Topic:

Diagnosis of Invasive Fungal Infection:

Role of Negative Predictive Value

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Discussion:

An increasing prevalence of invasive fungal infection (IFI) is widely observed in modern medical care due to a growing population of at-risk patients[1,2]. Diagnostic uncertainty regarding the potential presence of IFI in a patient is a major concern[3]. Given the extreme seriousness of IFI and its high morbidity and mortality, it is understandable that physicians, in the absence of accurate diagnostic guidance, often opt to utilize conservative preventative or therapeutic approaches[4]. This practice has resulted in significantly increased administration of systemic antifungal drugs at different stages of case management including prophylaxis and empiric therapy[5]. Over-prescription of systemic antifungals can create multiple problems, including excessive cost, adverse events, and potential antibiotic resistance[6]. These issues have become sufficiently prominent as to generate increasing efforts to employ classic anti-microbial stewardship approaches to systemic antifungal use with a heavy emphasis on cost analysis and reduction[7,8].

The use of tests with high negative predictive value (NPV) for IFI has the potential to reduce the over-use of systemic antifungals. The use of fungal antigen assays as adjuncts to the diagnosis of IFI has grown significantly over the last 10 years[9,10,11,12]. These antigens are typically cell wall structural components that are shed during the life cycle of the fungus within the host, and their levels in patients' blood are measured by a variety of assays from different manufacturers. These assays include Fungitell® (Associates of Cape Cod, Inc.), which measures serum (1→3)-β-D-glucan. Analyses of the diagnostic utility of these tests has indicated that their NPVs can be very high, which suggests their use to avoid unnecessary systemic antifungal therapy[13,14,15]. Refraining from prescribing systemic antifungals based upon fungal antigen test NPV still requires considerable physician confidence, but a growing literature is reporting promising results of pre-emptive therapy strategies based upon fungal antigen tests (including Fungitell®)[16,17,18,19].

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Recent Publications on Serum BG and Related Matters:

Pruller, F. *et al.* Automation of serum (1→3)-beta-D-glucan testing allows reliable and rapid discrimination of patients with and without candidemia. Medical Mycology, 2014, 00, 1–7 doi: 10.1093/mmy/myu023. This study reports the adaptation of the Fungitell test to use on a Siemens BCS XP coagulation analyzer for application in real time, robotic analysis of serum (1→3)-β-D-glucan. Between run and within run precision (CV) was reported as 3.1% to 5.5% and 3.0% to 5.0%, respectively. Clinical diagnostic correspondence between the standard method and the automated single patient assay was reported as follows: Sensitivity, 100% and 100%; Specificity, 96.8% and 97.8%; Positive Predictive Value, 83.3% and 88.2%; and Negative Predictive Value, 100% and 100%.

Poissy, J. *et al.* Presence of *Candida* cell wall derived polysaccharides in the sera of intensive care unit patients: relation with candidaemia and *Candida* colonization. Critical Care 2014, 18:R135 doi:10.1186/cc13953. This retrospective study evaluated serial serum (1→3)-β-D-glucan (BG) titers in 43 ICU patients and 67 controls. The BG data were compared with serum mannan antigen and antibody levels for diagnostic performance. Glucanemia was observed to occur before a positive blood culture (median 10 days) and was maximal during the week before a positive blood culture. A positive serum BG had a sensitivity of 97.1% during the period one week prior and after the blood culture-based diagnosis. Specificity was 30.6%. The negative likelihood ratio was 0.1. Sensitivity/specificity ratios were analyzed with varied cutoffs values yielding: 80 pg/mL, 0.97/0.31; 350 pg/mL, 0.65/0.75; and 800 pg/mL, 0.34/0.86. The authors proposed a treatment algorithm calling for pre-emptive antifungal therapy where BG titers are >800 pg/mL, evaluate for mannanemia where titers are >80 pg/mL but <800 pg/mL, and glucanemia surveillance for patients with risk factors for invasive candidiasis.

Nelson, G. *et al.* Resolution of a fungal mycotic aneurysm after a contaminated steroid injection: a case report. BMC Research Notes 2014, 7:327 doi:10.1186/1756-0500-7-327. This case report describes the diagnostic findings and management of a cerebrospinal fungal infection associated with receipt, by epidural injection, of microbially contaminated methylprednisolone. The female patient presented with a variety of neurological symptoms 37 days post-injection, after receiving notification of exposure to the contaminated drug. She was presumptively treated with antifungals based upon the history during a ten day hospitalization. Three days after discharge she was readmitted with worsening symptoms. Microbiological evaluation, including PCR was repeatedly negative. Retrospective (1→3)-β-D-glucan titer analysis of serial cerebrospinal fluid (CSF) specimens from the early course of the infection revealed >500 pg/mL in all samples. The patient was diagnosed with fungal meningitis based upon CSF pleocytosis and BG titers. The patient received appropriate antifungal therapy for 32 weeks and was considered cured at one year post-presentation.

Furfaro, E. *et al.* Bloodstream infections are an improbable cause of positive serum (1,3)-beta-D-glucan in 2 hematology patients. Clin. Vaccine Immunol. doi:10.1128/CVI.00214-14. This study evaluated the specificity of serum (1→3)-β-D-glucan (BG) in hematology patients with concomitant bacteremia. They noted that the association of positive serum BG results and bacterial infection, although generally indicated as a likely cause of false positives, is inconsistent among published studies. They evaluated 66 cases of documented bacterial blood stream infection (BSI) in 51 patients. 7 patients (14%) produced 11 (12%) BG-positive samples. Of the 7, 3 were diagnosed with probable aspergillosis and one with possible aspergillosis. They observed that the actual rate of BG positivity in patients with BSI and no invasive fungal disease was 6% on a per patient basis and 4% on a per sample basis. The authors concluded that bacterial BSI is an unlikely cause of serum BG positivity.

Lamoth, F. and Alexander, B. Nonmolecular Methods for the Diagnosis of Respiratory Fungal Infections. Clin. Lab. Med. 2014; 34 315–336. http://dx.doi.org/10.1016/j.cll.2014.02.006. The authors provide an updated review of the major antigen tests used as adjuncts to the diagnosis of invasive fungal infection. They present the major fungal infections and the application and interpretation of the results of their associated antigen tests in the context of the clinical presentation and pathogenesis.

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