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A Review of a Diagnostic Tool: Galactomannan

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ABSTRACT

Invasive fungal infections, including invasive aspergillosis are associated with a high morbidity and mortality especially in immunocompromised patients. Diagnosis is often difficult due to several factors such as delay in clinical suspicion and the lack of spesific clinical findings. Galactomannan is a polysaccharide cell wall component of *Aspergillus* and galactomannan antigen detection has become widely used for diagnosis of invasive aspergillosis. Here, we tried to discuss the diagnostic value of the galactomannan test in the context of literature review.

Introduction

Invasive fungal infections (IFI) have been increasing in neutropenic adult and pediatric patients. Invasive Aspergillosis (IA) became the most common form of IFI after the introduction of fluconazole prophylaxis[1,2]. It is also the most significant opportunistic fungal infection following hematopoietic stem cell transplantation (HSCT) which causes a 25-35% mortality despite the new antifungal agents such as voriconazole and echinocandins[3,4,5]. Early diagnosis of IA play an important role in the patients' survival outcome. The diagnosis of IA is often difficult because both the clinical and radiological findings are often non-specific. A high index of suspicion is required to successfully achieve a positive diagnosis. İnvasive procedures such as tissue biopsy and bronchoalveolar lavage (BAL) can not always be done due to the clinical condition of the patients[6]. The Platelia (Sanofi Diagnostic Pasterur, Marnes la Coquette, France) enzyme immunoassay (EIA) for the detection of galactomannan (GM) is currently one of the more used methods. The GM assay was approved by the Center for Devices and Radiological Health, Food and Drug Administration (FDA), in 2003 for the testing of serum samples as an aid to the diagnosis of IA.

Galactomannan is a polysaccharide that is a major constituent of A*spergillus* cell walls. It is a soluble, heat stable antigen released by especially *Aspergillus* species during active cell replication (during hyphal growth). Circulating GM can be detected in serum or plasma and may be present in BAL- fluid, cerebrospinal fluid (CSF) or other body fluids[11]. The GM EIA is performed with an optical read-out that is interpreted as a ratio relative to the optical density (OD) of a threshold control provided by the manufacturer; this ratio is called the OD index. The FDA has a suggested threshold OD index of 0.5 and an OD index ≥0.5 is generally considered to be a positive result.

The European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) guidelines recommend

Avcu G, Karapinar DY. A Review of a Diagnostic Tool: Galactomannan. J Immunol Sci. (2018); 2(5): 38-42

Journal of Immunological Sciences

detection of GM as a standalone microbiological criterion for diagnosis of probable patients in association with clinical and host factors. GM testing allows the early diagnosis of aspergillosis and the prompt initiation of antifungal therapy[7,8]. The new guidelines of the International Pediatric Fever and Neutropenia Guideline Panel also recommend considering prospective monitoring of serum GM twice weekly in high-risk hospitalized children, for early diagnosis of IA [recommendation strength is moderate (2B)][9]. The published guidelines of the Fourth European Conference on Infections in Leukemia (ECIL-4) recommend prospective monitoring, twice weekly, for early diagnosis of invasive aspergillosis in children at high-risk (strength of A-II)[10].

GM Testing in Serum

GM antigen has become an important diagnostic tool in the management of patients at risk for IA. GM can be detected in the serum in some patients before the presence of clinical signs or symptoms of IA. Monitoring for GM can be used in neutropenic patients who have a relatively high probability (>5–10%) of developing IA such as; Acute myeloid leukemia (AML) and myelodysplastic syndrome during intensive chemotherapy and patients at the early engraftment phase of the allogeneic HSCT. GM screening every 3–4 days in these groups can increase the detection rate of IFI and decrease the costs of antifungal drugs[12,13]. A single positive GM index of ≥0.7 or two consecutive samples of ≥0.5 should prompt a diagnostic work-up[10]. GM monitoring can be continued after antifungal therapy has been initiated. Several studies have shown that the course of the GM index during antifungal therapy is predictive of the outcome[14]. Persistent GM antigenemia during therapy is a poor prognostic sign and should prompt clinical reassessment. Mortality in IA patients with persistently elevated serum GM was reported to be higher than in those with negatively converted serum GM during antifungal therapy[15,16].

The specificity and sensitivity of the assay in serum samples varies across the different clinical studies at different cut-off points of the galactomannan index. The sensitivity of GM testing varies in the range of 30–100%, while specificity has been reported to be >75%[17]. A meta-analysis showed the efficacy of the GM test in case of proven IA had an overall sensitivity and specifity of 71% and 89% respectively[17]. The combined sensitivity and specificity of the five pediatric studies that had been considered adequate by the International Pediatric Fever and Neutropenia Guideline Panel, 0.76 (95% CI, 0.62 to 0.87) and 0.86 (95% CI, 0.68 to 0.95), respectively[9]. A retrospective pediatric study reported 0.91 sensitivity and 0.81 specificity; while the false positive rate was 18.3%[18].

A recent meta-analysis reported by Lehrnbecher et al.[9] showed that GM negative predictive values were high,

ranging from 85% to 100% for screening and 70% to 100% in the diagnostic setting, but failure to identify non-Aspergillus molds limits its usefulness. Among 10 studies including 100 patients in which serum GM was used as a screening test for IFI during neutropenia or post-HSCT, specificity ranged 50%–100%, sensitivity 0%– 100%, positive predictive value 0%–100%, and negative predictive value 85%–100%. Among 84 patients (in children with symptoms potentially suggestive of IFI) from 8 studies in which GM testing performed as a diagnostic test; specificity ranged 35%–100%, sensitivity 14%–100%, positive predictive value 0%–100%, and negative predictive value 70%–100%. Different age and characteristics of patient populations of these studies results may contribute wide range. Additionally, most of the studies eating habbits of the patients, and antibiotic usage or prophylaxis against fungal infetions were not discussed. They may have also effect on the results. There is a great necessity for a prospective study including children age who are on standardized antibiotic and antifungal therapy.

Serial GM testing is recommended both for early diagnosis and the follow-up of patients with IA as a prognostic marker to evaluate the course of the disease and the response to antifungal treatment[19]. Han et al.[20] investigated serum GM index for early prediction of mortality in immunocomromised children with invasive pulmonary aspergillosis. They found out that, serum GM levels were higher in the fatality group than in the survival group during the entire period of antifungal therapy, and serum GM at 1 week after antifungal therapy was most significantly associated with mortality. A serum GM > 1.50 at 1 week after antifungal therapy indicated a sensitivity and specificity of 61.5 % and 89.3 %, respectively, in predicting mortality within 12 weeks after antifungal therapy. They suggested more intensive antifungal therapy in patients at high risk for mortality, who show a persistently high level of serum GM within 1 week of antifungal therapy. Most of the studies recommended once to twice weekly sampling as in the 27 studies included in the meta-analysis by Pfeiffer et al.[17,21-23]. In Pfeiffer's[17] meta-analysis (children and adults), the range of sensitivity and specificity varied between 38% and 100%, and between 17% and 100%, respectively.

Gefen et al.[24] researched the serial serum GM screening for IA diagnosis in children after stem cell transplantation and with high risk leukemia prospectively. GM sensitivity and specificity were 0.8 and 0.66, respectively; positive- and negative-predictive values were 0.22 and 0.96, respectively. The rate of false positive cases was high (%78).

GM detection in the serum of non-neutropenic patients has limited importance because of its limited sensitivity[25]. A meta-analysis including 27 studies reported an overall sensitivity of serum galactomannan assay of 71% and specificity of 89%. However, when oncohematological

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38-42

Journal of Immunological Sciences

Table 1. The comparison of the results of studies on galactomannan.

study	patient group	sample type	sensitivity	specifity
Pfeiffer CD, et al. (2006)	Adult, neutropenic	serum	30-100%	>75%
Lehrnbecher T, et al. (2012)	Pediatric, neutropenic	serum	0%– 100%	50%–100%
Gefen A, et al. (2015)	Pediatric, neutropenic	serum	80%	66%
Zhou W, et al. (2017)	Adult, Non-neutropenic	serum	37.8%	87.1%
Zhou W, et al. (2017)	Adult, Non-neutropenic	BAL	75.6%	80.7%
Bergeron A, et al. (2010)	Adult, neutropenic	BAL	57.6%	95.6%
Desai R, et al. (2009)	Pediatric Neutropenic+non-neutropenic	BAL	78%	92%

patients were excluded from the analysis, the sensitivity and specificity of the test dropped to 22% and 84%, respectively[17]. In a recent prospective study of IA in nonneutropenic patients, Zhou et al.[26] found a sensitivity of serum GM of 37.8% and a specificity of 87.1%, with a positive predictive value of only 60.8%. (Table 1)

False positivity of GM assay may ocur by numerous factors. GM is found in many fungi and bacteria and can cause false positive results. Cross-reactivity with some beta-lactam antibiotics (piperacillin-tazobactam, amoxicillin-clavulanate) and with GM from other fungal species (*Fusarium*, *Penicillium*, *Cladosporium*, *Histoplasma*, *Blastomyces*, *Paracoccidioides*, *Cryptococcus*, *Nigrospora*, *Paecilomyces*, *Trichothecium*, *Lichtheimia ramosa*, and *Geotrichum*), as well as the epidemiological and biological factors are the conditions associated with it[27]. The proposed mechanism is that galactomannan in foods or bacteria having cross-reactive epitopes may translocate across the intestinal mucosa during periods of impaired mucosal integrity[11]. The sensitivity of detecting galactomannan in serum is decreased with the concurrent administration of mold-active antifungal therapy, for instance in patients receiving posaconazole or voriconazole prophylaxis which may prevent the circulation of GM[28,29]. In the study of Vena et al.[30] investigating the performance of the routine serum GM in the diagnosis of IA in high-risk haematology patients receiving prophylaxis with micafungin; Surveillance of asymptomatic patients receiving prophylaxis with micafungin using GM was found to be unnecessary, because the results were either negative or false-positive. GM testing was recommended in the diagnosis of breakthrough IA in symptomatic patients during prophylaxis.

False-positive results are more likely to occur during the first 100 days following HCT and in patients with gastrointestinal tract mucositis caused by chemotherapy or graft-versus-host disease (GVHD)[31]. Levels of serum GM were detected to increase up to 4.5 for a few days immediately after the infusion of stem cells in a recent study[24]. In neonates and infants, immaturity of the intestinal mucosa may lead to the translocation of lipoglycans of Bifidobacterium, resulting in false-positive GM antigenemia[27]. While high false positive rates were reported in pediatric patients, several recent studies have shown its usefulness in children and similar results to adult patients[5,32,33,34].

GM Testing in Bronchoalveolar Lavage Fluid

Detecting GM in BAL is a proposed tool to diagnose invasive pulmonary aspergillosis but the diagnostic value of BAL GM in children is rarely reported. A recommended cutoff by the manufacturer, a cutoff of 1 is used for BAL specimens[35]. It was shown that the GM levels appeared earlier in BAL fluid as compared to serum.

The FDA considers an OD index of ≥0.5 to be positive for GM EIA in both serum and BAL fluid. In a prospective cohort study that included 530 patients with hematologic malignancy who had signs or symptoms of IFI, 155 (29%) had a positive BAL GM result using an OD index threshold ≥0.5[36]. BAL GM had a sensitivity of 50% and a specificity of 73% for detecting proven or probable IA.

Sensitivities of BAL GM have been reported to be ranging 60 to 100% and specificities from 87.8% to 100% in several adult studies using a cutt-off index of ≥1.0[37,38,39]. Bergeron et al.[40] reported a sensitivity and a specificity of 57.6% and 95.6% respectively when using a cut-off index of BAL GM ≥0.5. A study including also immunocompetent patients reported sensitivity of 78% and specifity of 92% at a cut-off index of 0.98 in BAL in children[41]. (Table 1)

Sensitivity, specificity, positive predictive value, and negative predictive value of BAL GM for a diagnosis of proven and probable IPA were found to be 4%, 87.5%, 82.4%, and 87.5% in children in the study of de Mol M and et al.[42]. A significant relation was found for BAL GM and abnormal chest tomography. BAL GM and serum GM correlated significantly.

In non-neutropenic patients, IA is not always associated with angioinvasion. Symptoms of the disease are often nonspecific, typical radiological findings may be absent. Different from serum GM, BAL GM detection have been proven to be more advantageous in the non-neutropenic population and provides a great utility for diagnosis[43,44,45].

BAL GM sampling as a prognostic tool is not established and in vivo research suggests that it is not possible[46-50]. Although serum GM sampling during therapy to monitor response is highly useful, utility for BAL GM for the same purpose is not suggested.

Similar to serum samples, false positivity can constitue

Avcu G, Karapinar DY. A Review of a Diagnostic Tool: Galactomannan. J Immunol Sci. (2018); 2(5): 38-42

Journal of Immunological Sciences

a problem in BAL samples. False-positive results can occur, especially when the fluid that is used for BAL washes is contaminated with galactomannan and also common due to colonization as occurs in lung transplant recipients.

GM Testing in Other Specimens

GM can also be detected in cerebrospinal fluid (CSF), pleural fluid, sputum or urine, the experience with GM detection in these specimens are reported to be insufficient so there are no enough specific recommendations[35].

Conclusion

The incidence rates of IFI and IA are increasing day by day. Diagnosis of IA is challenging; clinical symptoms are often nonspecific and classical diagnosis is difficult and rare. Diagnostic tools in the mycology for IFI ara limited currently. The GM test is available in many centers around the world and it should be used to help diagnosis. However the low positive predictive value should be considered.

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