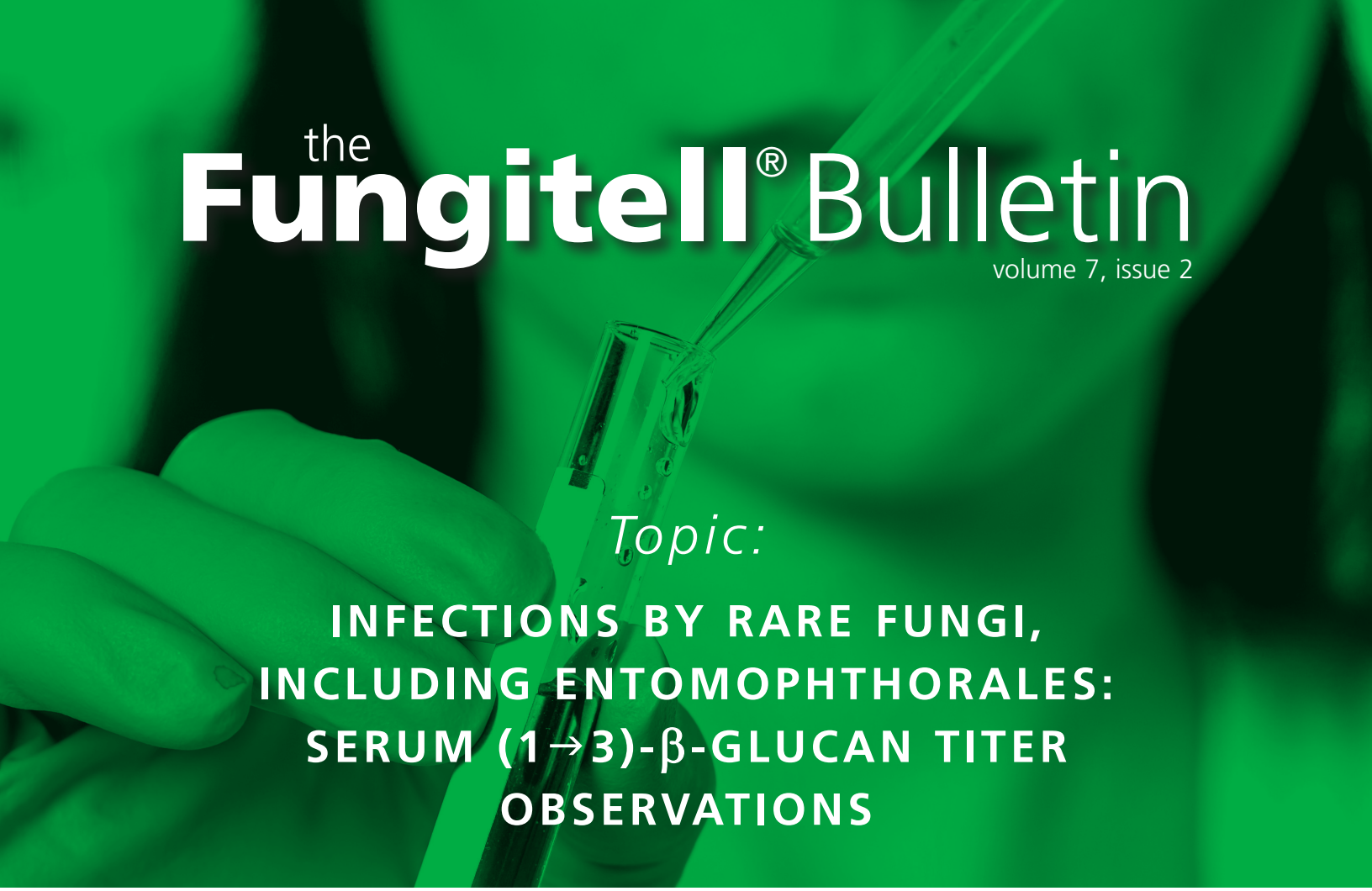
the Fungitell® Bulletin
volume 7, issue 2



Topic:

INFECTIONS BY RARE FUNGI, INCLUDING ENTOMOPHTHORALES: SERUM (1→3)-β-GLUCAN TITER OBSERVATIONS

Discussion:

Excluding the endemic fungal infections, the largest proportion of invasive fungal disease in humans is caused by a modest number of species including the genera *Candida, Aspergillus, Pneumocystis, Cryptococcus,* as well as the order Mucorales.[1,2] The full spectrum of invasive fungal disease-causing genera and species is much larger. These are termed rare or unusual fungal infections. Information concerning these is usually only found in individual case reports or reports of case series. From time to time, users of Fungitell®, the serum (1→3)-β-glucan (BG) measurement in vitro diagnostic kit, inquire about whether there are BG data for infections with rare organisms. In order to facilitate access to this information, Table 1, below, contains a compilation of rare fungi with published, as well as unpublished, reports containing BG titer data. While not comprehensive, the list provides evidence that the measurement of BG can assist in diverse, rare, and difficult to diagnose invasive fungal infections.

It is worth noting that the class *Zygomycetes*, which contains two orders, *Mucorales* and *Entomophthorales*, has been previously described as producing very low, or undetectable, levels of BG.[3] As noted in the table below, two members of the Entomophthorales, *Basidiobolus ranarum* and *Conidiobolus lamprauges*, have both been observed to produce diagnostically relevant levels of BG. Similarly, a case report (Ramirez, J. and Maguina, P. J. Burn Care Res. 2017; 38:e460-e463) observed positive serum BG in a burn patient infected with a *Conidiobolus sp.* On the other hand, a fatal *Conidiobolus incongruous* rhino-orbitocerebral infection did not provide evidence of serum BG elevation in spite of serial attempts (Wuppenhorst, N. *et. al.* JCM 2010; 48:4322-4325). Positive identification of the fungal infection was made by histological analysis of biopsy material from the ethmoid sinus. This case underscores that the interpretation of BG data in diagnosis, especially with rare or unusual molds, must be informed by host factors, clinical factors, as well as the potential influence of the site of infection and its connection to the circulation.

Fungitell®
(1→3)-β-D-Glucan Assay

Bulletin Volume 7, issue 2
Publish Date: October 2018

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

United Kingdom
Associates of Cape Cod Int'l., Inc.
Deacon Park, Moorgate Road
Knowsley, Liverpool L33 7RX
United Kingdom
Tel: (44) 151–547–7444
www.acciuk.co.uk

European Office
Associates of Cape Cod Europe GmbH
Opelstrasse 14
D-64546 Mörfelden-Walldorf, Germany
Tel: (49) 61 05–96 10 0
www.acciusa.de

INFECTIONS BY RARE FUNGI, INCLUDING ENTOMOPHTHORALES: SERUM (1→3)-β-GLUCAN TITER OBSERVATIONS

Table 1

Fungus	BG titer pg/ml	Publication Reference
Acremoniium spp	100 - >500	Fernandez-Silva *et. al.* Med. Mycol. 2013; 52: 29-35 (murine)
Alternaria infectoria	94	Cuetara, M.S. *et. al.* Clin. Vac. Immunol. 2009; 16: 423-6.
Aspergillus lentulus	>500	Alhambra, A. *et. al.* Rev. Iberoam. Micol. 2008;25: 246-249
Basidiobolus ranarum	141	Odabasi, Z. *et. al.* Med. Mycol. 2006; 44:267-72
	In vitro	
Bipolaris hawaiiensis	316	Chowdhary, A. *et. al.* Med. Mycol. 2011; 49: 760-5.
Blastoschizomyces capitatus	1313	Cuetara, M.S. *et. al.* Clin. Vac. Immunol. 2009; 16: 423-6.
Candida Kefyr	Elevated	Khan, Z. J. Mycol. Med. 2015;25:71-75
Cladosporium macrocarpum	71	Cuetara, M.S. *et. al.* Clin. Vac. Immunol. 2009; 16: 423-6.
Conidiobolus lamprauges	27	Kimura, M. *et. al.* J. Clin. Micro. 2011; 49: 752-56
	Wako test	[Possible mixed infection with *Candida*]
Fonsecaea monophora	>500	Koo, S. *et. al.* Med. Mycol. 2010; 48: 769-74.
Geotrichum capitatum	>500	Persat, F. *et. al.* J. Clin. Micro. 2008; 46: 1009-13.
Geotrichum clavatum	>500	Del Principe, M. *et. al.* 2016; Mycoses 2016;59:594-601
Lagenidium spp	>500	Finkelman, M. and Grooters, A. Unpublished, canine
Penicillium capsulatum	459	Chen, M. *et. al.* BMC Infectious Diseases 2013;13:496-500
Pythium insidiosum	80 - >500	Worasilchai, N. *et. al.* J. Clin. Micro. 2018: 56:pii: e00610-18. doi: 10.1128/JCM.00610-18
Prototheca zopfil	131	Takano, M *et. al.* J. Infect. Chemother. 2014;20(10):647-9
Scedosporium apiospermum	109-166	Cuetara, M.S. *et. al.* Clin. Vac. Immunol. 2009; 16: 423-6.
Triadelphia pulvinata	213	Ethathodu, J. *et. al.* J. Clin. Micro. 2013;51: 3426 – 29.
Trichosporon asahii	627	Odabasi, Z. *et. al.* CID. 2004; 39:199-205.
		Suzuki, K. *et. al.* Eur. J. Hematol. 2010; 84:441-7.

Discussion References:

1. Schiedel, Y. and Zimmerli, S. Common invasive fungal diseases: an overview of invasive candidiasis, aspergillosis, cryptococosis, and pneumocystis pneumonia. Swiss Med. Weekly. 2016; 146; w14281

2. Kontoyiannis, D.P., Yang, H., Song. J., Kelkar, S.S., Yang, X., Azie, N., Harrington, R., Fan. A., Lee, E., and Spalding, J.R. Prevalence, clinical and economic burden of mucormycosis-related hospitalizations in the United States: a retrospective study. BMC Infect. Dis. 2016;16:730.

3. Odabasi. Z., Paetznick, V.L., Rodriguez, J.R., Chen, E., McGinnis, M.R., and Ostrosky-Zeichner, L. Differences in beta-glucan levels in culture supernatants of a variety of fungi. Med. Mycol. 2006;44:267-72.

Recent Publications on Serum BG and Related Topics:

Carr A., Colley, P., Berhe, M., and Nguyen, H.L. Evaluating predictors of invasive candidiasis in patients with and without candidemia on micafungin. Proc (Bayl Univ. Med. Cent.). 2018;31:30-34. This study focused upon the risk factors for invasive fungal infection that result in widespread empirical therapy. A group of 127 patients with *Candida*-positive blood cultures was compared to 134 *Candida* blood culture-negative, micafungin-prescribed patients. Non-candidemics receiving empiric micafungin were observed to have higher rates of antibiotic therapy in the previous 10 days and be on immunosuppressive drugs. (1→3)-β-glucan diagnostic performance was observed as: Sensitivity, 95.0%; specificity, 65.0%; PPV, 57.6%; NPV, 96.3%.

Hartl, B., Zeller, I., Manhart, A., Selitsch, B., Lass-Flörl, C., and Willinger, B. A Retrospective Assessment of Four Antigen Assays for the Detection of Invasive Candidiasis Among High-Risk Hospitalized Patients. Mycopathologia. 2018 Jun;183:513-519. The authors compared the diagnostic performance of Fungitell® and 3 *Candida* antigen tests: Serion *Candida* antigen, Platelia mannan, Platelia *Candida* Antigen Plus. The blood of 305 hospitalized patients were tested with Fungitell, the Platelia, and the Serion kits while 289 were tested with the Platelia Plus kit. Nine patients were proven cases and the rest were diagnosed as probable/possible per the EORTC/MSG criteria (N=25) or no invasive candidiasis (N=271). Sensitivities for proven and proven/probable/possible were: Fungitell®, 100%/67%; Platelia, 65%/41%; Platelia Plus, 85%/39%; Serion, 52%/37%. Specificities for proven and proven/

continued on page 3...

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

United Kingdom
Associates of Cape Cod Int'l., Inc.
Deacon Park, Moorgate Road
Knowsley, Liverpool L33 7RX
United Kingdom
Tel: (44) 151–547–7444
www.acciuk.co.uk

European Office
Associates of Cape Cod Europe GmbH
Opelstrasse 14
D-64546 Mörfelden-Walldorf, Germany
Tel: (49) 61 05–96 10 0
www.acciusa.de

INFECTIONS BY RARE FUNGI, INCLUDING ENTOMOPHTHORALES: SERUM (1→3)-β-GLUCAN TITER OBSERVATIONS

probable/possible were: Fungitell®, 58%/58%; Platelia, 98%/98%; Platelia Plus, 89%/89%; Serion, 58%/58%. Negative Predicitive Value results for all of the tests were all very high. The combined use of the BG and mannan assays was recommended.

Guitard. J., Isnard, F., Tabone, M.D., Antignac, M., Brissot, E., Senghor, Y, Petit, A., Leverger, G., and Hennequin C. Usefulness of β-D-glucan for diagnosis and follow-up of invasive candidiasis in onco-haematological patients. J. Infect. 2018 May;76(5):483-488. This study evaluated the diagnostic performance of serum (1→3)-β-glucan for candidemia and chronic disseminated candidiasis (CDC) in pediatric hematological patients (N=3027; 23 candidemia, 10 probable and 1 possible CDC). The incidence rates for candidemia and chronic disseminated candidiasis were, respectively, 0.74% to 0.77% and, 0.30% to 0.4%. The level of BG found at diagnosis of candidemia was found to correlate with outcome (p= 0.022). Negative BG in CDC was observed to pre-date radiological lesion resolution by 2-6 months. The authors determined that blood culture, mannan antigen, BG, and all three in combination would result in a sensitivity of 45.4%, 66.9%, 72.7% and 90.9%, respectively.

Della Pepa, R., Cerchione, C., Pugliese, N., Colicchio, R., Salvatore, P., Sirignano, C., Soscia, E., Pagano, L., Sanguinetti, M., Pane, F., and Picardi, M. Diagnostic-driven antifungal approach in neutropenic patients at high risk for chronic disseminated candidiasis: preliminary observations on the role of (1→3)-β-D-glucan antigenemia and multiphasic contrast-enhanced computed tomography. Support Care Cancer. 2018 Jun;26(6):1691-1694. The authors provide a case report citing BG measurement, with Fungitell®, in a diagnostic-driven approach to the use of pre-emptive antifungal therapy in patients at high risk for chronic disseminated candidemia. The case involved an autologous stem cell transplant patient who had a complicated febrile neutropenia phase post-transplant. Resolution of complications led to discharge at day 29 post-chemotherapy, however, the patient was readmitted due to fever. BG was 500 pg/ml while cultures and other tests were negative. Following the hospital protocol, a BG positivity-driven intensive diagnostic workup was performed including contrast-enhanced computed tomography. 2-4 millimeter hypodense nodules were observed in the liver, suggestive of abscesses. Liver enzymes became elevated ten days later and biopsy and culture found *Candida albicans* infection. Liposomal Amphotericin B therapy was started and after 36 days the liver lesions were almost completely resolved. Concomitantly, serum BG levels returned to normal. In a broader case series, including this case, the authors reported a 77% reduction in antifungal therapy using a diagnostic-driven strategy.

Träger, J., Melicharm V.O., Meyer, R., Rauh, M., Bogdan, C., and Held, J. Serum (1→3)-β-D-glucan and galactomannan levels in patients with cystic fibrosis: a retrospective cohort study. BMC Pulm Med. 2018 Mar 27;18(1):52. doi: 10.1186/s12890-018-0614-8. In a study of fungal infection markers in the serum of cystic fibrosis patients (N=104), the investigators observed that both BG and galactomannan (GM) were significantly elevated in *Aspergillus*-positive patients (BG, 89 pg/ml) versus *Aspergillus*-negative (40 pg/ml) [p=0.022]. In addition, BG-positive patients had lower forced expiry volume in one second (FEV1) than BG-negative patients (61.6% vs 77.1%, p=0.0007). Multivariate analysis revealed that BG, but not GM or Aspergillus culture, was an independent predictor of FEV1.

Hammarström H., Stjärne Aspelund A., Christensson B., Heußel C.P., Isaksson J., Kondori N., Larsson L., Markowicz P., Richter J., Wennerås C., Friman V. Prospective evaluation of a combination of fungal biomarkers for the diagnosis of invasive fungal disease in high-risk haematology patients. Mycoses. 2018 Mar 25. doi: 10.1111/myc.12773. [Epub ahead of print] This study focused upon adult hematology patients (N=135). Once to twice weekly serum BG, GM, bismethyl-g; iotoxin, and urinary D-arabinitol were measured and their diagnostic utility evaluated. 13 proven and probable cases of invasive fungal disease were found and analyzed. In the population tested, both BG and GM were observed to have a negative predictive value (NPV) <0.9 but positive predictive value (PPV) was low. 91% of IFD patients had "patterns of consecutively positive and increasing BG levels." Bismethyl-gliotoxin was not dtected in 15 of the patients deemed to have proven, probable , or possible IFD.

Furfaro, E., Giacobbe, D.R., Del Bono, V., Signori, A., Guolo, F., Minetto, P., Clavio, M., Ballerini, F., Gobbi, M., Viscoli, C., and Mikulska, M. Performance of serum (1→3)-β-D-glucan screening for the diagnosis of invasive aspergillosis in neutropenic patients with haematological malignancies. Mycoses. 2018 Apr 25. doi: 10.1111/myc.12787. [Epub ahead of print] This report describes screeneing results with BG in a population of neutropenic hematological malignancy patients. The attack rate was 12% (20 of 167 developed invasive aspergillosis). BG sensitivity and specificity for a single positive, at a cutoff of 80 pg/ml, were 60% and 78%, respectively. For two consecutive positive results, sensitivity was 40% while specificity achieved 93%. If GM results were combined with BG, the specificity was 97%. BG was positive before GM in 33% of cases with both markers positive (N=12).

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

United Kingdom
Associates of Cape Cod Int'l., Inc.
Deacon Park, Moorgate Road
Knowsley, Liverpool L33 7RX
United Kingdom
Tel: (44) 151–547–7444
www.acciuk.co.uk

European Office
Associates of Cape Cod Europe GmbH
Opelstrasse 14
D-64546 Mörfelden-Walldorf, Germany
Tel: (49) 61 05–96 10 0
www.acciusa.de