhuber S, Lass-Flörl C. Bronchoalveolar Lavage Fluid (1,3)-β-D-Glucan for the Diagnosis of Invasive Fungal Infections in Solid Organ Transplantation: A Prospective Multicenter Study. Transplantation. 2015;99:e140-4. Solid organ transplant patients (n=233) were investigated for invasive pulmonary mycosis. This study analyzed the diagnostic performance of (1→3)-β-D-glucan analysis in broncho-alveolar lavage fluid (BAL), an unvalidated matrix for BG testing. Using a 100 pg/mL cutoff for BAL (samples, N=135), the per test sensitivity, specificity, PPV, and NPV were 79.2%, 38.5%, 27.6%, and 86.3%, respectively. For serum (samples, N=109), the sensitivity, specificity, positive and negative predictive values were 79.2%, 81.8%, 69.2%, and 83.1%, respectively. The authors concluded that the NPV value showed utility for the exclusion of pulmonary IFD in this patient cohort.

Reischies FM, Prattes J, Prüller F, Eigl S, List A, Wölfler A, Buzina W, Zollner-Schwetz I, Valentin T, Rabensteiner J, Flick H, Krause R, Raggam RB, Hoenigl M. Prognostic potential of 1,3-beta-d-glucan levels in bronchoalveolar lavage fluid samples. J Infect. 2016;72:29-35. This study evaluated broncho-alveolar lavage fluid (BALF, N=300) from 252 patients, from various clinical services within a single tertiary care academic medical center. The largest proportion came from ICU (44.3%) and pulmonary disease (49%). 31% had *Candida* in BALF culture. Stratifying BALF BG to <200 pg/mL and ≥200 pg/mL dichotomized propensity for mortality at 30 days: <200 pg/mL (18/144 (12.5%) and ≥200 pg/mL (24/108 (22.2%); p=0.040 and at 90 days <200 pg/mL (26/144 (18.1%) and ≥200 pg/mL (35/108 (32.4%); p=0.008). The authors observed that each 100 pg/mL increase in BALF BG tier carried an incremental 5% risk of 90 day mortality.

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Discussion References:

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