invasive
aiding the diagnosis of
fungal
disease

September, 2010

the Fungitell® Bulletin

volume 1, issue 3

Introduction:

Invasive fungal disease (IFD) occurs in a variety of clinical contexts. In general, patients who are experiencing immunosuppression are at the greatest risk. The classical patient characteristics include cancer therapy, hematological malignancy, prolonged periods in intensive care units, and transplantation. The major risk factors have been reviewed by a number of investigators (Ostrosky-Zeichner *et al*., 2010). The incidence of IFD shows two peaks, one in the very young and one in the elderly (Pfaller and Diekema, 2007). The former represents the high incidence of invasive candidiasis in neonatal intensive care units (NICUs) and the latter reflects the period of immunosuppression associated with various underlying diseases and their therapy. As IFD has a high level of morbidity and mortality, it is important for physicians to identify fungal infection early when it is more effectively treated. This has generated great interest in the use of blood-borne biomarkers of IFD, including (1→3)-β-D-glucan.

A critical element of the successful application of beta-glucan in the diagnosis of fungal disease is the ability to distinguish positive results due to non-IFD related causes such as beta-glucan-rich food and the administration of beta-glucan-contaminated drugs or other therapeutics. A number of investigations have addressed this and provided useful information. Some recent publications and presentations addressing this, and other aspects of beta-glucan related diagnostic studies, are discussed below.

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Recent Publication:

Spriet *et al.* (2010) No interference of the 1,3-β-D-glucan containing nutritional supplement ImunixX with the 1,3-β-D-glucan serum test. Mycoses epub. July 19, 2010.

One area of theoretical concern in the interpretation of serum beta-glucan test results is the possible introduction of beta-glucan in nutritional supplements containing beta-glucan. The authors of this study examined serum beta-glucan levels in six healthy volunteers who ingested a beta-glucan nutritional supplement (ImmunixX) daily over a 7 day period. Group one (N=3) ingested 500 mg/day for 5 days, followed by 100 mg/day for two days. Group two ingested 100 mg/day for seven days. Sampling occurred on Day 0, pre-administration, and on Day 5 and 7, one hour post administration. Only one sample was positive, 84 pg/mL, and it occurred on Day 0, pre-administration of beta-glucan. The authors concluded that the nutritional supplement could be safely used by inpatients with an intact mucosal barrier. The results of this study mirror an earlier report (Finkelman and Lempitski, 2006) in which 8 healthy subjects ingested single dose multi-gram quantities of either Curdlan (3 grams) or Fibercel (7.5 grams) and were observed to experience no change in serum beta-glucan, compared to baseline, over an 8 hour period.

Recent Conference Information:

Krishnan et al. (2010) Kinetics of (1→3)-β-D-glucan (BG) in patients with hematological malignancies receiving voriconazole (VOR) prophylaxis. Poster M-417 Inter-Science Conference on Anti-Microbial Agents and Chemotherapy, Boston, MA.

This study evaluated the potential of the antifungal drug, voriconazole, to be associated with elevated but false positive serum beta-glucan levels. An earlier study had suggested that serum BG false positives were frequent in VOR-treated patients (Ostrosky-Zeichner, *et al*., 2008).182 samples were obtained from a group of ten patients receiving VOR prophylaxis. Six sporadic samples were observed to have confirmed BG levels above 60 pg/mL. The authors concluded that the administration of VOR is not systematically associated with false positive BG levels.

Sendid et al. (2010) Circulating (1→3)-β-D-glucans and anti-mannan antibodies as diagnostic adjuncts for *Candida* endocarditis (CE). Poster M-1073 Inter-Science Conference on Anti-Microbial Agents and Chemotherapy, Boston, MA.

This study evaluated 63 sera from 18 patients with CE (culture-proven). Controls consisted of 26 patients suspected of CE and whose valves had either bacterial endocarditis (6) or were sterile (20). BG was detected in 91% of the CE sera while mannan and anti-mannan antibodies were detected in 80%. For the controls, mannan positivity was observed in 3% (1 pt), anti-mannan in 11%, (3 pts), and BG 11% (3 pts). The authors concluded that monitoring for both BG and Mn/Anti-mannnan in at-risk patients would contribute to the diagnosis of CE.

Tissot et al. (2010) Monitoring of (1→3)-β-D-glucan in high risk surgical ICU patients for early diagnosis of Invasive Candidiasis: A prospective study of the Fungal Infection Network of Switzerland (FUNGINOS). Poster M-1071 Inter-Science Conference on Anti-Microbial Agents and Chemotherapy, Boston, MA.

This study evaluated the diagnostic utility of serum BG in a high risk patient cohort in which 37 of 106 (35%) patients developed Invasive Candidiasis (IC). Serum BG positivity was observed prior to conventional diagnosis of invasive candidiasis. For a single positive sample with a cutoff of ≥80 pg/mL (FDA-cleared cutoff), performance was: Sensitivity, 97%; specificity, 20%, efficiency, 76%. The best diagnostic yield was observed using two consecutive positive serum BG with a cutoff of ≥150 pg/mL; diagnostic performance: sensitivity 73%; specificity, 78%; efficiency, 76%. The authors concluded that two consecutive serum BG levels ≥ 150 pg/mL provided early discrimination of invasive candidiasis from colonization in high risk surgical ICU patients.

Mikulska et al. (2010) Performance of the beta-D-glucan in HSCT recipients with positive serum galactomannans. Poster M-416 Inter-Science Conference on Anti-Microbial Agents and Chemotherapy, Boston, MA.

This study evaluated the utility of serum BG testing for resolving controversial positive galactomannan-influenced diagnostic decisions concerning invasive aspergillosis (IA). The group evaluated consisted of 40 stem cell transplant (SCT) patients who had a positive galactomannan (GM) and who had received lung computed tomography scans were evaluated. 18/40 were diagnosed with probable IA and 22 without IA. 15/22 without IA had a single positive GM result and 7/22 had multiple positive GM results. Comparison of serum BG result comparison to the final diagnosis of the 40 patients showed the following: Sensitivity, 100%; specificity, 90%. The authors concluded that serum BG may be useful to confirm or exclude the presence of IA in SCT patients with a positive serum GM.

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