Topic:

Bacterial producers of (1→3)-β-D-Glucan (BG): Clinically relevant sources and physiological role of BG.

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Discussion:

A small number of papers have addressed the issue of BG derived from bacterial sources and its potential to confound serum BG-assisted diagnosis of invasive fungal disease (IFD). In recent years, strains of *Pseudomonas aeruginosa* have been described by Dutch investigators as being able to synthesize BG and to cause elevated serum levels[1]. The same study reported a similar finding for a strain of *Streptococcus pneumonia*. BG production in certain bacteria has been observed at the level of extra-cellular polysaccharide[2] (EPS) and in the periplasmic space where it is termed osmoregulatory periplasmic glucan (OPG)[3]. The OPGs are typically cyclic polymers comprised of 12-16 glucose units linked by either (1→3)-β or (1→2)-β linkages.[4] With the above-listed notable exceptions, the majority of bacterial strains which produce BG are not usually pathogenic. The bacteria reported to produce BG in their EPS include the following: *Alcaligenes faecalis var. myxogenes, Agrobacterium spp., Rhizobium japonicum,* and *S. pneumoniae* Type 37. Certain probiotic microorganisms have also been characterized as producing BG including strains of *Lactobacillus plantarum* and *Pediococcus parvulus*[5]. Biological roles for these BGs vary. The phosphoglycerol-substituted extracellular cyclic BG of P. aeruginosa has been implicated in aminoglycoside antibiotic resistance.[6] It has also been determined that micafungin, one of the echinocandin class of antifungal antibiotics, can inhibit the formation of biofilm in some strains of *P. aeruginosa*.[7]

While the potential for a narrow spectrum of pathogenic bacteria to provide positive serum burdens of BG appears to exist, published data to date is decidedly mixed. Recently Held *et. al.* presented data evaluating the serum BG levels of 100 bacteremic patients. In this report, the specificity of BG testing for bacteremics was 81.0% and the average serum BG burden for bacteremic and non-bacteremic patients was 17 pg/mL and 21 pg/mL, respectively.[8] Metan and co-workers examined the potential for bacteremia-induced false positives in 83 episodes of bacteremia in 71 patients.[9] Fourteen of the patients had serum BG values that were positive. Detailed investigation revealed that 13 of 14 patients met EORTC-MSG criteria (2008) of proven (2), probable (4), or possible (7) invasive fungal

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disease (IFD). In the single patient that was not suspected of having IFD, the serum BG value was 126 pg/mL and the next day's sample tested at 26 pg/mL, suggesting a possible non-IFD source of the positivity. The authors concluded that a careful analysis of host and clinical factors were required in evaluating positive serum BG in the context of bacteremia.

A very recent communication by Koya *et. al.* presents data indicating that 6 of a series of 47 *P. aeruginosa* bacteremia patients presented elevated serum BG levels.[10] Interestingly, a preliminary finding showed a pattern of rising pro-calcitonin levels preceding rising BG levels in the case of fungal infection whereas the respective levels rise more or less simultaneously in the case of *P. aeruginosa* infection. Although the data are preliminary and observed in a small number of patients, the authors suggest that this pattern might allow fungal infection to be distinguished from *P. aeruginosa* infection where longitudinal levels of both BG and procalcitonin are available.

The above-described information suggests that cases of bacteria-related beta glucanemia do occur but their numbers are low. Additional studies are needed to characterize the occurrence frequency and to determine how best to differentiate these from beta-glucan elevation due to invasive fungal disease."

Recent Publications on Serum BG and Related Matters:

Dellinger, R.P. *et. al.*, Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Intensive Care Med. 2013; 39:165-228. This is the report of a consensus committee of 68 international experts tasked with evaluating the published evidence concerning various approaches to the diagnosis and therapy of severe sepsis and septic shock. In the category of diagnosis, a grade 2B recommendation is made for the use of (1→3)-β-D-glucan testing where the differential diagnosis included invasive candidiasis. The article discussed the utility of rapid antigen and antibody tests over slower standard methods such as culture.

Tissot, F. *et. al.*, Beta-Glucan antigenemia anticipates diagnosis of blood culture-negative intra-abdominal candidiasis. Am. J. Resp. Crit. Care. Med. 2013 Jun 19. [Epub ahead of print]. This study evaluated the utility of BG antigenemia in the diagnosis of intra-abdominal candidiasis (IAC). Of 89 enrolled patients, 29 had IAC. 27/29 were blood culture negative. The sensitivity and specificity of 2 consecutive positive BG for IAC was 65% and 78%, respectively. BG was reported to anticipate IAC diagnosis by 5 days and antifungal therapy by 6 days. A cutoff of 400 pg/mL dichotomized clinical severity and death (p= 0.05).

Wood, B.R. *et. al.*, Test performance of blood beta-glucan for *Pneumocystis jirovecii* pneumonia in patients with AIDS and respiratory symptoms. AIDS 2013; 27: 967-972. Multiple studies have demonstrated the utility of BG testing in the setting of *Pneumocystis jirovecii* pneumonia (PJP or PCP (Karageorgopoulos, D.E., *et. al.* Accuracy of β-D-glucan for the diagnosis of Pneumocystis jirovecii pneumonia: a meta-analysis. Clin. Microbiol. Infect. 2013; 19: 39-49.)). This study re-analyzed data from an earlier study evaluating the performance of BG testing in AIDS patients with opportunistic infections, looking specifically at utility in AIDS patients with respiratory symptoms. In a group of 159 AIDS patients with at least one respiratory symptom, 139 had PCP. The sensitivity of BG positivity for PCP was 92.8%. Of 134 patients with a positive BG level and respiratory symptoms, 129 had PCP (positive predictive value of 96.3%). 15/25 patients not positive for BG did not have PCP (negative predictive value = 60%).The authors proposed an algorithm for the use of BG on the basis of pre-test probability of PCP in AIDS patients with respiratory symptoms.

De Pascale, G. *et. al.*, Why we should monitor (1→3)-β-D-glucan during invasive candidiasis. Just ask you opthamologist. J. Clin. Micro. 2013; 51:1645-6. The authors presented a case series in which BG levels were monitored in ICU patients with invasive candidiasis (IC). All three developed metastatic ocular candidiasis (OC) after the initial diagnosis of IC (Range: 11-35 days). BG levels were determined thrice-weekly. It was noted that after 7 days of antifungal therapy, and although catheters had been removed, cultures became negative, and clinical status was improving, BG levels remained high. A thorough search for other potential sources of fungal infection revealed OC in all three patients. The authors reported that this finding led to the cessation of anidulafungin therapy and the commencement of liposomal amphotericin B. The authors opined that a sustained high BG value might be an indicator of occult infection.

Discussion References:

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