Topic:

Update: Practice Guideline Recommendations for Serum (1→3)-β-D-glucan in the Diagnosis of Invasive Fungal Disease

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Discussion:

It has been more than 12 years since Fungitell® received FDA clearance as an in vitro diagnostic test for (1→3)-β-D-glucan, for use as an adjunct test in the diagnosis of invasive fungal disease (IFD). In that time, the number of peer-reviewed publications concerning Fungitell's diagnostic utility have risen to over a hundred. Over the years, the accumulating experience in the use of beta-glucan testing in IFD diagnosis has resulted in its inclusion discussion and/or recommendations for use appearing in numerous national and international practice guidelines that focus upon IFD diagnosis and management. For the reader's convenience, a list of these guidelines with references and or links, has been compiled and is presented in the below-listed table.

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Table 1: Invasive Fungal Disease Guidelines with (1→3)-β-D-Glucan Recommendations

Title	URL or Reference
Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America	**Clin. Infect. Dis. 2016; DOI: 10.1093/cid/civ933** http://cid.oxfordjournals.org/content/early/2015/12/15/cid.civ933.full.pdf+html
Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012	**Crit. Care Med. 2013; 41(2): 580-637** https://www.sccm.org/Documents/SSC-Guidelines.pdf
An Italian consensus for invasive candidiasis management (ITALIC)	**Infection.** 2014;42:263-79
Clinical practice guidelines for the treatment of invasive *Aspergillus* infections in adults in the Middle East region: Expert panel recommendations	**J Infect. Public Health. 2014; 7:20-31** http://www.jiph.org/article/S1876-0341(13)00106-8/pdf
Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer; 201 Update by the Infectious Diseases Society of America	**Clin. Infect. Dis. 2011;52(4):e56–e93** http://cid.oxfordjournals.org/content/52/4/e56.full.pdf+html
Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group	**Clin. Infect. Dis. 2008;46;1812-21** http://cid.oxfordjournals.org/content/46/12/1813.full.pdf+html?sid=dd65b8f1-be4a-4554-94a5-214788d81a7d
HIV-Exposed and HIV-Infected Children: Recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2821196/
Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America	**Clin. Infect. Dis. 2008; 46:327–60** http://cid.oxfordjournals.org/content/46/3/327.1.full.pdf+html
Diagnosis and antimicrobial therapy of lung infiltrates in febrile neutropenic patients (allogeneic SCT excluded): updated guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO)	**Annals of Oncology 2015;26: 21–33** http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4269340/pdf/mdu192.pdf
Diagnosis of invasive fungal infections in hematology and oncology--guidelines from the Infectious Diseases Working Party in Haematology and Oncology of the German Society for Haematology and Oncology (AGIHO)	**Ann. Oncol. 2012:823-33.** http://annonc.oxfordjournals.org/content/23/4/823.full.pdf+html
β-Glucan antigenemia assay for the diagnosis of invasive fungal infections in patients with hematological malignancies: a systematic review and meta-analysis of cohort studies from the Third European Conference on Infections in Leukemia (ECIL-3)	**Clin. Infect. Dis. 2012;54:633-43.** http://cid.oxfordjournals.org/content/54/5/633.full.pdf+html
Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America	**Clin. Infect. Dis. 2011;52:e56-93** http://cid.oxfordjournals.org/content/52/4/e56.full.pdf+html
ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: diagnostic procedures	**Clin. Microbiol Infect. 2012; 18 (Suppl. 7): 9–18** http://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(14)60764-3/pdf
Laboratory Manual for Diagnosis of Fungal Opportunistic Infections in HIV/AIDS Patients	**WHO;2009 SEA-HLM-401** http://apps.searo.who.int/PDS_DOCS/B4416.pdf

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Recent Publications on Serum BG and Related Matters:

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. This study evaluated the utility of serum beta-glucan titer for pre-emptive therapy and antimicrobial stewardship in the clinical management of 66 ICU patients at-risk for IFD. BG titer was used to start or stop anti-fungal (AF) therapy. Initial AF therapy was begun in 40 patients and withheld in 26. Based upon serum BG, AF therapy was discontinued in 13 of the 40 receiving it and begun in 7/26 not receiving it. None of the 13 patients whose AF was discontinued progressed to develop IFD. Serum BG titers were not significantly different in patients with or without abdominal surgery.

Rhein, J. *et al.,* Detection of High Cerebrospinal Fluid Levels of (1→3)-β-D-Glucan in Cryptococcal Meningitis. Open Forum Infect. Dis. 2014; 1:ofu105. The utility of both serum and CSF BG titers in the diagnosis of cryptococcal meningitis were evaluated in a cohort of Ugandan and South African patients (N=109). The sensitivity and specificity of CSF BG titers was 89% and 85%, respectively. Serum sensitivity was 79%. CSF sensitivity increased with increasing CSF microbial burdens, achieving 98% at ≥ 10,000 CFU/ml. Baseline CSF BG titer correlated with CSF fungal burden, CSF CRAG titer, and MCP-1 protein titer. Increased 10 week mortality was observed in patients with BG titers ≥ 500 pg/ml.

Khan, Z. *et al., Candida kefyr* as a cause of bloodstream infection and adjunctive role of biomarkers in its diagnosis. J. Mycol Med. 2015; 25:71-5. This case report described the first instance of a serum BG positivity in a blood stream infection caused by *Candida kefyr*. Of the two samples tested for BG (days 14 and 21, respectively), only the second sample yielded a positive titer of 190 pg/mL.

Levesque, E. *et al.,* Contribution of (1,3)-beta-D-glucan to diagnosis of invasive candidiasis after liver transplantation. J. Clin Microbiol. 2015;53: 771-6. Liver transplant recipients are at elevated risk of IFD, experiencing rates of 5-10%. IFD in this population is associated with severely increased morbidity and mortality. This study enrolled 52 liver transplant recipients and evaluated serial serum BG titer determination for IFD diagnostic utility. In 4/52 patients, there were 6 episodes of proven (5) or probable (1) invasive candidiasis (IC). A ROC analysis indicated an AUC of 0.71 with 146 pg/mL being the titer offering the best discrimination. At 146 pg/mL, the sensitivity, specificity, PPV and NPV were 100%, 61%, 25%, and 1005, respectively. Two sequential positives increase the specificity and PPV to 87% and 45%, respectively. All patients with IC experienced declining BG titers with AF therapy.

Prattes, J. *et al.,* Reliability of serum 1,3-beta-D-glucan assay in patients undergoing renal replacement therapy: a review of the literature. Mycoses. 2015; 58:4-9. This review evaluated the potential utility of serum (1→3)-β-D-glucan measurement in the management of renal replacement therapy (RRT) patients who are, as a class, at higher risk of IFD. The authors examined the literature regarding the reliability of BG measurement in this patient class and examined the potential of the dialysis membranes used in RRT to contribute to diagnostic false positives. The strong association of un-modified and modified cellulose membranes with BG leaching and elevated patient BG titer is described. Conversely, the use of synthetic membranes is rarely associated with BG elevation in the patients' blood. Additionally, the authors summarize data on the high proportion of blood fractionation products which contain significant levels of BG, largely due to the use of depth filters in the processing of plasma. As RRT patients often receive blood fractionation products, this represents a potentially confounding variable when evaluating RRT membranes in this context.

Corrales, I. *et al.,* Detection of fungal DNA in peritoneal fluids by a PCR DNA low-density microarray system and quantitation of serum (1-3)-β-D-glucan in the diagnosis of peritoneal candidiasis. Med. Mycol. 2015; 53: 199-204. This study evaluated approaches to the diagnosis of peritoneal candidiasis. BG antigenemia was evaluated along with culture and PCR techniques. The sensitivities of PCR and culture were 93.5% and 74.2%, respectively. The sensitivity and specificity of serum BG using a cutoff of 82.6 pg/ml was 84.6% and 76%, respectively. Five patients who died due to multiple organ failure had significantly higher serum BG compared to survivors, 269.1 and 93.7 pg/ml, respectively.

Naselli, A. *et al.,* Persistence of high-level (1,3)-β-D-glucan after candidemia following autologous peripheral SCT in a pediatric patient. Bone Marrow Transplant. 2015;50:137-8. This case report describes the phenomenon of persistently elevated serum BG levels after clinical and microbiological resolution of IFD. The case involved a pediatric patient who, post-successful therapy of candidemia, demonstrated elevated serum BG for more than 80 days. The slow wash-out of BG from the patient was described and no cause was evident in the factors analyzed.

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