Topic:

Elevated Serum (1→3)-β-D-Glucan:

Potential Role of Enteropathogenic Bacteria and Gut Epithelial Barrier Impairment

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Discussion:

Elevated serum (1→3)-β-D-glucan (BG) is thought to be caused by one of three mechanisms: a) Invasive fungal infection (IFI); b) Iatrogenic patient contamination; c) Translocation of intestinal luminal contents due to intestinal barrier impairment. In the absence of other clinical and/or laboratory data supportive of invasive fungal infection, BG positivity is normally characterized as a diagnostic false positive. However, an impaired intestinal barrier has been shown to represent a significant risk factor for IFI.[1] This is in addition to permitting an influx of inflammatory intestinal luminal material into the bloodstream.[2] In recent years the role of an impaired intestinal barrier has focused upon the degradation of tight junctions between enterocytes and the potentiation of molecular infiltration by paracellular translocation.[3,4] Similarly, inflammatory hypoxia has been implicated in the potentiation of trans-epithelial translocation by bacteria.[5] The role of enteropathogenic bacteria in the phenomenon known as "leaky gut" has been investigated and additional mechanisms leading to "leaky gut" have been elucidated. These mechanisms may explain the association of elevated serum BG with certain enteropathogenic bacteremias. For example, multiple studies have shown an association between infections with *Enteroccocus faecalis* and *E. faecium* and elevated serum BG.[6,7,8] Held *et al.* (2011) demonstrated that the median level of serum BG in all bacteremic patients was 17 pg/mL.[6] In cases of *Enterococcus* bacteremia the median level was 135 pg/mL. Similarly, Menon *et al.* (2007)[8] reported on 5 cases of *Enterococcus* bacteremia with serum BG values greater than 80 pg/mL, which is the cut-off level for IFI positivity with the Fungitell® test.[9] Enteropathogenic *Enterococci* expressing the gelE gene are known to secrete a gelatinase that degrades the intestinal barrier.[10] Recently, Bucker *et al.* (2014) have described intestinal mucosal pathology produced by an enteropathogenic strain of *E. coli* that produces an alpha-hemolysin.[11] Strikingly, infection in a murine model with the hemolysin-producing strain resulted in lesions in the colon mucosa with areas ranging from 2,000 – 50,000 μ^2. With this degree of barrier damage, translocation of gut luminal materials to sub-epithelia tissues can include particulates such as whole microorganisms. The observations noted above suggest that, absent other evidence of IFI or identifiable iatrogenic contamination with BG, a positive serum BG may indicate a damaged intestinal mucosal barrier with an increased risk of IFI.

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Recent Publications on Serum BG and Related Matters:

Alonso, R. *et al.* Alzheimer's disease and disseminated mycoses. Eur. J. Microbiol. Infect. Dis. DOI 10.1007/s10096-013-2045-z. This study investigated the hypothesis that disseminated mycoses may play a role in the etiology of Alzheimer's disease (AD). The principal data evaluated for the AD patients (N=29) and controls (N=60) were the presence or absence of antibodies specific for six individual species of *Candida*, presence of *Candida* antigens in blood, and serum (1→3)-β-D-Glucan (BG) levels (controls; N =34). The findings indicated that 19/29 of the AD patients had antibodies against one or more *Candida* species and that all had evidence of high levels of *Candida* antigens in their blood. In addition, serum BG positivity (≥80 pg/mL) in the AD patients was 86.2% while only 8.8% of the controls were positive. The authors concluded that their findings support the potential of occult fungal infection to be a part of the etiology of AD.

Fernandez-Silva, F. *et al.* Experimental murine acremoniosis: an emerging opportunistic human infection. Med. Mycol. 2014; 52: 29-35. This study reported on the virulence of a series of *Acremonium spp*. in a murine infection model. *Acremonium spp*. Is characterized as an emerging fungal pathogen that is capable of causing disseminated infection in immunocompromised hosts and which is difficult to identify. (1→3)-β-D-Glucan and fungal load were utilized as surrogates for characterizing the virulence of the individual *Acremonium spp*. tested. They observed that all uninfected animals were negative for serum BG (54 ± 0.38 pg/mL) while infected animals were all positive (≥80 pg/mL). The level of serum BG was dependent upon the infective inoculum used and levels varied between species. The authors concluded that "BG detection could be considered a useful tool for prompt detection of disseminated infections by uncommon fungi like *Acremonium*." This study added *Sarocladium (Acromonium) kiliense* and other *Acremonium spp*. to the list of fungal pathogens that contribute to a positive serum BG burden.

Fernandez-Silva, F. *et al.* Evaluation of the efficacies of amphotericin B, posaconazole, voriconazole, and anidulafungin in a murine disseminated infection by the emerging opportunistic fungus *Sarocladium (Acremonium) kiliense* Antimicrob. Agents Chemother. 2013; 57: 6265-9. This study evaluate the efficacy of systemic anti-fungal drug therapy against *Sarocladium (Acremonium) kiliense*, an emerging fungal pathogen associated with epithelial infections in the immunocompetent and disseminated infections in the immunocompromised. Amphotericin B, posaconazole, voriconazole, and anidulafungin were tested. As judged by organ fungal load, mortality, and serum BG, the effects of the different antibiotics were modest and not-significantly different from each other. Serum BG in the uninfected controls was reported as 39.28 ± 0.42 pg/mL while that of the infected controls were reported to be in the range of 210.2 – 499.8 pg/mL.

Ostrosky-Zeichner, L. *et al.* MSG-01: A randomized, double-blind, placebo-controlled trial of caspofungin prophylaxis followed by pre-emptive therapy for invasive candidiasis in high risk adults in the critical care setting. Clin. Infect. Dis. On-line publication: February 18, 2014 doi:10.1093/cid/ciu074. This multi-center (N=15) study compared the efficacy of prophylaxis with caspofungin, an antifungal drug, to placebo and pre-emptive therapy in the of intensive care unit patients at high risk for invasive fungal infection (IFI). Real-time serum (1→3)-β-D-Glucan surveillance testing was performed in order to provide BG-directed pre-emptive therapy. 219 patients were evaluated using the pre-emptive approach along with 186 prophylaxis controls. The incidence of proven invasive candidiasis (IC) was 0.9 % for the caspofungin prophylaxis arm and 6.9% for the placebo arm (p=0.02). 7/8 (87.5%) of proven IC had ≥ 1 positive BG. Probable cases had to have two positive BG values plus signs and symptoms. Mean BG (+Standard Deviation) values were 88.1 (+114.1) pg/mL for no IC; 402.1 (+730.5) pg/mL for probable IC; and 296.6 (+194.3) pg/mL for probable IC. The authors opined that "the cases of IC based on BG positivity were diagnosed earlier than expected from previous studies."

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