Discussion:

Over the last one and a half decades, the use of clinical assays for serum (1→3)-β-glucan (BG), as an adjunct diagnostic test for invasive fungal disease (IFD), has become widespread. In the course of both routine clinical testing and targeted research efforts, it has become apparent that certain clinical contexts are associated with elevated serum BG, in the absence of IFD. Accordingly, it is important for both clinicians and clinical investigators to be aware of recent observations concerning non-IFD clinical factors that can result in elevated serum BG and contribute to diagnostic false positive results for IFD. Recent publications describing the conditions in which this has been demonstrated have included the following:

**Sepsis-Septic Shock**: A very significant elevation of serum BG from negative to strongly positive was observed in sepsis and septic shock of Febrile Neutropenics (Mean: 28 ± 4 vs. 195 ± 49 pg/ml) and Febrile Non-Neutropenics (28 ± 9 vs. 258 ± 194 pg/ml), respectively.

**Cystic Fibrosis**: Higher serum BG titers were observed in CF patients with pancreatic insufficiency relative to the pancreatic sufficient (Median: 55.3 vs. 25.3 pg/ml, respectively) or CF-related diabetes versus non-diabetic (Median: 82.3 vs. 30.6 pg/ml, respectively).

**Systemic Lupus Erythematosus**: Serum BG titers in excess of 60 pg/ml were observed in 7/14 inactive lupus patients (Mean: 74 ± 12 pg/ml) and 12/14 active lupus patients (Mean: 133 ± 19 pg/ml). A murine model of lupus demonstrated intestinal translocation of both BG and FITC-dextran.

**HIV infection**: A correlation between serum BG titer and cognitive decline was observed, (Spearman r=0.47; P=0.042), along with correlations with markers of inflammation and microbial translocation.

**Burn Trauma**: Baseline serum BG was observed to be 60 pg/ml in 20% of patients with <20% Total Burn Surface Area (TBSA) but >60 pg/ml in 77% of patients with ≥20% TBSA. Serum BG titer correlated positively with TBSA but gauze coverage did not have an impact.

**Antibiotic Unresponsive Neutropenic Fever**: Among hematological oncology patients without IFI, a higher proportion of those with continuing high levels of serum BG (Mean: 191.8 ± 55.8 pg/ml) were observed to have enterocyte damage (enterocolitis) or severe mucositis compared to those with low levels of serum BG (Mean: 44.9 ± 3.4 pg/ml), P = 0.002.

These data, coupled to observations of higher mortality rates among patients with more elevated serum BG titers, should inform the interpretation and use of serum BG titers in the diagnostic work-up for IFD.
ELEVATED SERUM (1→3)-β-GLUCAN IN THE ABSENCE OF INVASIVE FUNGAL DISEASE

Discussion References:


Recent Publications on Serum BG and Related Matters:
Boch, T., Reinwald, M., Spiess, B., Liebgertg, T., Schellongowski, P., Meybohm, P., Rath, P.M., Steinmann, J., Trinkmann, F., Britsch, S., Michels, J.D., Jabbour, C., Hofmann, W.K., and Buchheidt, D. Detection of invasive pulmonary aspergillosis in critically ill patients by combined use of conventional culture, galactomannan, 1-3-beta-D-glucan and Aspergillus specific nested polymerase chain reaction in a prospective pilot study. J Crit Care. 2018;47:198-203. This study evaluated the utility of multiple diagnostic modalities, alone and in combination, in a cohort of 44 ICU patients who were mechanically ventilated due to respiratory failure. Matrices tested included broncho-alveolar lavage fluid (BAL) and serum. Nine of the patients were deemed to have putative invasive pulmonary aspergillosis (IPA), 3 each with hem-onc, solid tumor, or non-oncological underlying disease. 7/9 met EORTC criteria for probable IPA. 2 patients had confirmed disseminated candidiasis and two had imaging consistent with pneumocystosis. GM specificity in serum and BAL was high while sensitivity was low. Corresponding BG sensitivity and NPV was high while specificity and PPV values were low. Aspergillus PCR sensitivity and specificity in BAL and serum were low and high, respectively. The role of NPV utility for combinations of these tests was extensively discussed

Leelahavanichkul, A., Worasilchai, N., Wannalerdsakun, S., Jutivorakool K, Somporn P, Issara-Amphorn J, Tchabooon S., Srisawat N, Finkelman M, and Chindamporn A. Gastrointestinal Leakage Detected by Serum (1→3)-β-D-Glucan in Mouse Models and a Pilot Study in Patients with Sepsis. Shock. 2016;46(5):506-518. This study evaluated both sepsis/septic shock patients and a murine sepsis model for evidence of (1→3)-β-glucan (BG) translocation from the intestinal tract. Serum BG titers of febrile neutropenic and febrile non-neutropenic patients differed considerably in sepsis and septic shock, Means: 28 ± 4 vs. 195 ± 49 pg/ml and 28 ± 9 vs. 258 ± 194 pg/ml, respectively. Similar results were observed in the murine model and intestinal

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translocation was verified using FITC-dextran as an orthogonal method. Symptom severity and mortality were worse with increasing serum BG titer.

Bansal, N., Gopalakrishnan, R., Sethuraman, N., Ramakrishnan, N., Nambi, P.S., Kumar, D.S., Madhumitha, R., Thirunarayan, M.A., and Ramasubramanian, V. Experience with V. Experience with Symptom severity and mortality were worse with increasing serum BG titer.

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