Topic:

(1→3)-β-D-Glucan measurement in non-serum matrices.

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Discussion:

Invasive fungal disease is a widespread problem in a number of clinical contexts, including immunosuppression, gastrointestinal surgery with complications, long term intensive care, and parenteral feeding. Improved methods to assist with diagnosis have been sought and Fungitell® a (1→3)-β-D-glucan measurement kit, was introduced by Associates of Cape Cod, Inc. to address this need.

The measurement of serum levels of (1→3)-β-D-glucan using Fungitell has been widely documented as aiding both the detection of invasive fungal disease and in providing support for its absence[1]. In the latter, the high negative predictive value (NPV) of the test is used to help rule out the presence of fungal infection. Since the test's inception, there has been interest in assessing the (1→3)-β-D-glucan levels in physiological fluids other than serum[2,3,4,5,] which is the validated matrix for the Fungitell kit, and the only one listed in the Instructions For Use. These fluids include blood plasma, broncho-alveolar lavage fluid (BALF), urine, cerebrospinal fluid, and tissue extracts. While analytically feasible, the results obtained using these matrices suffer from the absence of validated reference ranges for interpretation. Recently, there has been interest in the analysis of fungal antigens in BALF[6,7]. The drawbacks of using this matrix include the highly variable methods used to perform the procedure, the potential for the lavage fluid to be contaminated, the variability of the volumes infused and recovered, the possibility of pushing airway colonizing fungi into the lungs with the bronchoscope, the possibility of contaminating the bronchoscope with (1→3)-β-D-glucan from gauze or surgical sponges used to wipe or cover the bronchoscope, and the possibility that the section of lung evaluated may not be representative of the potentially infected lung. In spite of these concerns, there is still much enthusiasm among clinical investigators to assess the utility of (1→3)-β-D-glucan in BALF for invasive fungal disease work-ups. While testing in these matrices is an appropriate subject for research studies, in the absence of analytical validation and reference ranges results from such studies should not be used in the support of clinical diagnoses.

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Recent Publication:

Sax, P.E. *et al.* Blood (1→3)-β-D-glucan as a Diagnostic Test for HIV-Related *Pneumocystis jirovecii* Pneumonia. Clin. Inf. Dis. 2011;53:197–202.

This study evaluated the potential of serum (1→3)-β-D-D-glucan in the diagnosis of *Pneumocystis jirovecii* pneumonia (PCP) in HIV+ subjects. Of 282 subjects in the study cohort, 252 had evaluable serum beta-glucan. 173 of these had a clinical diagnosis of PCP. The median beta glucan level in individuals with PCP was 408 pg/mL (under-estimated as values higher than 500 pg/mL, which is the upper limit of the standard curve, were reported as 500 pg/mL). The median serum beta-glucan of those without PCP was 37 pg/mL. The sensitivity and specificity of the beta-glucan test for PCP were 92% and 65%, respectively. The study concluded that serum beta-glucan was strongly correlated with PCP and that the test might reduce the need for bronchoscopy and empirical therapy of PCP.

Shupp, J.W. *et al.* Early serum (1→3)-β-D-glucan levels in patients with burn injury. Mycoses 2011 Published on-line July 19 DOI: 10.1111/j. 1439-0507.2011.02068.x.

The potential of (1→3)-β-D-glucan leached from medical gauze used to dress severe burns was evaluated in this study. Severely burned patients (N = 18) were enrolled and were sampled immediately prior to dressing application and 12 hours post-application. Positive serum beta-glucan levels were recorded in 1/5 patients with <20% total burn surface area (TBSA) and in 10/13 patients with > 20% TBSA. No beta-glucan positivity was recorded in the non-burned trauma patients who served as controls. In the burned patients, mean levels of serum beta-glucan declined during the 12 hours after dressing application. The study found that the serum beta-glucan correlated with the TBSA and not the exposure to gauze. The possibility that the breakdown in gut mucosal integrity associated with severe thermal injury could be a factor in the elevated serum beta-glucan levels was discussed.

Marchetti, O. *et al* ECIL recommendations for the use of biologicalmarkers for the diagnosis of invasive fungal diseases in leukemic patients and hematopoietic SCT recipients. Bone Marrow Transplant. 2011 Sep 19. doi: 10.1038/bmt.2011.178. [Epub ahead of print].

The European Committee for Infections in Leukemia have presented the results of their evaluation of the use of bio-markers as aids in the diagnosis of invasive fungal infection in leukemia and stem cell transplant patients. The biomarkers evaluated include (1→3)-β-D-D-glucan. Serum beta-glucan testing was given a B-II recommendation for the diagnosis of invasive candidiasis.

Mackay, C.A. *et al.* Serum (1→3)-β-D-glucan assay in the diagnosis of invasive fungal disease in neonates. Pediatric Reports 2011; v3:e14.

Invasive fungal disease is a significant problem in neonates. This multi-center, prospective study evaluated the utility of the beta-glucan assay in 72 neonates with clinically suspected late onset (>72 hours post-birth) sepsis who were at risk of fungemia. The diagnostic performance relative to clinically defined fungemia were, for a cutoff of 80 pg/mL: Sensitivity, 70.7%; specificity, 77.4%; positive predictive value, 80.6%; and negative predictive value, 66.7%. A receiver-operator analysis gave an area under the curve of 0.753. The authors concluded that the (1→3)-β-D-glucan test is a useful adjunct in the diagnosis of fungemia in neonates.

Chowdhary, A. *et al.* *Bipolaris hawaiiensis* as etiologic agent of allergic bronchopulmonary mycosis: first case in a paediatric patient. Med Mycol. 2011 Oct;49(7):760-5. Epub 2011 Mar 14.

This study reports an unusual case of the fungus *Bipolaris hawaiiensis* causing allergic bronchopulmonary mycosis in a pediatric patient. Direct examination, culture, and PCR of specimens retrieved from bronchoscopy permitted the identification of the organism. A serum (1→3)-β-D-glucan of 316 pg/mL offered additional evidence of invasive fungal disease. The authors emphasized the importance of clinical suspicion, as well as laboratory and clinical observations in arriving at a diagnosis in order to prevent irreversible broncho-pulmonary damage.

Other Recent Publications of Note

Hope, W. *et al.* Optimizing management of invasive mould diseases. J AntimicrobChemother 2011; 66 Suppl1:i45–53 doi:10.1093/jac/dkq441.

Posteraro, B. *et al.* Update on the laboratory diagnosis of fungal infections. Mediterranean J. of Hematol. Infect. Dis. 2011;3(1):e2011002. Epub 2011 Jan 14.

Slavin, M.A. and Chakrabarti, A. Opportunistic fungal infections in the Asia-Pacific region. Med Mycol. 2011 Sep 12. [Epub ahead of print].

de Armas Rodriguez, Y. *et al.* Pneumocystis jirovecii pneumonia in developing countries. Parasite. 2011 Aug;18(3):219-28

Discussion References

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2. Kaji, Y., Hiraoka, T., and Oshika, T. (2009) Increased level of (1,3)-beta-glucan in tear fluid of mycotic keratitis. Graefes Arch. Clin. Exp. Ophthalmol. Electronic Publication: DOI 10.1007/s00417-008-1032-z
3. Hale, T.W., Bateman, T.L., Finkelman, M.A., and Berens, P.D. (2009) The absence of Candida albicans in milk samples of women with symptoms of ductal candidiasis (2009) Breastfeeding Med. 4: 57-61.
4. Kawayama, T., Fujiki, R., Honda, J., Rikimaru, T., and Aizawa, H. (2003) High concentration of (1→3)-β-D-glucan in BAL fluid in patients with acute eosinophilic pneumonia. Chest Journal123:1302-1307.
5. Petraitiene, R., Petraitis, V., Hope, W.W., Mickiene, D., Kelaher, A.M., Murray, H.A., Mya-San, C., Hughes, J.E., Cotton, M.P., Bacher, J., and Walsh, T.J. (2008) CSF and Plasma (1→3)-β-D-glucan as surrogate markers for detection and therapeutic response of experimental hematogenous candida meningoencephalitis Antimicrobial Agents and Chemotherapy Antimicrob. Agents. Chemo. 52: 4121-4129.
6. Hage, C.A. *et al.* Antigen detection in bronchoalveolar lavage fluid for diagnosis of fungal pneumonia. Curr Opin Pulm Med. 2011 May;17(3):167-71.
7. Luong, M. *et al.* Clinical utility and prognostic value of bronchoalveolar lavage galactomannan in patients with hematologic malignancies. Diagn Microbiol Infect Dis. 2010 Oct;68(2):132-9

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