Topic:

Pan-fungal screening versus genus/species targeted testing in invasive fungal disease

August, 2015

the Fungitell® Bulletin

volume 5, issue 4

Discussion:

Two related aspects of the field of invasive fungal infection are receiving increased attention. First, growing populations of at-risk individuals are associated with an increasing prevalence of invasive fungal disease (IFD).[1,2,3] Second, clinical research and antibiotic stewardship programs have demonstrated that the population of patients receiving systemic anti-fungal drugs often includes a high proportion of patients who do not have IFD.[4,5] This can be attributed to the high morbidity and mortality associated with IFD and, often, inadequate diagnostic information.[6] These considerations inform the development of various approaches to the diagnosis of IFD, including those that support withholding antifungals where they would be inappropriate. These include the evaluation of the relative merits of pan-fungal diagnostic methodologies versus those that are specific to particular genus/species targets. (1→3)-β-D-glucan (BG) is an example of a pan-fungal test with a high sensitivity and a high negative predictive value (NPV).[7,8] From a clinical strategy approach, if this test is positive, in the appropriate at-risk patient population, the clinician has laboratory support for either treating appropriately and/or continuing the investigation through the use of multiple, more targeted genus/species-specific tests and, potentially, more invasive procedures to recover specimens for examination.[9] If the BG test is negative, the high NPV offers support for withholding what would likely be inappropriate antifungal therapy, while continuing the diagnostic effort to determine the cause of the symptoms. From a laboratory resources approach, given the number of genus/species-specific tests available, using a BG test for screening offers the opportunity to reduce or eliminate multiple expensive tests in the circumstance where the BG result is negative. Conversely, where BG is positive, multiple, additional tests may then be justified in order to intensify the investigation. Recently, Prattes *et al.* described the application of the BG test in the routine clinical practice of a large tertiary care academic medical center. Guided by BG results, systemic antifungal therapy was withheld from approximately one third of the at-risk patients, none of whom progressed to IFD. Conversely, BG results increased the yield of patients requiring antifungal therapy.[10]

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 USA
T (508) 540–3444
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

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

Recent Publications on Serum BG and Related Matters:

Abe, M. *et al.* Serum (1,3)-beta-D-glucan is an inefficient marker of breakthrough candidemia. Medical Mycology, 2014; 52: 835-840. This study evaluated beta-glucan utility for candidaemia detection over a 5 year period at two Japanese tertiary care centers. The WAKO turbidimetric serum beta-glucan kit was used with a cut-off of 11 pg/mL. Serum BG testing was performed on blood draws taken at or within 7 days of blood culture draws. Of 147 candidaemia cases observed during the study period, 67 non-breakthrough and 25 breakthrough cases had serum BG examined. 44% of the breakthrough candidemia serum BG titers were below the cutoff (11.0 pg/mL) versus 19% for the non-breakthrough. The proportion of non-albicans species (92.0% in breakthrough versus 61.8% in non-breakthrough) was not considered to be a factor.

Xu, W.M. *et al.* The serum glucan level and pathological changes of antifungal treatment for lower respiratory tract infection of *Candida albicans*. Medical Mycology, 2015; 53: 153-159. The potential of serum beta-glucan titers to evaluate pulmonary candidiasis progression and antifungal therapeutic efficacy was evaluated in this pre-clinical study in rats. The authors observed a linear correlation ($p < 0.01$) between pulmonary colony count and serum beta-glucan for both micafungin-treated and saline control rats. They concluded that serum beta-glucan may be a tracking marker for micafungin therapeutic efficacy.

Worasilchai, N. *et al.* (1→3)-β-D-glucan and galactomannan testing for the diagnosis of fungal peritonitis in peritoneal dialysis patients, a pilot study. Medical Mycology, 2015; 53: 338–346. Peritoneal dialysis-associated fungal peritonitis is a serious complication. This study evaluated the beta-glucan titer of peritoneal dialysis fluid using the Fungitell® kit. Sensitivity, specificity, positive predictive value, and negative predictive value were 100%, 71%, 65%, and 100% and 100%, 83%, 76%, and 100%, for 120 pg/mL and 240 pg/mL, respectively.

Ceesay, M.M. et al. A comprehensive diagnostic approach using galactomannan, targeted β-D-glucan, baseline computerized tomography and biopsy yields a significant burden of invasive fungal disease in at risk haematology patients. Br. J. Haematol. 2015;168:219-29. This study evaluated the impact of serial serum galactomannan and targeted serum beta-glucan upon the yield of invasive fungal disease diagnoses in a broad cohort of patients with therapy-induced neutropenia. Using galactomannan alone, the IFD yield was 10.5%; for beta-glucan alone the yield was 16.3%. Combining galactomannan and beta-glucan results gave a yield of 19.6%. With all tests included (computed tomography, biopsy, etc.), the yield was 21.1%. The authors conclude that the use of a combination approach to the diagnosis of invasive fungal disease revealed a high incidence.

Desjardins, A. *et al.* Lack of 1-3-β-D-glucan detection in adults with bacteraemia. Medical Mycology, 2015; 53: 405-408. The issue of whether bacteremia is associated with elevated beta-glucan has been raised in multiple studies without definitive result. This study evaluated serum beta-glucan using the Fungitell® kit in a prospective study of consecutively recruited bacteremic patients (N=21). Seven Gram positive infections, eleven Gram-negative, and one polymicrobial infection were evaluated. Using the recommended cut-off of 80 pg/mL, all sera were found to be negative for beta-glucan.

Koncan, R. *et al.* Cross-reactivity of Nocardia spp. in the fungal (1→3)-β-D-Glucan assay performed on cerebral spinal fluid (CSF). Diag. Microbiol. Infect. Dis. 2015; 81: 94-95. This case study examined the BG reactivity of *Nocardia abscessus* recovered from a brain abscess. Fungal and bacterial cultures of CSF were negative. Multiple fungal antigens were assayed in serum and CSF. Galactomannan and cryptococcal antigen were negative in both serum and CSF., Beta-glucan was also negative in serum. However, CSF beta-glucan was positive and greater than 523 pg/mL. Analysis of multiple *in-vitro* grown species of Nocardia were examined and shown to be highly positive for beta-glucan, in contrast to the controls which were negative. The species showing beta-glucan positivity were *N. neocaledoniensis, N. abscessus, and N. cyriacigeorgica*.

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 USA
T (508) 540–3444
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

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

Discussion References:

1. Calderone, R. *et al.* Antifungal drug discovery: The process and outcomes. Future Microbiology 2014; 9: 791-805.
2. Taccone, F. *et al.* Epidemiology of invasive aspergillosis in critically ill patients: clinical presentation, underlying conditions, and outcomes. Crit. Care 2015; 19: 7. DOI 10.1186/s13054-014-0722-7.
3. Slavin, M. *et al.* Invasive infections due to filamentous fungi other than Aspergillus: epidemiology and determinants of mortality. Clin Microbiol Infect. 2015 May;21:490.e1-490.e10. DOI: 10.1016/j.cmi.2014.12.021.
4. Hoenigl, M. *et al.* Epidemiology of invasive fungal infections and rationale for antifungal therapy in patients with haematological malignancies. Mycoses. 2011;54:454-9.
5. Munoz, P. *et al.* Antifungal stewardship in daily practice and health economic implications. Mycoses, 2015, 58 (Suppl. 2), 14–25.
6. Lestner, J.M. *et al.* Systemic antifungal prescribing in neonates and children: Outcomes from the antibiotic resistance and prescribing in European children (ARPEC) study. Antimicrob. Agents Chemother. 2015; 59: 782-788.
7. Hou, T.Y., *et al.* The Screening Performance of Serum 1,3-Beta-D-Glucan in Patients with Invasive Fungal Diseases: A Meta-Analysis of Prospective Cohort Studies. PLoS One 10(7): e0131602. doi:10.1371/journal.pone.0131602
8. Held, J. *et al.* Comparison (1→3)-β-D-glucan, mannan/anti-mannan antibodies, and Cand-Tec *Candida* antigen as serum biomarkers for candidemia. J Clin Microbiol. 2013;51:1158-64.
9. Ceesay, M.M. *et al.* A comprehensive diagnostic approach using galactomannan, targeted β-D-glucan, baseline computerized tomography and biopsy yields a significant burden of invasive fungal disease in at risk haematology patients. Br. J. Haematol. 2015;168:219-29.
10. Prattes, J. *et al.* Serum 1,3-beta-d-glucan for antifungal treatment stratification at the intensive care unit and the influence of surgery. Mycoses. 2014;57:679-86

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 USA
T (508) 540–3444
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

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