

Topic:

# **(1→3)-β-D-Glucan and the US fungal meningitis outbreak associated with contaminated methylprednisolone acetate injections.**

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### **Discussion:**

Fungitell<sup>®</sup> is an *in vitro* diagnostic kit for the measurement of serum (1→3)-β-D-glucan (BG). The results are utilized as adjunct information in the diagnosis of invasive fungal infection. Since September of 2012, a multi-state outbreak of fungal infections, including both meningitis and paraspinal sites (injection sites), has been reported<sup>1</sup>. As of March 26, 2013, the CDC has reported a case count of 730 including 51 deaths. As of this writing, only one published report of a positive serum BG level in an at-risk patient has been reported (Lyons et al., 2013)<sup>2</sup>. In that case, a nidus of infection exterior to the spinal cord dura was observed near the injection site. It should be noted that this is the first report of a positive serum BG value associated with presumptive *Exserohilum rostratum* infection. While the majority of invasive fungal infections are caused by either *Candida* or *Aspergillus* species<sup>3</sup>, a variety of relatively rare fungal pathogens have been shown to contribute sufficient BG to the circulation to be useful in aiding diagnosis<sup>4</sup>. Additional data on patients with proven *E. rostratum* infection are awaited to allow the assessment of serum BG diagnostic utility in this national emergency.



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### Recent Publications on Serum BG and Related Matters:

**Karageorgopoulos, D.E. et al. Accuracy of  $\beta$ -D-glucan for the diagnosis of *Pneumocystis jirovecii* pneumonia; a meta-analysis. Clin. Microbiol. Infect. 2013;17(1):7-14.** The authors performed a meta-analysis of the utility of serum (1 $\rightarrow$ 3)- $\beta$ -D-glucan in the diagnostic workup for *Pneumocystis* pneumonia (PCP). Fourteen studies were analyzed which included 357 PCP cases including 1723 controls. Mean sensitivity and specificity, including 95% confidence intervals (in parentheses) were reported as 94.8% (90.8 – 97.1%) and 86.3% (81.7 – 89.9%), respectively. The area under the hierarchical summary receiver operator curve was 0.965. The authors noted that even with these very good numbers for sensitivity and specificity, in the clinic, test results needed to be evaluated in the clinical context of the individual patient.

**Tasaka, S. and Tokuda, H. Recent advances in the diagnosis of *Pneumocystis jirovecii* pneumonia in HIV-infected patients. Expert Opin Med. Diagnosis. 2013; 7: 85-97.** The authors present a review of, and recommendations for, the diagnosis of *pneumocystosis* in the HIV-positive population. They present a background on mycological aspects, prevalence, host response and clinical features and then a review of current diagnostic procedures and their utility. (1 $\rightarrow$ 3)- $\beta$ -D-glucan is covered under a section entitled "serum markers for diagnosis." Among other recommendations, the Expert Opinion section concludes that 'a combination of  $\beta$ -D-glucan and PCR should be used taking into account their usefulness and costs.'

**Vargas, S.A. et al. Near-universal prevalence of *Pneumocystis* and associated increase in mucus in the lungs of infants with sudden unexpected death. Clin. Inf. Dis. 2013; 56: 171-179.** This study examined, by PCR or immunofluorescence, the levels of *Pneumocystis* lung colonization in deceased (Sudden Infant Death Syndrome) infants (N = 128; mean age, 101 days). Prevalence was 84%, 97%, and 100% at 2, 3, and 4 months respectively. The colonization prevalence was not significantly different in infants succumbing to accidental death. The study also examined the levels of mucus (MUC5AC) and determined that elevated levels of MUC5AC were significantly associated with *Pneumocystis* colonization (p = 0.0134) and were independent of observed *Pneumocystis* burden. The authors discussed the potential role of host inflammatory responses, including elevated mucus secretion, to *Pneumocystis* colonization as a factor in infant fatality and, potentially, in other respiratory conditions such as chronic obstructive pulmonary disease and cystic fibrosis. The authors concluded that the presence of *Pneumocystis* colonization may be an important co-cause of sudden infant death syndrome.

**Mitchell, K.F. et al. Role of Matrix  $\beta$ -1,3 Glucan in Antifungal Resistance of Non-*albicans* *Candida* Biofilms. Antimicrob. Agents Chemother. 2013; 57: 1918-1920.** The mechanisms of fungal resistance to anti-fungal drugs are the subject of this investigation. The authors examined the role of (1 $\rightarrow$ 3)- $\beta$ -D-glucan in non-*albicans* *Candida* species. The authors observed

that, in the biofilms generated on a polystyrene surface, most of the fluconazole challenge was bound to the extracellular matrix and not found intracellularly or in the cell wall. Reduction of (1 $\rightarrow$ 3)- $\beta$ -D-glucan content using Zymolyase, an (1 $\rightarrow$ 3)- $\beta$ -D-glucanase-containing enzyme preparation, resulted in a large reduction in biofilm, relative to (1 $\rightarrow$ 3)- $\beta$ -D-glucanase-treated controls. Based upon the observation of an important role for biofilm matrix (1 $\rightarrow$ 3)- $\beta$ -D-glucan in drug resistance, the authors opined that targeting (1 $\rightarrow$ 3)- $\beta$ -D-glucan synthesis was an attractive target for improving the efficacy of current therapeutics.

**Fisher, BT. The Role of Biomarkers for Diagnosis of and Therapeutic Decisions Related to Invasive Aspergillosis in Children. Curr. Fungal Infect Rep. 2013;1;7(1):7-14.** This review addresses the issue of the application of fungal biomarkers in the setting of pediatric invasive aspergillosis (IA). The issues associated with the paucity of pediatric-centered data for markers such as (1 $\rightarrow$ 3)- $\beta$ -D-glucan and galactomannan are described and discussed.

**Held, J. et al. Comparison of (1 $\rightarrow$ 3)- $\beta$ -D-glucan, mannan/anti-mannan antibodies, and Cand-Tec *Candida* antigen as serum biomarkers for candidemia. J. Clin. Micro. 2013; 51:1158-1164.** This study evaluated the above-listed markers in the setting of candidemic patients (n=56). Controls consisted of patient cohorts with negative blood culture (N=100) and bacteremias (N=100). The sensitivity and specificity of (1 $\rightarrow$ 3)- $\beta$ -D-glucan testing were 87.5% and 85.5%, respectively. The area under the receiver-operator curve for (1 $\rightarrow$ 3)- $\beta$ -D-glucan was 0.925. No significant differences were observed for (1 $\rightarrow$ 3)- $\beta$ -D-glucan levels between different *Candida* species (p=0.296). Of the three types of diagnostic approaches, the best performance was observed with (1 $\rightarrow$ 3)- $\beta$ -D-glucan testing.

### Discussion References:

1. <http://www.cdc.gov/hai/outbreaks/meningitis-map-large.html>
2. Jennifer L. Lyons MD, Karen L. Roos MD, Kieran A. Marr MD, Henry Neumann MD, Julie B. Trivedi MD, Dorlan J. Kimbrough MD, Lisa Steiner PA-C, Kiran T. Thakur MD, Daniel M. Harrison MD, and Sean X. Zhang MD, PhD. Cerebrospinal fluid (1 $\rightarrow$ 3)- $\beta$ -D-glucan detection as an aid to diagnose iatrogenic fungal meningitis. JCM Accepts, published online ahead of print on 30 January 2013. J. Clin. Microbiol. doi:10.1128/JCM.00061-13
3. Azie N, Neofytos D, Pfaller M, Meier-Kriesche HU, Quan SP, Horn D. The PATH (Prospective Antifungal Therapy) Alliance® registry and invasive fungal infections: update 2012. Diagn Microbiol Infect Dis. 2012;73:293-300.
4. Cuétara MS, Alhambra A, Moragues MD, González-Elorza E, Pontón J, del Palacio A. Detection of (1 $\rightarrow$ 3)-beta-D-glucan as an adjunct to diagnosis in a mixed population with uncommon proven invasive fungal diseases or with an unusual clinical presentation. Clin Vaccine Immunol. 2009;16:423-6.



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