invasive
aiding the diagnosis of
fungal
disease

December, 2010

the Fungitell® Bulletin

volume 1, issue 4

Introduction:

Immuno-suppressed patients are at high risk of infection from a broad range of microorganisms. The risk attends not only to their in-patient treatment period, but also to the follow-up recovery period where they are at risk of community acquired infection. Fungal infections, in particular, are noted for their high mortality rates and for limited diagnostic approaches. This has been observed for infections involving a wide spectrum of pathogenic genera including Candida[1], Aspergillus[2] and Pneumocystis[3,4]. Recent research has pointed to early diagnosis and the application of appropriate therapy as being critical to reducing mortality[5,6]. Early studies using Fungitell-based surveillance have reported 8 – 10 days earlier detection of fungal infection, based upon elevated serum (1→3)-β-D-glucan, than observed conventionally[7,8,9]. The addition of elevated serum (1→3)-β-D-glucan to the differential diagnosis has allowed physicians to initiate early antifungal therapy with success[5,10]. In this installment of the Fungitell Bulletin, we will review recent progress in clinical research involving serum (1→3)-β-D-glucan measurement, fungal infection diagnosis and the relationship between post-hospitalization (1→3)-β-D-glucan levels and health outcome.

ASSOCIATES OF CAPE COD INCORPORATED
Specialists in Endotoxin and Glucan Detection

Corporate Headquarters
Associates of Cape Cod, Inc.
124 Bernard E. Saint Jean Drive,
East Falmouth, MA 02536
T (508) 540–3444
F (508) 540–8680
www.acciusa.com

UK Office
Associates of Cape Cod Int'l Inc.
Deacon Park, Moorgate Road,
Knowsley, Liverpool L33 7RX
United Kingdom
T (44) 151-547-7444
F (44) 151-547-7400

European Office
PYROQUANT DIAGNOSTIK GmbH
Opelstrasse 14,
D-64546 Morfelden-Walldorf,
Germany
T (49) 61 05-96 10 0
F (49) 61 05-96 10 15

Recent Publication:

Mohr, J. *et al.* 2010. A prospective survey of (1→3)-β-D-glucan and its relationship to invasive candidiasis in the ICU setting. J. Clin Micro. (In Press).

Invasive candidiasis (IC) is an important infection affecting patients in the intensive care setting. This study evaluated the diagnostic utility of serum (1→3)-β-D-glucan (BG) in the diagnosis of IC in the ICU (N=57). Samples were taken twice per week during the ICU stay. Key observations of this study were that post-operative serum BG levels during days 1-3 were elevated but unrelated to IC, possibly due to medical care, including surgery. Overall, on the day of IC diagnosis, the sensitivity and specificity of serum BG were 75% and 73%, respectively. In patients with proven IC the serum BG was positive 4-8 days prior to the diagnosis.

De Boer, M. *et al.* 2010. β-D-Glucan and S-adenosylmethionine serum levels for the diagnosis of Pneumocystis pneumonia in HIV-negative Patients: A prospective study. Journal of Infection (In Press).

This study evaluated the diagnostic utility of S-adenosyl methionine (Ado-Met) and serum BG in the diagnosis of *Pneumocystis* pneumonia (PCP) in a non-HIV setting. All of the patients were immuno-compromised, the majority due to solid organ transplant. 21 PCP+ and 10 PCP- subjects were enrolled. The authors reported that Ado-Met did not discriminate between patients with or without PCP while serum BG was a reliable indicator. Using a 60 pg/mL cutoff, serum BG gave a sensitivity and specificity of 90% and 89%, respectively; at 80 pg/mL these were 86% and 89%, respectively. The median serum BG level was reported as 956.9 pg/mL in the PCP+ group and 25.3 pg/mL in the controls. BAL PCR for the Pneumocystis dihydropteroate gene was performed and found to be significantly associated with the serum BG values in the PCP group.

Finkelman. M. *Pneumocystis jirovecii* infection: Cell wall (1→3)-β-D-glucan biology and diagnostic utility. Crit. Rev. Microbiol. 2010; 36: 271-281.

This is a review article covering the biology of *Pneumocystis* BG including its synthesis and role in the organism (synthesized in the cyst form only), BG's pro-inflammatory immunomodulatory role and its possible involvement in Pneumocystis pathophysiology, and the data for serum BG in the diagnosis of *Pneumocystis pneumonia*. This review also describes the nature of BG measurement using LAL-based reagent.

Acosta, J. *et al.* A prospective comparison of galactomannan in bronchoalveolar lavage fluid for the diagnosis of pulmonary invasive aspergillosis in medical patients under intensive care: Comparison with the diagnostic performance of galactomannan and of (1→3)-β-D-glucan chromogenic assay in serum samples. Clin. Microbiol. Infect. 2010; (In Press)

Acosta *et al.* have described a comparative assessment of the utility of measuring galactomannan (GM) (serum and broncho-alveolar lavage (BAL) and (1→3)-β-D-glucan (serum) in critically ill patients. Patients (N=51) had a variety of serious underlying conditions that typify large tertiary care centre critical care populations. 13/51 were diagnosed with invasive fungal disease, including 4 proven invasive aspergillosis (IA), 5 probable IA, 3 PCP, and 1 mixed fungal pneumonia (IA + PCP). For IA, BAL GM was superior to serum GM; diagnostic accuracy 0.98 and 0.85. Serum BG's accuracy was 0.815 in this group. For IA patients, 90% of the BAL GM and 80% of the serum BG were positive a mean of 4.3 days prior to positive culture.

Yamanouchi, K. *et al.* Significance of serum β-D-glucan levels in recipients of living donor liver transplantation J. Hepatobiliary Pancreat. Sci. 2010; (In Press).

The authors characterized longitudinal serum beta-glucan levels in living donor liver transplant recipients (N=100) and their association with clinically diagnosed invasive fungal infection (IFI) and mortality. They observed that 47.2% had early (≤5 days) serum BG elevations (SKK Fungitec G; cutoff ≥20 pg/mL). They observed that surgery-related factors (administered therapies, gauze) may contribute BG and, hence, false positives. Patients with high levels of BG had higher levels of positive fungal cultures (29.6%) than those without high levels (10.3%). Mortality rates during the hospitalization period were not different for patients with high or low levels of serum BG. However, patients with elevated serum BG in the post day 15 period had a mortality rate of 33.3% compared to patients who had elevated serum BG in the day 0-14 period (4.3%). Of the 25 patients with high serum BG post day 15, deceased patients had higher mean levels than survivors; 159.6 pg/mL versus 56.3 pg/mL, respectively. The authors concluded that late, high serum levels of BG after living donor liver transplant indicate fungal infection, even in the absence of positive fungal culture.

References

1. Ostrosky-Zeichner, L., Kullberg, B.J., Bow, E.J., Hadley, S., Leon, C., Nucci, M., Patterson, T.F., and Perfect, J.R. Early treatment of candidemia in adults: A review. Med. Mycol. 2010 In Press
2. Pagano, L. *et al.* Fungal infections in recipients of hematopoietic stem cell transplants: Results of the SEIFEM B-2004 stidy – Sorveglianza Epidemiologica Infezione Nelle Emopatie Maligne. Clin. Infect. Dis.2010; 45: 1161-70.
3. Miller, R.F. *et al.* Seasonal variation in mortality of *Pneumocystis jirovecii* pneumonia in HIV-infected patients. Int. J. STD AIDS. 2010; 21: 497-503
4. Su, Y.S. *et al. Pneumocystis jirovecii* pneumonia in patients with and without human immunodeficiency virus infection. J. Microbiol. Immunol. Infect. 2008; 41: 478-482.
5. Akamatsu, N. *et al.* Preemptive treatment of fungal infection based upon plasma (1→3)-β-D-glucan levels after liver transplantation. Infection. 2007; 35: 346-51.
6. Hardak, E. *et al.* Impact of PCR-based diagnosis of invasive pulmonary aspergillosis on clinical outcome. Bone Marrow Transplant 2009; 44: 595-599.
7. Odabasi, Z. *et al.* β-d-Glucan as a Diagnostic Adjunct for Invasive Fungal Infections: Validation, Cutoff Development, and Performance in Patients with Acute Myelogenous Leukemia and Myelodysplastic Syndrome. Clin. Inf. Dis. 2004; 39: 199-205.
8. Pazos, C. *et al.* Contribution of (1→3)-β-D-glucan Chromogenic Assay to Diagnosis and Therapeutic Monitoring of Invasive Aspergillosis in Neutropenic Adult Patients: a Comparison with Serial Screening for Circulating Galactomannan. 2005; 43: 299-305.
9. Pazos, C. *et al.* Contribution of (1→3)-β-D-Glucan Chromogenic Assay to Diagnosis and Therapeutic Monitoring of Invasive Aspergillosis in Neutropenic Adult Patients: a Comparison with Serial Screening for Circulating Galactomannan. Rev. Iberoam Micol. 2006; 23: 209-215.
10. Takesue, Y. *et al.* Combined assessment of beta-D-glucan and degree of *Candida* colonization before starting empiric therapy for candidiasis in surgical patients. World Surg. Journal 2004; 28: 625-630.

ASSOCIATES OF CAPE COD INCORPORATED

Specialists in Endotoxin and Glucan Detection

Corporate Headquarters
Associates of Cape Cod, Inc.
124 Bernard E. Saint Jean Drive,
East Falmouth, MA 02536
T (508) 540–3444
F (508) 540–8680
www.acciusa.com

UK Office
Associates of Cape Cod Int'l Inc.
Deacon Park, Moorgate Road,
Knowsley, Liverpool L33 7RX
United Kingdom
T (44) 151-547-7444
F (44) 151-547-7400

European Office
PYROQUANT DIAGNOSTIK GmbH
Opelstrasse 14,
D-64546 Morfelden-Walldorf,
Germany
T (49) 61 05-96 10 0
F (49) 61 05-96 10 15