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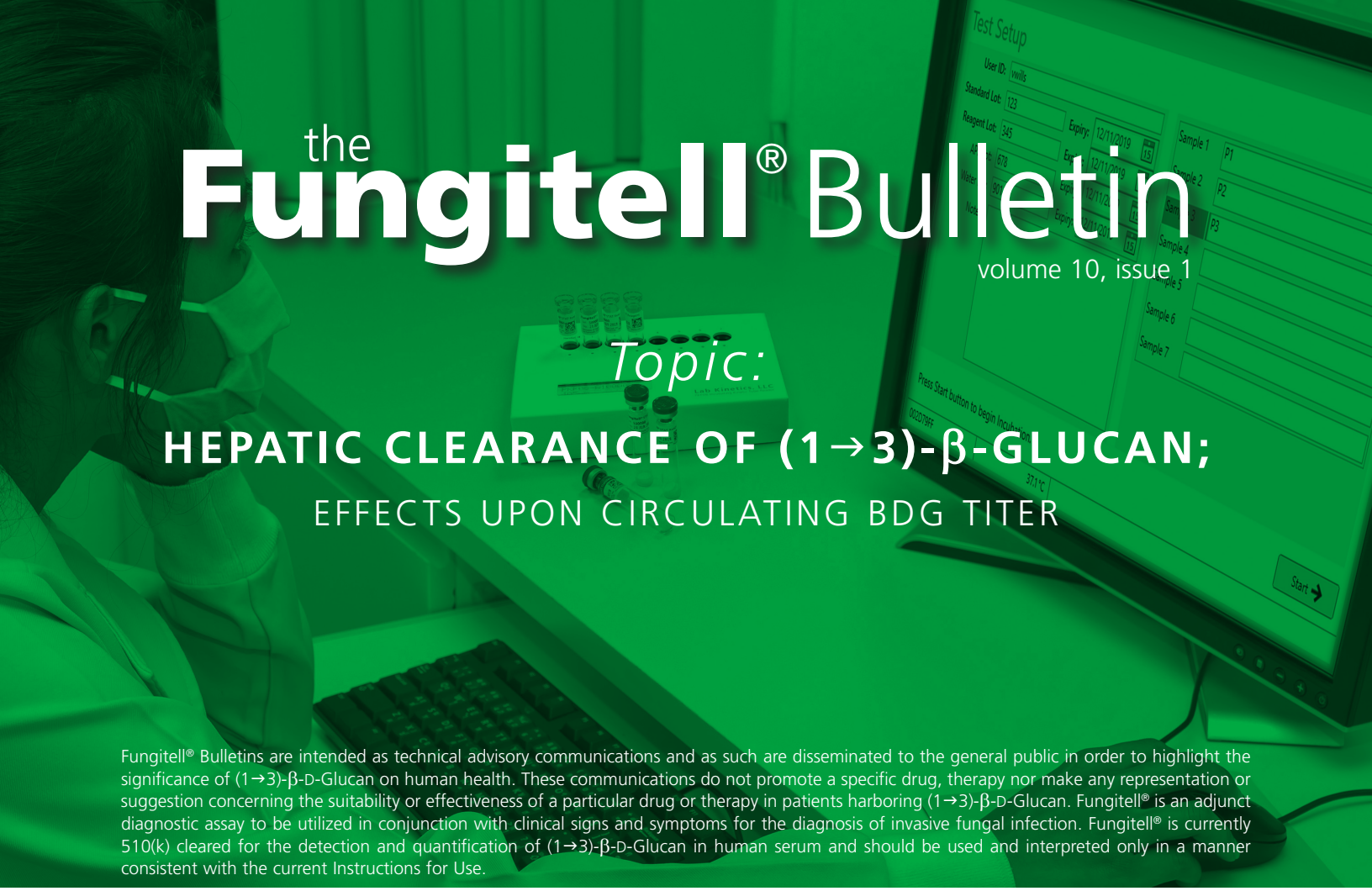

Topic:

HEPATIC CLEARANCE OF (1→3)-β-GLUCAN;

EFFECTS UPON CIRCULATING BDG TITER

Fungitell® Bulletins are intended as technical advisory communications and as such are disseminated to the general public in order to highlight the significance of (1→3)-β-D-Glucan on human health. These communications do not promote a specific drug, therapy nor make any representation or suggestion concerning the suitability or effectiveness of a particular drug or therapy in patients harboring (1→3)-β-D-Glucan. Fungitell® is an adjunct diagnostic assay to be utilized in conjunction with clinical signs and symptoms for the diagnosis of invasive fungal infection. Fungitell® is currently 510(k) cleared for the detection and quantification of (1→3)-β-D-Glucan in human serum and should be used and interpreted only in a manner consistent with the current Instructions for Use.

Discussion:

In the setting of invasive fungal disease, the (1→3)-β-Glucan (BDG) titer measured in circulating blood is a function of multiple factors. These include the fungal organism, the amount of fungal biomass or fungal burden, the anatomical site of infection, access to the circulation, and clearance efficiency (Garcia-Rubio, R. *et. al.,* 2020; Agnelli, C. *et. al.,* 2020; Liu, L. *et. al.,* 2021; Ergun, M. *et. al.,* 2021; Yan, J. *et. al.,* 2000). To date, both animal models and patient studies have demonstrated that hepatic clearance is the major route to the reduction of circulating BDG. Yoshida, M. et al (1997) measured the clearance of I^{125} -labeled *Candida albicans* BDG injected *iv* into rabbits and found rapid clearance with a circulatory half-life of 1.4 and 1.8 minutes, for high (222 μ/kg) and low (9.3 μ/kg) doses, respectively. Assessing the BDG distribution 24 hours post-injection, they also demonstrated that approximately 80% of the injected BDG was associated with the liver. Cushion, M. and Finkelman, M.A. (unpublished data) also evaluated clearance in *Pneumocystis murina*-infected mice which were injected with BDG at intervals post infection with p. *murina*. An initial hyperbolic decay of titer was observed, followed by slower clearance (Fig. 1). The presence of P. *murina* infection did not hinder BDG clearance, as the same pattern of clearance was observed at 3, 5, and 7 weeks post-infection, albeit less complete at the later timepoints.

Additional studies have shown that the binding and clearance of BDG from the circulation occurs in liver sinusoids through binding to Kuppfer cells (Yang, A.M., *et. al.,* 2017). Kuppfer cells are resident macrophages of the liver and bear Dectin-1 and Complement Receptor-3, both BDG binding receptors. Thus, with each transit of the liver, the blood has some of its BDG burden bound and removed from the circulation. In normal physiological status, this will lead to a steady state in the 10-40 pg/mL range for most individuals. In the circumstance of invasive fungal disease, this removal process may be overwhelmed leading to increased circulating BDG burdens (Miura,N. N. *et. al.,* 1996).

Fungitell®
(1→3)-β-D-Glucan Assay
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HEPATIC CLEARANCE OF (1→3)-β-GLUCAN; EFFECTS UPON CIRCULATING BDG TITER

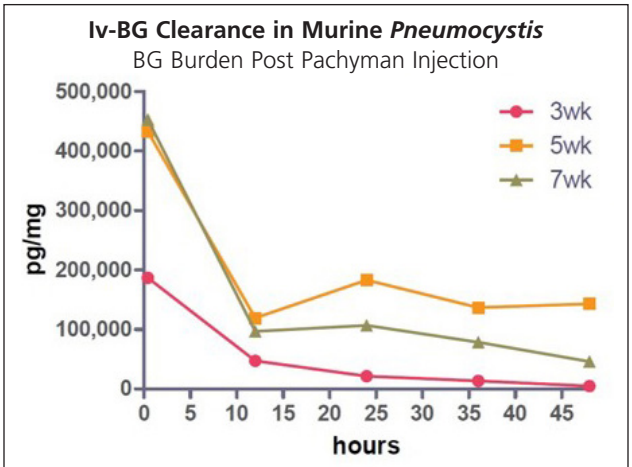
In the circumstance of pulmonary invasive fungal disease, the translocation of BDG to the pulmonary circulation and subsequently to the heart results in the distribution of BDG-enriched blood to the peripheral circulation absent hepatic filtration. This may be a factor leading to the much higher peripheral blood BDG titers observed in pneumocystosis, relative to most other invasive fungal disease conditions (Costa, J.M., 2012).

Liver disease can result in decreased BDG clearance and higher peripheral blood BDG titers. Sanada, Y. *et. al.,* (2012) evaluated serum BDG titers in pediatric liver failure patients, pre- and post-hepatic transit, by sampling from the portal vein and the peripheral circulation. They observed significantly higher BDG titer in the portal circulation compared to the peripheral blood, illustrating hepatic clearance. They also observed a negative correlation of PELD Score and BDG clearance, indicative of a reduction in hepatic clearance function. In a follow-up study of 20 patients indicated for liver transplant (Sanada, Y. *et. al.,* 2014), similarly higher portal BDG burden was observed compared to the peripheral circulation ($P<0.001$). The median post-hepatic BDG clearance was 87.9%. It is important to note that in liver transplantation, early post-operative BDG titer may be difficult to interpret, due to the significant opportunity for patient contamination associated with the extensive intra-cavity use of gauze and surgical sponges (Levesque, E. *et. al.,* 2015). These commonly used materials are observed to leach very large amounts of BDG which can result in elevated circulating BDG titers (Styczynski *et. al.,* 2018).

The timing of post-operative circulating BDG titer observations in fungal infection diagnosis in the setting of liver transplantation is also of significance. Yamanouchi, K. *et. al.,* (2011) observed that 47.2% of living donor transplant recipients had elevated serum BDG in the first five days post-transplant. The overall mortality rate of those with elevated versus non-elevated serum BDG was not different. However, the mortality rate of those with elevated BDG at ≥ 15 days post-transplant was 33.3% compared to 4.3% for those with high serum BDG at < 15 days. The later elevated BDG was felt to be associated with invasive fungal infection as opposed to potential contamination during surgery. Early high BDG values that exceeded cutoff thresholds were considered, potentially, to be the result of both surgical materials contamination and delayed transplanted liver clearance function restoration.

As indicated above, the interpretation of circulating BDG titers in the setting of suspected invasive fungal disease requires a thorough understanding of the multiple host, clinical, and mycological factors which can assist the diagnostic process. In this context, attention to hepatic function is important.

Figure 1.



Cushion, M. & Finkelman, M. Unpublished

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