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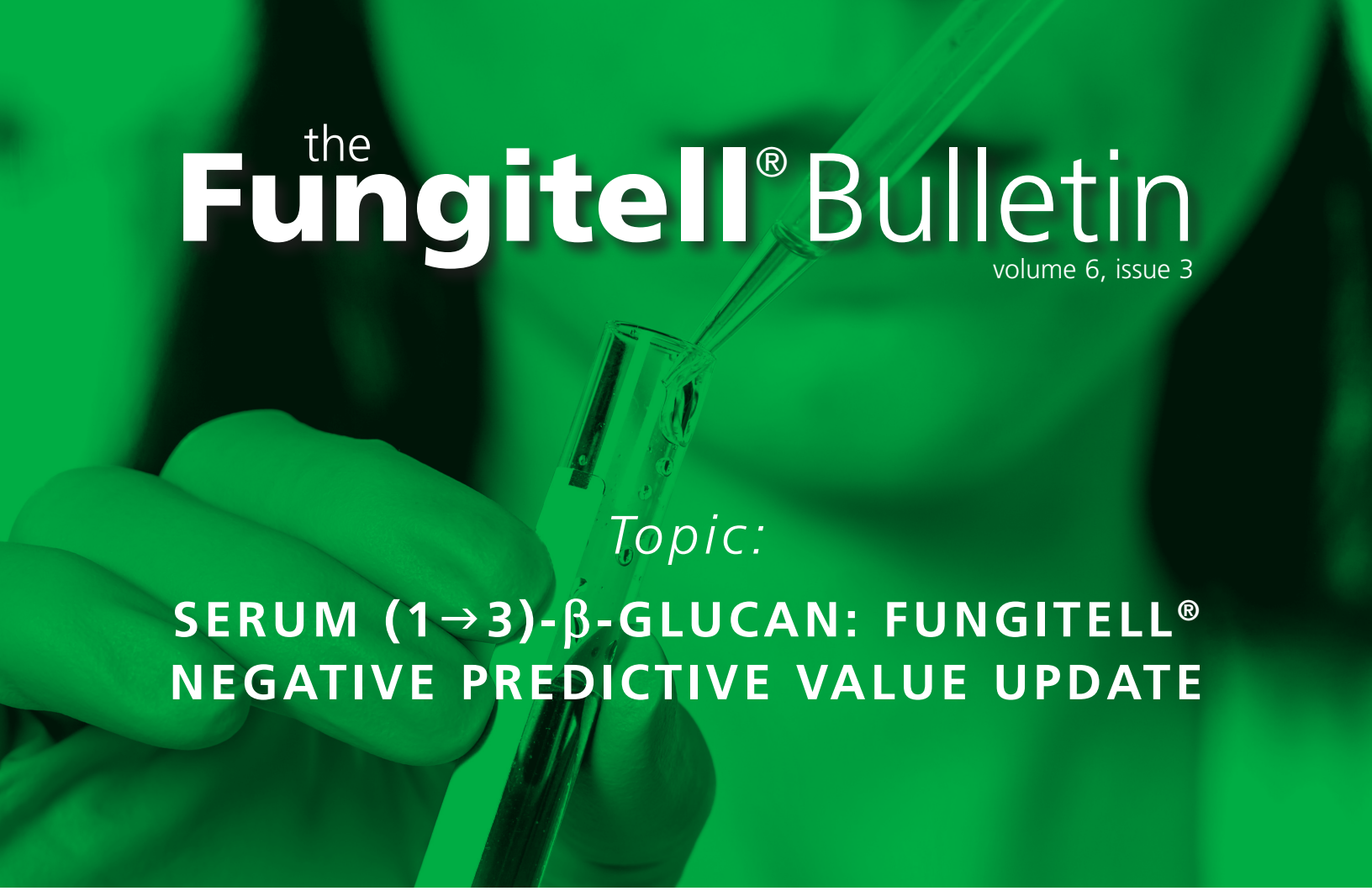

Topic:

SERUM (1→3)-β-GLUCAN: FUNGITELL® NEGATIVE PREDICTIVE VALUE UPDATE

Discussion:

Modern discussions of antimicrobial stewardship are centered on the urgent problems of both over-prescribing and inappropriate prescribing of systemic antibiotics, in the setting of uncertain infection status.[1] Both problems reflect a conservative response of clinical management to the possibility of a potentially delayed and inadequate response to life-threatening infections. These factors hold true for invasive fungal disease, where published studies have shown very significant increases in mortality in the absence of early, appropriate therapy[2,3,4]. Significantly, procedurally-directed antifungal (AF) stewardship programs have permitted considerable reductions in inappropriate AF administration, with patient safety[5]. Facile laboratory tests with high Negative Predictive Value (NPV) would help this effort immensely. NPV (True Negatives/True Negatives + False Positives) reflects the proportion of test results that truly represent the absence of the disease in the at risk patients tested. Thus, the higher the NPV, the greater the confidence of disease absence when the test is negative.

Recently, new evidence from prospective cohort studies has been published demonstrating that negative serum (1→3)-β-glucan titers can assist in the reduction of inappropriate AF administration in a variety of clinical contexts. In 2014, Prattes, J. *et. al.*, described the reduction, by 1/3, of ICU patients receiving systemic AF therapy, through the use of negative serum BG titers. Importantly, none of these patients developed invasive fungal disease[6]. Similarly, Posteraro, B. *et. al.* (2016), in a cohort of 193 critically ill patients with sepsis, were able to avoid or curtail systemic AF therapy in patients who would otherwise have received it, based upon a negative Fungitell result. The authors stated that their cost savings amounted to nearly €439,000. and no patients who did not receive antifungals died of candidemia.[7] In an analogous study, Nucci, M., *et. al.* (2016) utilized a Fungitell-based strategy to curtail empiric AF therapy in a group of 85 high risk ICU patients. 21 patients had their AF withdrawn at day 4 and none developed candidemia at Day 30.[8] Validation of this approach, in an at-risk, non-neutropenic population using a randomized approach has been described by Rouzé, A. *et. al.* (2017) who utilized a combination biomarker strategy to halt empirical antifungal therapy: Negative Fungitell and mannan/antimannan antibodies on days 0 and 4. 109 patients were enrolled. Empirical antifungal therapy was discontinued in 1/55 and 29/54, in the control and intervention groups, respectively.[9] Collectively, these studies indicate that serum BG titers may be used to assist clinical management and provide laboratory support for antifungal stewardship.

Fungitell®
(1→3)-β-D-Glucan Assay

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Recent Publications on Serum BG and Related Matters:

McKeating, C., White, P.L., Posso, R., Palmer, M., Johnson, E., McMullan, R. Diagnostic accuracy of fungal PCR and β-D-glucan for detection of candidaemia: a preliminary evaluation. J. Clin. Pathol. 2017 Sep 28. pii: jclinpath-2017-204692. doi: 10.1136/jclinpath-2017-204692. [Epub ahead of print]. The sensitivity and specificity of a PCR test and the Fungitell (1→3)-β-glucan (BG) serum test were compared in a cohort of 49 subjects (10 candidemics and 39 controls. PCR and BG sensitivity and specificity were determined to be 44.4%/87.2% and 80%/89%, respectively. Combined test results' sensitivity/specificity were 90%/79.5%. For two sequential positives, sensitivity increased to 60% and 90% for PCR and BG, respectively.

Giacobbe D.R., Del Bono, V., Viscoli, C., Mikulska, M. Use of 1,3-b-D-glucan in invasive fungal diseases in hematology patients. Expert Rev. Anti-Infect. Ther. 2017;15:1101-1112. This paper provided a systematic review of the use of (1→3)-β-glucan (BG) testing in the diagnosis of invasive fungal disease (IFD) in hematology patients. The authors concluded that BG testing is a valid tool to manage the early diagnosis and treatment of IFD. The authors asserted that the lack of specificity with respective causative fungal organism may be an advantage in allowing the observation of diverse organisms including *Aspergillus, Candida,* and *Pneumocystis*. Limitations mentioned included cost, lower sensitivity in hematology patients, and susceptibility to contamination-linked false positives. Rapid turn-around-time was deemed to be an advantage.

Giacobbe D.R, Mikulska, M., Tumbarello, M., Furfaro, E., Spadaro, M., Losito, A.R., Mesini, A., De Pascale, G., Marchese, A., Bruzzone, M., Pelosi, P., Mussap, M., Molin, A., Antonelli, M., Posteraro, B., Sanguinetti, M., Viscoli, C., Del Bono, V.; ISGRI-SITA (Italian Study Group on Resistant Infections of the Società Italiana Terapia Antinfettiva). Combined use of serum (1,3)-β-D-glucan and procalcitonin for the early differential diagnosis between candidaemia and bacteraemia in intensive care units. Crit. Care. 2017;2:176. This study examined the power of combining the results of two tests, serum BG and procalcitonin (PCT), in discriminating between candidemia and bacteremia, in an intensive care unit (ICU) population. The study involved three ICUs in two Italian Hospitals. 73 candidemics and 93 bacteremics were enrolled. Using the standard serum cutoff for BG, 80 pg/ml, and <2 nanograms/ml for PCT, the candidemia Positive Predictive Value was 96% (79% for BG alone). The Negative Predictive Value for candidemia for BG <80 pg/ml and PCT >2 ng/ml was 95% (93% for BG alone).

Donato, L., González, T., Canales, M., Legarraga, P., García, P., Rabagliati, R. The 1,3-β-D-glucan in critical adult patients as diagnostic tool for invasive *Candida* spp. infection, performance evaluation. Rev. Chilena Infectol. 2017;34:340-346. The authors conducted an evaluation of BG diagnostic performance in an ICU setting with proven (culture confirmed) candidemia or invasive candidiasis (C/IC). The performance of two sequential BG results (sequential days) was compared. The median BG titer for C/IC was 224.3 ± 213.7 pg/ml. In patients without C/IC it was 63.8 ± 76.7 pg/ml. The sensitivity/specificity for C/IC diagnosis were 60 and 92%, respectively. PPV was 60% and NPV was 92%.

McCarthy, M.W., Petraitiene, R., Walsh, T.J. Translational Development and Application of (1→3)-β-D-Glucan for Diagnosis and Therapeutic Monitoring of Invasive Mycoses. Int. J Mol. Sci. 2017;18. pii: E1124. doi: 10.3390/ijms18061124. Review. The authors have presented a review of the application of (1→3)-β-glucan testing in a variety of clinical settings and with the major invasive fungal disease pathogens. Specific fungal diseases covered include invasive candidiasis, pneumocystosis, and aspergillosis. In addition, recent findings involving BG testing in broncho-alveolar lavage fluid and cerebrospinal fluid testing (not approved matrices for BG testing), with a variety of infectious fungal pathogens, are reviewed and discussed.

Pang, Y.K., Ip, M., You, J.H. Potential clinical and economic outcomes of active beta-D-glucan surveillance with preemptive therapy for invasive candidiasis at intensive care units: a decision model analysis. Eur. J. Clin. Microb ol. Infect. Dis. 2017;36:187-194. This paper analyzes the theoretical economic impact of (1→3)-β-glucan surveillance for invasive candidiasis in an adult ICU setting in Hong Kong. The basic question addressed was whether or not BG surveillance and pre-emptive therapy would yield sufficient benefit as to be economically worthwhile. The basic findings were that the invasive candidiasis mortality rate would be reduced from 1.426 to 0.653 per 100 admissions at a cost of USD1,387. vs. 664. for the surveillance and control groups, respectively. The incremental cost per Quality-Adjusted Life Year (QALY) was USD5,329. Simulation showed this value to be cost effective in 50% and 100% of 10,000 simulations at health care

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policy willingness to pay thresholds (WTP) of USD7,200. and USD27,800., respectively. These thresholds were found to be substantially less than the WTP of USD40,596.(WHO basis) calculated for Hong Kong.

Ramos, J.T., Villar, S., Bouza, E., Bergon-Sendin, E., Perez, Rivilla, A., Collados, C.T., Andreu, M., Reyes, C.S., Campos-Herrero, M.I., de Heredia, J.L., Herrera, M.C.L., Alonso, P.A., Pallás-Alonso, C.R., Cuenca-Estrella, M; CANDINEO Study Group. Performance of a Quantitative PCR-Based Assay and Beta-d-Glucan Detection for Diagnosis of Invasive Candidiasis in Very-Low-Birth-Weight Preterm Neonatal Patients (CANDINEO Study). J.Clin. Microbiol. 2017;55:2752-2764. This multicenter (N=17) study compared serum BG, *Candida* PCR, and culture in the diagnosis of invasive candidiasis (IC) in very low birthweight (VLBW) preterm neonates. 159 episodes were analyzed. 7 proven and 2 probable cases of IC occurred (prevalence 5.7%). PCR and BG sensitivity/specificity were 87.5%/81.6% and 75.0%/64.6%, respectively. Where culture was negative, PCR and BG were positive in 17.4% and 33.5% of the cases, respectively. The authors concluded that serum BG and *Candida* PCR could be complementary diagnostic techniques in VLBR neonates.

Passos, A.I.M., Dertkigil. R,P,, Ramos, M.C., Busso-Lopes, A.F., Tararan, C., Ribeiro, E.O., Schreiber, A.Z.., Trabasso, P., Resende, M.R., Moretti, M.L. Serum markers as an aid in the diagnosis of pulmonary fungal infections in AIDS patients. J Infect Dis. 2017;21:606-612. The diagnosis of invasive fungal disease in HIV-infected individuals is often an AIDS-defining opportunistic infection. This study evaluated BG, galactomannan (GM), and lactate dehydrogenase (LH) in the diagnosis of pulmonary fungal infection in HIV-positive patients. Sixty-seven patients were screened and 60 enrolled in a single center in Campinas, Brazil. 19/60 were diagnosed with pneumocystosis (PJP). Their mean BG titer was 240 pg/ml and was significantly higher than those with community-acquired non-PJP pneumonia (CAP), 67.3 pg/ml. Of the 8 non-PJP patients with BG titers >80 pg/ml, infections included: Histoplasmosis, 1; strongyloidiasis, 1; tuberculosis, 1; cryptococcosis, 1; CAP, 1; undiagnosed, 2. Based upon a BG cutoff of 80 pg/ml, the BG sensitivity/specificity was 0.90/0.80. BG was <80 pg/ml in two PJP patients.

Discussion References:

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