

Topic:

# Antifungal Drug Stewardship: Role of high negative predictive value assays in ensuring appropriate therapy.

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### Discussion:

Antimicrobial drug stewardship concerns have become increasingly prominent over the last few years<sup>1</sup>. This has been driven by factors that include antimicrobial resistance development, inappropriate therapy decisions, drug-related adverse reactions, and costs<sup>2,3,4,5</sup>. These concerns have all been raised for the antifungal subset of antimicrobials, a class in which a variety of new, lower toxicity drugs have achieved licensure, leading to greatly increased prescribing. The chief concern in inappropriate prescribing lies with the inadequacy of traditional diagnostic methods for invasive fungal disease (IFD)<sup>6</sup>. Fungal culture, the gold standard, has a relatively low sensitivity and timeliness<sup>7</sup>. Thus, a tendency toward widespread prophylaxis or empirical therapy based upon the inclusion of IFD in the differential diagnosis, has driven up antifungal use<sup>8</sup>. In 2004, Fungitell<sup>®</sup>, a (1→3)-β-D-Glucan (BG) detection assay was cleared for marketing by the US Food and Drug Administration, with an indication as an adjunct to the diagnosis of invasive fungal infection (IFI). Since that time, numerous studies of the diagnostic performance of the BG assay have described very high negative predictive values for IFD. The utilization of diagnostic negative predictive values to inform the prescribing of antifungals has the potential to play a role in antifungal stewardship and to direct diagnostic efforts more appropriately.



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### Recent Publications on Serum BG and Related Matters:

**Jajakul, S. et al., (1→3)-β-D-Glucan as a prognostic marker of treatment response in invasive candidiasis. Clin. Inf. Dis. 2012; [Epub ahead of print].**

This study evaluated the utility of serum (1→3)-β-D-glucan (BG) as a prognostic marker in invasive candidiasis being treated with anidulafungin. The overall results were that a negative serum BG titer slope correlated with therapeutic success [positive predictive value (PPV) = 90%]. A positive serum BG titer slope correlated with therapeutic failure with a negative predictive value (NPV) of 90%.

**Sims, C.R. et al., Correlation of clinical outcomes with β-glucan levels in patients with invasive candidiasis. J. Clin. Microbiol. 2012; 50:2104-2106.**

This study of patients with invasive candidiasis whose serum BG levels were monitored twice weekly observed that treatment success or failure was associated with respective decrease and increase of serum BG titers.

**Koo, S., et al., Post-diagnosis kinetics of the (1→3)-β-D-Glucan assay in invasive aspergillosis, invasive candidiasis, and *Pneumocystis jirovecii* pneumonia. Clin. Microbiol. Infect. 2012; 18:E122-127.**

This study examined the kinetics of serum BG levels in a patient population that included 69 patients with invasive aspergillosis, 40 with invasive candidiasis, and 18 with *Pneumocystis jirovecii* pneumonia. The initial serum BG value and trend were not predictive of 6 or 12 week clinical failure or mortality and the BG titers lacked prognostic value in a clinically meaningful time frame.

**Ginocchio, F. et al., Case report of the reliability of (1→3)-β-D-Glucan monitoring during the treatment of peritoneal candidiasis in a child receiving continuous peritoneal dialysis. Clin. Vacc. Immunol. 2012; 19: 626-7.**

This report described the use of serial serum and peritoneal fluid BG monitoring in a case of pediatric fungal peritonitis in the setting of peritoneal dialysis (PD). Blood sampling was performed through a central venous catheter and peritoneal fluid sampling was initially through the PD catheter and then, after its removal, by paracentesis. Therapy included fluconazole initially, followed by caspofungin. Blood and peritoneal fluid cultures were initially positive for *C. parapsilosis* and became sterile with caspofungin therapy. BG titers which were initially highly positive in both serum and peritoneal fluid, resolved to negative levels after six weeks and four days, respectively, consistent with clinical outcome success.

**Lamoth, F. et al., 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). 2012;54:633-43.**

This report describes a meta-analysis conducted on behalf of the Third European Conference on Infections in Leukemia (ECIL-3). Multiple manufacturers' BG-test kits were represented in the publications utilized. The analysis covered six published studies comprising a total of 1771 patients and 414 invasive fungal infections (IFI) diagnosed using European Organization for Research and Treatment of Cancer -Mycosis Study Group (EORTC-MSG) criteria. Key findings

were that sensitivity and specificity were better for two consecutive positive tests (sensitivity and specificity, 49.6% and 98.9%, respectively). For an IFI prevalence of 10%, the estimated positive and negative predictive values were 83.5% and 94.6%, respectively.

**Nguyen, M.H. et al., Performance of *Candida* real-time polymerase chain reaction, β-D-glucan assay, and blood cultures in the diagnosis of invasive candidiasis. Clin. Inf. Dis. Advanced Access, Mar. 19, 2012.**

The authors evaluated the performance of the three-above-listed diagnostic techniques in a cohort of hospitalized patients and controls. For invasive candidiasis (IC), either positive BG or PCR testing produced sensitivities and specificities of 95% and 56%, respectively. In IC patients with blood culture (BC) results, addition of a positive BG or BC result had a sensitivity of 79%. The paper stressed that a key finding was that combined BC and PCR or BG testing were superior to BC for the diagnosis of deep-seated candidiasis.

**Onishi, A., et al., Diagnostic accuracy of serum 1,3-β-D-glucan for *Pneumocystis jirovecii* pneumonia, invasive candidiasis, and invasive aspergillosis: Systematic review and meta-analysis. J. Clin. Microbiol. 2012; 50: 7-15.**

This meta-analysis pooled the data for 35 studies to derive pooled data for the evaluation of the diagnostic accuracy of serum BG analysis in the diagnosis of *Pneumocystis jirovecii* pneumonia. The pooled analysis data found the following: Sensitivity, 96%; specificity, 84%; Diagnostic odds ratio, 102.3; and AUC (area under curve) for a Receiver Operator Curve of 0.96. They found that, for HIV+ or HIV - status, the diagnostic accuracy was not significantly different.

### Discussion References

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