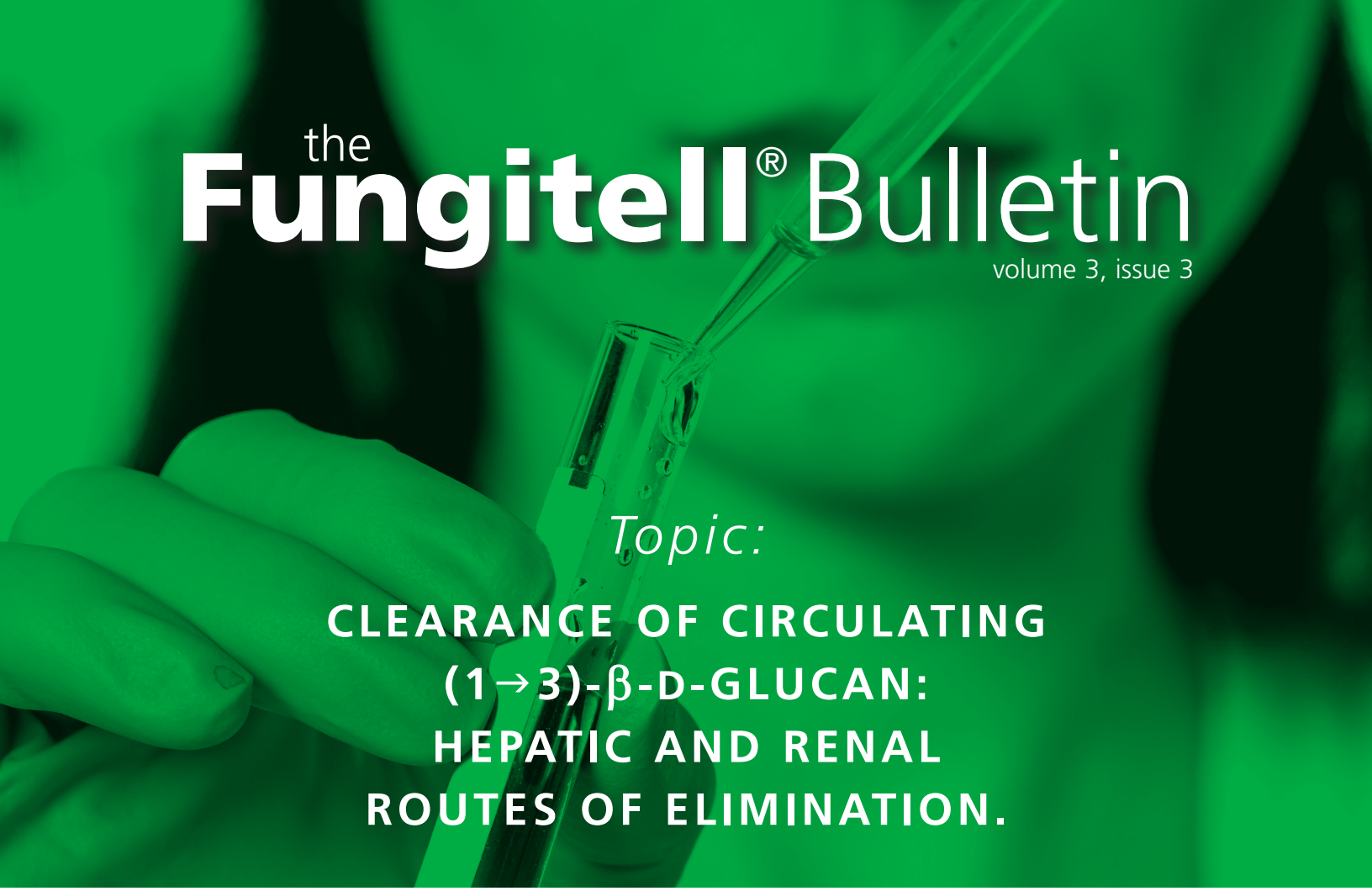
the Fungitell® Bulletin
volume 3, issue 3



Topic:

CLEARANCE OF CIRCULATING (1→3)-β-D-GLUCAN: HEPATIC AND RENAL ROUTES OF ELIMINATION.

Discussion:

(1→3)-β-D-Glucan (BG) is not natively produced by human physiology. BG can be introduced to the body in a variety of ways, including: Invasive Fungal Disease, translocation from the alimentary tract (chiefly from intestinal luminal contents) and finally, through iatrogenic contamination of the patient[1,2,3]. Additionally, there are no human-native enzymatic mechanisms for its degradation. Oxidative breakdown is hypothesized for the degradation of phagocytosed BG[4]. Once in the circulation, BG elimination is through hepatic and renal routes, with the former accounting for about 80-85% of the clearance[5]. In the liver, the clearance process begins with the phagocytic Kuppfer cells, which are macrophage lineage cells specifically adapted for function in the liver sinusoids[6]. Kuppfer cells express the Dectin-1 receptors that bind BG specifically[7]. Clearance of BG in mice and rabbits has been studied. Following intravenous administration of BG in mice at doses of 10 µg/animal and 100 µg/animal, half-lives of 6.7 hr. and 4.9 hr., respectively, were recorded[8]. In rabbits the intravascular half-life was calculated as 18 minutes for a dose of 9.3 µg/kg and 1.4 minutes for a dose of 222 µg/kg[5]. As larger half-lives are associated with larger doses, the higher doses in mice (roughly 5,000 and 500 µg/kg) may contribute to the much longer clearance times. In the rabbit, over 80% of the ^{125}I-labeled BG was found in the liver[5] and a similar proportion of intra-peritoneally injected BG was reported in the livers of mice[9]. In rabbit blood, over 97% of the ^{125}I-labeled BG was associated with the cell-free plasma[5]. In the same study, at 40 minutes post-administration, 9.7% of injected ^{125}I-labeled BG was recovered in the urine[5].

These studies suggest that the hepatic clearance is a very important elimination mechanism for BG. Thus, considerations of the adequacy of hepatic function in critically ill patients, especially those who may be candidates for transplantation, may be important in the interpretation of serum BG surveillance for invasive fungal disease.

Fungitell®
(1→3)-β-D-Glucan Assay

Bulletin Volume 3, issue 3
Publish Date: October, 2012

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Recent Publications on Serum BG and Related Matters:

Fontana, C. *et al.* (1→3)-β-D-Glucan vs. galactomannan antigen in diagnosing invasive fungal infections. Open Microbiology Journal 2012; 6: 70-73. This study compared the utility of serum galactomannan (GM) and serum beta-glucan (BG) as aids to the diagnosis of invasive fungal infection (IFI), in a series of hematological oncology patients (N=46). 18 subjects were diagnosed with probable invasive aspergillosis (IA) and 3 with proven IA. An additional 3 had proven invasive candidiasis (IC). 22 subjects were not suspected of IFI. All of the proven/probable cases of IA and IC were beta-glucan positive. 4/23 proven/probable IA were negative for GM. None of the IFI-negative cases were positive for BG while 12/22 were positive for GM. BG was positive earlier than GM in 5 of the 24 IFI cases (mean ~ 7 days) and in 2/3 of the proven IA cases GM and BG were positive on the same day. GM was never positive earlier than BG. In 22/24 patients with IFI, BG fell over the course of 4 weeks of therapy. The authors described the pros and cons of the two fungal antigen tests in clinical setting use.

Goudjil, S. *et al.* (1→3)-β-D-Glucan levels in candidiasis infections in the critically ill neonate. J. Maternal-Fetal & Neonatal Med. 2012; epub prior to publication. Doi: 10.3109/14767058.2012.722716. NICU candidal infections are a major contributor to morbidity and mortality. The authors conducted a study in neonates (mean gestational age, 28.5 weeks; mean birth weight, 1,000 gm.) with IFI (N=18) and without IFI (N=43). Serum beta-glucan (BG) was examined retrospectively. The mean serum BG was 364 pg/mL in the IFI group and 89 pg/mL in the non-IFI group. Selecting 125 pg/mL as an optimal cutoff resulted in a sensitivity of 0.84 and a specificity of 0.75. The Receiver-Operator Curve yielded an area under the curve of 0.86. Over the course of therapy, the mean BG level fell from 364 pg/mL to 58 pg/mL (range: 28-81). No differences between the serum BG levels were observed between patients with or without bacteremia.

Hanson, K.E. *et al.* β-D-glucan surveillance with preemptive anidulafungin for invasive candidiasis in intensive care unit patients: A randomized pilot study. PLoS One 2012; 7: e42282. This study evaluated the utility of guiding pre-emptive antifungal therapy by using biweekly serum (1→3)-β-D-glucan (BG) surveillance in an ICU sub-population with elevated risk for invasive fungal infection (IFI). 64 patients were enrolled. Of these, were 1 case of proven and 4 cases of probable invasive candidiasis (IC). 59/64 patients were described as having ≥3 risk factors for IC. The study evaluated several BG levels and sequential positive requirements in order to determine optimum diagnostic performance. It was determined that requiring two sequential positives of ≥80 pg/mL produced diagnostic performance as follows: Sensitivity, 100%; specificity, 75%; Positive Predictive Value, 30%; and Negative Predictive Value, 100%.

Sanada, Y. *et al.* The efficacy of measurement of serum beta-D-glucan in patients with biliary atresia. Pediatric. Surg. Int'l. 2012; Published online August. This study explored a novel application of serum (1→3)-β-D-glucan (BG) monitoring, that of being a biomarker for liver failure. This concept is based upon the critical role of the liver in the clearance of BG from the bloodstream. The study enrolled 21 pediatric end-stage-liver-disease (PELD) patients and correlated the levels of serum BG to hepatic function (PELD Score). Hepatic clearance was estimated by comparing peripheral circulation serum BG to portal vein blood at the time of liver transplant. Total clearance by the liver was estimated for each patient by difference analysis. Correlation of hepatic clearance was not significant for the entire group of patients (N=21, p=0.14)), but was quite significant for the sub-group that was recommended for liver transplant (p,0.01). The authors concluded that serum BG may be used as a non-invasive indicator of the progression of liver failure.

Tasaka, S. and Tokuda, H. *Pneumocystis jirovecii* pneumonia in non-HIV-infected patients in the era of novel immunosuppressive therapies. J. Infect. Chemother. Published on-line August. DOI 10.1007/s10156-012-02453-0. This review addressed the issue of *Pneumocystis* pneumonia (PCP) in non-HIV populations. PCP is increasing in this population for a variety of reasons and the review analyzes the biology, prevalence, morbidity and mortality, and diagnostic techniques associated with PCP. The section on serological diagnosis reviews the BG tests of several manufacturers and their performance as adjuncts in the diagnosis of PCP diagnosis

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Thompson, G.R. *et al.* Serum (1→3)-β-D-Glucan measurement in coccidioidomycosis. J. Clin. Micro. Epub ahead of print. This study examined the distribution of serum (1→3)-β-D-glucan (BG) in patients with coccidioidomycosis, one of the fungal diseases that is endemic to certain regions of the USA, particularly in the state of Arizona. 148 patients were enrolled including those with acute (N=47), past (asymptomatic, N=52), disseminated (N=45) coccidioidomycosis as well as 44 uninfected controls. Samples were tested by a reference laboratory blinded to the patients' status. Serum BG was not found to correlate with coccidiodal CF antigen antibody (IgG). Evaluation of the hospitalized patients (N=86) demonstrated the following diagnostic values: Sensitivity, 43.9%; Specificity, 91.1%; Positive Predictive Value, 81.8%; and Negative Predictive Value, 64.1%. The authors concluded that BG utility may exist in hyperacute coccidioidomycosis but much additional study is needed.

Discussion References

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