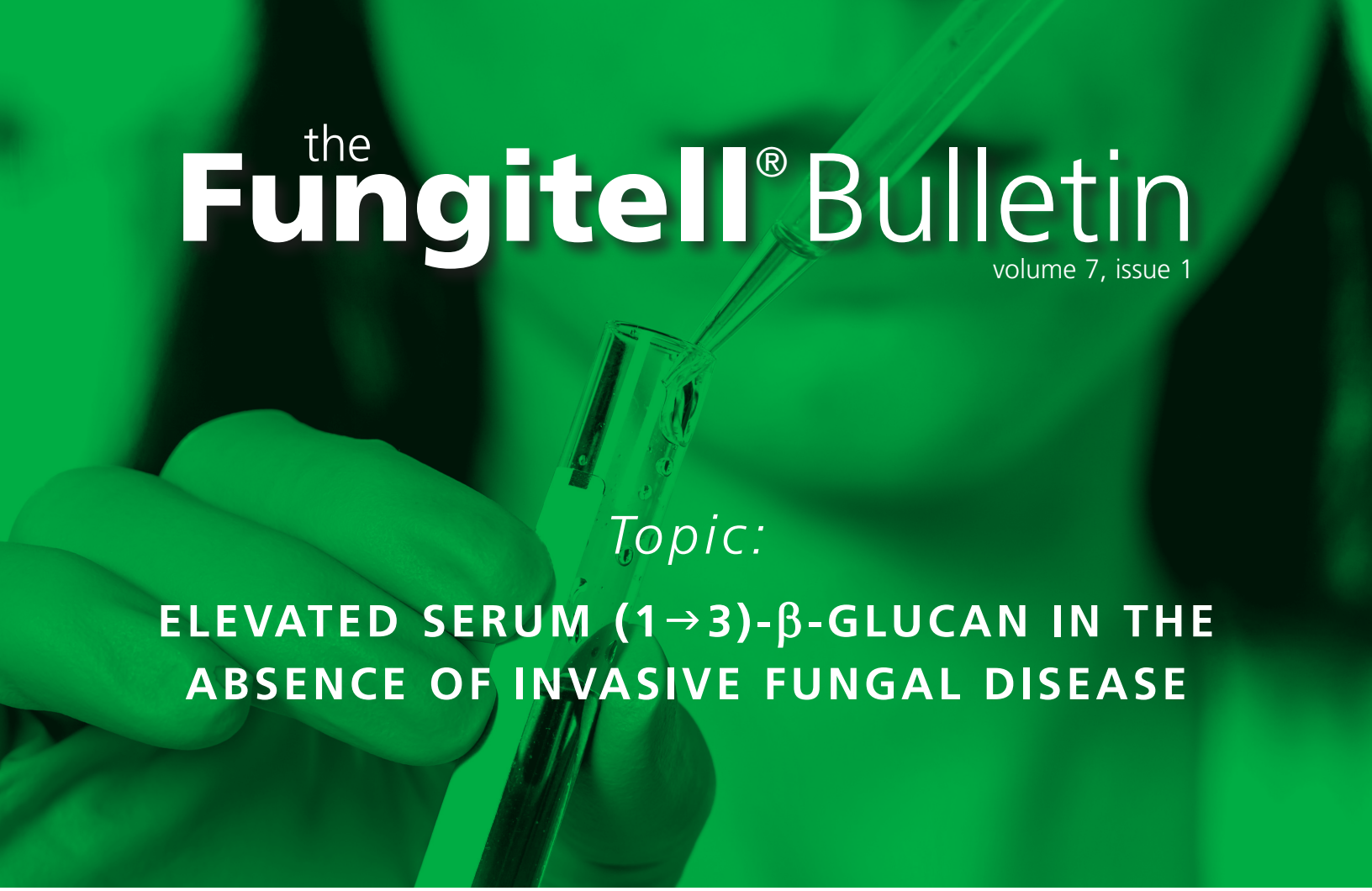

# the Fungitell® Bulletin

volume 7, issue 1

*Topic:*

## ELEVATED SERUM (1→3)-β-GLUCAN IN THE ABSENCE OF INVASIVE FUNGAL DISEASE

### 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[1]. 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**[2]: 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**[3]: 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**[4]: 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**[5,6]: 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**[7]: 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**[8]: 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[9], should inform the interpretation and use of serum BG titers in the diagnostic work-up for IFD.

Fungitell®
(1→3)-β-D-Glucan Assay

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## Recent Publications on Serum BG and Related Matters:

**Boch, T., Reinwald, M., Spiess, B., Liebregts, 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., Somparn, P., Issara-Amphorn, J., Tachaboon, 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 neutropenics and febrile non-neutropenics 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

*continued on page 3...*

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# ELEVATED SERUM (1→3)-β-GLUCAN IN THE ABSENCE OF INVASIVE FUNGAL DISEASE

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 β-D-Glucan Assay in the Management of Critically ill Patients with High Risk of Invasive Candidiasis: An Observational Study. Indian J Crit Care Med. 2018;22(5):364-368.** This study reported on antifungal administration management using serum (1→3)-β-glucan (BG) titers in critically ill adult patients (N=154). Three cohorts were compared: A. Confirmed invasive candidiasis; B. Alternative diagnosis or severe sepsis; and C. High *Candida* score, a positive BG, and no confirmed diagnosis of invasive candidiasis. BG titers were; Group A, N=32: 448.75 ± 88.30; Group B, N=60: 144.46 ± 82.49; and Group C, N=62; 292.90 ± 137.0 pg/mL, respectively. Antifungal administration was discontinued when BG titers were <80 pg/ml. The specificity of ruling out candidemia or invasive candidiasis was determined to be 97.8%. Antifungal drug savings associated with early discontinuation were estimated at US$2150. per patient. The mortality rate for patients with serum BG titers ≥400 pg/ml and <400 pg/ml were 54.6% and 7.5%, respectively, P <0.001.

**Panpetch, W., Somboonna, N., Bulan, D.E., Issara-Amphorn, J., Worasilchai, N., Finkelman, M., Chindamporn, A., Palaga, T., Tumwasorn, S., and Leelahavanichkul, A. Gastrointestinal Colonization of *Candida albicans* Increases Serum (1→3)-β-D-Glucan, without Candidemia, and Worsens Cecal Ligation and Puncture Sepsis in Murine Model. Shock. 2018;49(1):62-70.** *Candida* is a human intestinal commensal organism but is absent in mice. This study evaluated the impact of introduced intestinal *Candida* (gavage) on the symptoms and mortality of cecal ligation and puncture driven sepsis. Symptoms, bio-markers of inflammation, and mortality all worsened in the presence of *Candida*. Investigation of the impact of heat-killed *Candida* and heat-killed *Candida* lysate, and with each in combination with LPS, showed synergistic increases in TNF-alpha and Il-6 elicitation from macrophages in culture.

**Issara-Amphorn, J., Surawut, S., Worasilchai, N., Thim-Uam, A., Finkelman, M., Chindamporn, A., Palaga, T., Hirankarn, N., Pisitkun, P., and Leelahavanichkul, A. The Synergy of Endotoxin and (1→3)-β-D-Glucan, from Gut Translocation, Worsens Sepsis Severity in a Lupus Model of Fc Gamma Receptor IIb-Deficient Mice. J Innate Immun. 2018;10(3):189-201.** Translocation of innate immune elicitors from the intestinal tract has been implicated in the etiology of numerous disease syndromes. This study characterized serum (1→3)-β-glucan titers in lupus patients and evaluated the impact of gut leakage in a murine model of lupus. Serum beta-glucan titers were observed to be significantly higher in active lupus patients compared to those with inactive lupus. Both were higher than healthy controls. A rodent lupus model, FcδRIIb-/- mice, was used to evaluate the impact of gut permeability, induced by either dextran sulfate solution (DSS) or LPS administration, upon symptoms. Co-elevation of BG and endotoxin exposure was observed to be associated with worsened symptoms and mortality relative to wild-type mice (FcδRIIb+/+).

**Novy, E., Laithier, F.X., Machouart, M.C., Albuisson, E., Guerci, P., and Losser, M.R. Determination of 1,3-β-D-glucan in the peritoneal fluid for the diagnosis of intra-abdominal candidiasis in critically ill patients: a pilot study. Minerva Anestesiol. 2018 Jul 9. doi: 10.23736/S0375-9393.18.12619-8. [Epub ahead of print].** This study evaluated the utility of serum (1→3)-β-glucan titer in peritoneal fluid (PF) in the diagnosis of cohort which included intra-abdominal candidiasis (IAC), intra-abdominal bacterial peritonitis (N=14), and unclassified peritonitis (N=12). There were cases of IAC (N=7) and 33 peritoneal PF samples were analyzed. Median SAPS and SOFA scores were 44 [9-94] and 9 [4-15], respectively. The BG titers the IAC and non-IAC cases were 1461 (325-5,000) pg/ml and 224 (68-1357) pg/ml, respectively. A BG cutoff titer of ≤310 pg/ml gave a 100% negative predictive value.

*Fungitell® is an IVD kit cleared for the detection of serum (1→3)-β-D-glucan (BDG) as an adjunct to the diagnosis of invasive fungal disease. Descriptions of serum BDG, or BDG levels in other biological fluids, are presented as either research results or as potential explanations of diagnostic false positives in other clinical contexts and are not to be construed as recommendations for off-label use.*



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