invasive
aiding the diagnosis of
fungal
disease

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Introduction:

The use of Fungitell for the detection of (1→3)-β-D-Glucan is growing. Since its 2004 clearance by the US Food and Drug administration as an *in vitro* diagnostic kit, Fungitell has been adopted as a diagnostic tool in a growing number of countries. In addition to the FDA marketing clearance, Fungitell is CE-marked and thus available in all of the European Union member states. Most recently, it was licensed for marketing by Health Canada. The interest in the utilization of Fungitell as an aid to the diagnosis of invasive fungal infection has risen to the point that major US national commercial reference laboratories are offering it in their test menus and performing the test routinely. These include Quest Diagnostics® Focus Diagnostics subsidiary (Cypress, California), ARUP Laboratories (Salt Lake City, Utah, and Viracor - IBT Laboratories, (Kansas City, Missouri). In addition, Associates of Cape Cod, Inc's Beacon Diagnostics Laboratory, which pioneered the provision of Fungitell testing in a reference laboratory setting, continues to offer the test to all US-based clinical facilities.

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Technical Points

Specificity for (1→3)-β-D-glucan: The question of the specificity of the Fungitell assay for (1→3)-β-D-glucan is often asked by those who are not familiar with the test. Studies have shown that the activation of Factor G, the (1→3)-β-D-glucan-recognition protein in the reagent is highly specific. Tanaka and co-workers described, in 1991, the Factor G activation capabilities of a variety of fungal, bacterial, and plant beta-linked polysaccharides.[1] Only the (1→3)-β-D-linked glucans were capable of efficiently activating Factor G. Some polysaccharides with different linkages that were thought to be activators were found to be contaminated with (1→3)-β-D-glucan. Digestion with highly purified and specific (1→3)-β-D-glucanase abolished the activating capability. Even (1→3)-β-D-galactan, in which the monosaccharide differs from glucose by only the orientation of the C4 hydroxyl, was a million-fold less efficient at activating Factor G.

Other sources of (1→3)-β-D-glucan: Papers have been published in which there has been a description of a positive Fungitell response in the absence of other signs of invasive fungal infection. Such responses are considered false positives. The higher the diagnostic specificity of a test, the fewer false positives it produces. Clinicians who are interpreting Fungitell test results need to be aware of factors that could introduce (1→3)-β-D-glucan into the patient's circulation, resulting in a false positive. The Fungitell Instructions For Use contains information describing potential sources of contamination. Areas of investigation to explain this include the following: Production of (1→3)-β-D-glucan by certain bacteria[2], contamination of drugs and infusions with (1→3)-β-D-glucan[3,4], leakage of intestinal contents into the bloodstream due to damage to the intestinal wall[5,6], and recent invasive exposure to medical gauze and sponges.[7] at this point, there is no clear picture of the source of these elevated levels of (1→3)-β-D-glucan (in the absence of invasive fungal infection) but this is an area of important ongoing research.

From Recent Meetings:

Advances Against Aspergillosis (February 4-10, 2010, Rome):

Koo, S. et al. Post-diagnosis kinetics of serum (1→3)-β-D-glucan in invasive aspergillosis. Poster-152. The authors evaluated the post-diagnosis levels of serum (1→3)-β-D-glucan against patient outcome. Neither initial BG levels nor rates of decline were predictive of 6 or 12 week "all cause" mortality. BG levels declined slowly in invasive aspergillosis patients even though they had a response to therapy.

Wiederhold, NP et al. (1→3)-β-D-glucan and galactomannan are detectable earlier with bronchoalveolar lavage fluid compared to serum in a guinea pig model of invasive aspergillosis. Poster-86. The study evaluated the above-mentioned bio-markers in a guinea pig model of invasive pulmonary aspergillosis. In this inhalational inoculation model system, the biomarkers were evident in the broncho-alveolar lavage fluid prior to serum. At all time points post inoculation, both bio-markers were at higher concentrations in BALF compared to serum. [Note: BALF is not a validated matrix for the measurement of (1→3)-β-D-glucan or for galactomannan.]

Focus on Fungal Infection 20 (March 3-5, 2010, New Orleans):

Chen, TK., Groncy, PK., Javahery, R.,Nagpala, P., and Walsh, TJ. Management of Aspergillus Ventriculitis: Adaptive Pharmacotherapy and Therapeutic Monitoring of (1→3)-β-D-glucan in Cerebrospinal Fluid. Poster-0025 The authors described a pediatric case of central nervous system mycosis in the context of treatment for a brain malignancy. (1→3)-β-D-glucan monitoring of the cerebrospinal fluid (CSF) was utilized in the management of this case. The CSF levels of (1→3)-β-D-glucan were observed to decline from a high of 1,575 pg/mL to 575 pg/mL and the authors stated their intent to utilize CSF (1→3)-β-D-glucan levels in the continued management of the case. [Note: CSF is not a validated matrix for the measurement of (1→3)-β-D-glucan.]

European Conference on Clinical Microbiology and Infectious Diseases (April 10-13, 2010,Vienna):

Alhambra et al. Prospective diagnostic performance of the (1→3)-β-D-glucan assay in hematological patients with invasive candidiasis. Poster-856. The study reported the performance of the Fungitell assay versus EORTC-MSG 2008 criteria for proven or probable IFI in 98 patients with 181 episodes. Receiver-Operator curve analysis yielded an optimal cutoff of ≥80 pg/mL. At this cutoff, the diagnostic performance was reported as 80%, 64.52%, 10.8%, and 98.36%, respectively for sensitivity, specificity, positive predictive value, and negative predictive value. The authors concluded that the beta-glucan test can reasonably exclude invasive candidiasis in haematological patients.

Fungitell® & (1→3)-β-D-Glucan Links

- ACC Clinical: http://www.acciusa.com/clinical/index.html
- Beacon Diagnostics® Laboratory: http://www.acciusa.com/clinical/beacon/index.html
- Revised EORTC-MSG Definitions (2008): http://www.journals.uchicago.edu/doi/pdf/10.1086/588660
- Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-infected Adults and Children (NIH/CDC): http://aidsinfo.nih.gov/contentfiles/Pediatric_OI.pdf

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