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Review

Utility of Fungal Cell Markers in Pediatric Bone Marrow Transplant Recipients for Screening and Diagnosis of Invasive Fungal Infections

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Abstract

Invasive fungal disease (IFD) is a significant contributor to morbidity and mortality in pediatric patients undergoing hematopoietic stem cell transplantation (HSCT). Early detection and timely initiation of antifungal therapy is important for improved outcome, but diagnosis remains difficult, especially when relying on conventional microbiology methods such as culture and microscopy. Data on the use of fungal biomarkers for screening and diagnosis of IFD in HSCT pediatric patients are limited, precluding the development of specific guidelines in this population. In this review, we have summarized available literature on kinetics, diagnostic and prognostic performance, and limitations of fungal biomarkers for screening and diagnosis of IFD in pediatric HSCT recipients to help guide their use and interpretation.

Keywords

β-D-glucan; galactomannan; invasive fungal disease; pediatric bone marrow transplant recipients

1. Introduction

Invasive fungal disease (IFD) is a significant contributor to morbidity and mortality in pediatric patients undergoing hematopoietic stem cell transplantation (HSCT). Early detection and timely initiation of antifungal therapy is important for improved outcome, but diagnosis remains difficult, especially when relying on conventional microbiology methods such as microscopy and culture. Use of biomarkers for early diagnosis of IFD in high risk patients have been introduced over the last 2 decades [1]. Galactomannan (GM) and 1,3-β-D-glucan are used as adjunctive diagnostic tools in adults and are now incorporated into the diagnostic criteria of IFD established by the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group (MSG) [2]. However, less data are available for children as compared to adults and pediatric guidelines are lacking specifically pertaining to their use for surveillance in asymptomatic pediatric HSCT recipients and their use in monitoring response to therapy. In this review, we have summarized available literature on kinetics, diagnostic and prognostic performance, and limitations of fungal biomarkers for screening and diagnosis of IFD in pediatric HSCT recipients to help guide their use and interpretation.

2. 1,3-β-D-Glucan (BDG)

2.1 BDG

BDG is the most important and abundant fungal wall polysaccharide of most fungi, estimated to comprise as much as 65–90% of total wall glucans[3]. BDG plays a role in the immune response to fungal infections through interaction with the macrophage through beta-glucan receptors[4]. An elevated serum BDG level has been shown to be a surrogate to invasive fungal infection. However, certain fungal infections may not result in detectable serum BDG levels including *Cryptoccocus neoformans* (encapsulation of the yeast), the yeast phase of *Blastomyces dermatitidis,* and *zygomycetes* [5-7]. With *Blastomyces dermatitidis*, it has been demonstrated that transition from the mould to the yeast form causes significant depletion of the cell wall BDG concentration [7]. The cell wall of *zygomycetes* consists of primarily chitin and chitosan. However, evidence suggests that the cell wall of *zygomycetes* may contain small amounts of 1,3-β-D-glucan which might explain the reported susceptibility of *R. oryzae* to ecchinocandins, which inhibit the 1,3-β-D-glucan synthase as their mechanism of antifungal activity [8].

2.2 BDG Detection Assays

At least five commercial BDG detection assays have been developed [9, 10], but only the Fungitell assay is cleared by the Food and Drug Administration (FDA) in the United States. This assay is based on modification of the Limulus Amebocyte Lysate (LAL) pathway by eliminating reactivity to bacterial endotoxin so that it only reacts to 1,3-β-D-glucan, through the Factor G-mediated side of the pathway. When activated by BDG, factor G converts the inactive pro-clotting enzyme to the active clotting enzyme, which in turn cleaves a chromogenic substance, creating a

chromophore, para-nitroaniline, which absorbs at 405 nm. BDG concentration is then estimated based on the rate of optical density increase produced by the sample [10].

2.3 Conditions Associated with Elevated BDG Other Than Fungal Infections

It has been demonstrated that immunoglobulin products may have high burdens of BDG which may cause elevation in serum BDG with intravenous administration. BDG level may remain elevated for 3-4 days after discontinuation of immunoglobulin therapy but overall the duration and extent of that elevation depends on the brands, lots, and doses of immunoglobulin products administered [11]. Other blood products including albumin and blood coagulation factors may cause an elevation in serum BDG attributed to the cellulose membranes of depth-type filters used to process the blood [12, 13]. Similarly, serum BDG level increases significantly after hemodialysis using cellulose membrane, which was not seen with hemodialysis using Cellulose triacetate, polymethyl methacrylate, or synthetic polysulfone membranes [14, 15]. Elevation in BDG was also reported with a cupro-ammonium rayon membrane used in hemodialysis [16]. Additionally, some gauze products contain BDG to which transient elevation in serum BDG is attributed in postsurgical patients [17, 18]. Some studies showed false-positive results (i.e., positive findings not related to invasive fungal infection) in patients with *Pseudomonas* bacteremia and *Streptococcus pneumoniae* bacteremia, which were not related to known causes of reactivity including use of fungal-derived antimicrobials [19]. Mennink-Kersten et al. determined the reactivity of BDG in several bacterial culture supernatants using the Fungitell assay. Among the clinical isolates tested, *Alcaligenes faecalis*, *S. pneumoniae* and *Pseudomonas aeruginosa* showed 1,3-β-D-glucan reactivity [19]. Marty et al. tested forty-four intravenous antimicrobial agents commercially available in the US for the presence of BDG using the Fungitell assay [20]. None of the tested antimicrobial solutions had detectable BDG at the usual drug maximum plasma concentration including piperacillin-tazobactam. In contrast, Liss et al. [21] reported detectable BDG levels in twenty-five ready-to-use antimicrobials including antifungals that may be enough to trigger a positive test in the serum.

2.4 BDG Kinetics

The metabolism pathway of 1, 3-β-D-glucan is not yet known [15]. β-glucanase does not exist in humans which precludes enzymatic degradation [11]. Ikemura et al. [11] reported that BDG was detected in the urine for only 2 h after administration (through BDG containing immunoglobulin products) in adult patients and that no more than 5% of the total amount administered was excreted in urine. Kato et al. estimated the median half-life of BDG in the plasma to be 20 hours (range 3.1 to 181.3 hours). There was no relationships between the plasma half-life of BDG and serum creatinine, creatinine clearance, urine volume, prothrombin activity, or serum albumin concentration which indicates that hepatic and renal functions have no effect on the half-life of plasma BDG [15]. Data specific to pediatric patients is not available.

2.5 Performance of Serial BDG to Screen for Invasive Fungal Infections in Pediatric Bone Marrow Transplant Recipients

Data from a recent meta-analysis in adults suggests that BDG is a useful screening tool for invasive fungal diseases in high risk populations [22]. The pooled studies included patients with hematological malignancy, solid tumors, liver transplant, and other hospitalized patients who are at high risk for IFD. Patients with proven or probable IFDs who were diagnosed according to the EORTC/MSG classification [2], as well as patients with possible IFDs were also included in the analysis. The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio with 95% confidence intervals, were 0.82 (0.68, 0.90), 0.86 (0.81, 0.92), 5.85 (3.46, 9.35), 0.22 (0.12, 0.39) and 26.52 (11.72, 60.07), respectively, using the Fungitell assay [22].

Only one prospective study published to date has specifically evaluated the value of serial BDG screening for the early detection of invasive fungal infections in pediatric patients undergoing allogeneic HSCT [23]. The results of this study showed that BDG screening has a relatively good sensitivity and a good negative predictive value, whereas the positive predictive value was less than 30% (reported prevalence of invasive fungal disease was 17.6%) suggesting limited usefulness of BDG application as a screening tool in HSCT patients. This study showed that the diagnostic performance of two consecutive positive BDG values was higher than a single one. Performance also varied based on the cut-off used and the time point at which the test was performed with relation to onset of fungal infection. When BDG was measured at the time of a first pathological result suggestive or consistent of IFD, such as blood culture results or biopsy sample, pulmonary infiltrates, or pathological GM test result, having a single BDG level higher than the respective cutoff value was associated with a sensitivity of 100% and specificity of 73% at a cutoff of 60 pg/ml, and a sensitivity of 100% and specificity of 78% at a cut off of 80 pg/ml. Having two consecutive positive BDG values above the cutoff used was associated with improved specificity to 78% and 82% at cut-off of 60 pg/ml and 80 pg/ml, respectively. BDG had a lower sensitivity at 2 and 4 weeks prior to the first pathological signs. Up to 2 weeks prior to first pathological sign, two consecutive BDG values above the cutoff of 60 pg/ml had a sensitivity of 82% and specificity of 79%. For two consecutive BDG values above the cutoff of 80 pg/ml, the sensitivity was 69% with specificity of 83%. At 4 weeks prior to first pathological sign, sensitivity was 70% and 58% at cutoff of 60 pg/ml and 80 pg/ml, respectively. Associated specificities were 79% and 83% at cutoff of 60 pg/ml and 80 pg/ml, respectively [23].

2.6 Diagnostic Performance of BDG in Pediatric HSCT Recipients with Suspected Fungal Infections

Adult data suggests that BDG could be an adjunctive diagnostic tool for IFD in patients with appropriate pretest probability and symptoms suggestive of fungal infection, especially when checked serially in patients not receiving factors associated with falsely elevated BDG levels [24, 25].

Few studies evaluated BDG testing in hematology/oncology patients for diagnosis of IFD in pediatric patients whose clinical, radiological, or mycological signs were suspicious for a fungal infection [26, 27]. Badiee et al. [28] included patients with hematologic malignancies and did not include any HSCT recipients. This study reported poor diagnostic performance of BDG for diagnosis of invasive aspergillosis with reported sensitivity of 50%, specificity of 46%, positive likelihood

ratio of 0.9, and negative likelihood ratio of 0.9. The prevalence of proven and probable aspergillosis in this cohort was 19.1% with a corresponding positive predictive value of 26% and a negative predictive value of 70.6%. Guitard et al. [29] obtained serial measurements of BDG in patients with hematologic malignancies (the cohort did not include any HSCT recipient patients) during their febrile neutropenia episodes. The reported incidence of proven or probable fungal infections was 10.5%. The sensitivity and specificity of BDG for detecting proven or probable IFD was 75% (95% CI, 69%-81%) and 56% (95% CI, 50%-62%), respectively using a BDG cut-off of 80 pg/ml. Using a lower cutoff was associated with higher sensitivity (75%) and lower specificity. Having two consecutive positive samples increased the specificity to above 93%, while decreased the sensitivity to 42%. Performance of BDG was higher in patients not receiving antifungals prior to the test, approaching a sensitivity and specificity of 100% and 91%, respectively, using a single positive BDG at a cut off of 75 pg/ml. It is important to note that the majority of cases of proven or probable IFD in this cohort were secondary to yeast infections, and only one patient had *Fusarium* infection. Comparable results were reported by Gupta et al. [30] who included patients with hematologic malignancies and solid tumors. The following values were reported: sensitivity 80.2%, specificity 47.2%, PPV 68.9 and NPV 71.4%. The reported incidence of invasive fungal infections was exceptionally high in that study, the author reported 2 proven and 60 probable cases of IFD out of the included 125 patients which would calculate to a prevalence of 49% of the cohort and did not report on the pathogens isolated. Zhao et al. [31] included pediatric patients with hematologic malignancies and HSCT recipients. In this study, the GKT-5M Set Kinetic Fungus Detection Kit was used for BDG assay. The sensitivity, specificity, positive and negative predictive values for plasma BDG detection were 81.8%, 82.4%, 48.6% and 95.7%, respectively (16.9% prevalence of proven/probable IFD).

2.7 BDG as a Prognostic Marker of Response to Treatment in Invasive Fungal Infections

A decrease in BDG levels was reported to be associated with treatment response [32]. However, even with appropriate antifungal therapy, serum BDG declines slowly. Neither its height at diagnosis nor its early trajectory predicts clinical outcome or mortality [33]. It often lingers above the usual threshold for positivity long after clinical resolution of the original infection, reportedly for weeks to months, and up to 1.8 years after successful treatment [33, 34]. Accordingly, negative BDG levels may not be a suitable marker for successful treatment outcome and has no discernible prognostic value after initiation of antifungal therapy.

3. Galactomannan (GM)

3.1 Galactomannan and Conditions Associated with False Positive GM Reactivity

Galactomannan is a polysaccharide component of the cell wall of *Aspergillus* species. It consists of a mannose backbone and a variable number of galactofuran side chains. GM antigens are secreted during mycelial growth [35, 36]. The most commonly used method to determine GM in serum is a double sandwich enzyme-linked immunosorbent assay (ELISA) using EB-A2 monoclonal antibodies (Platelia *Aspergillus* antigen, Bio-Rad, Marnes-la-Cocquette, France) [37]. These antibodies bind to the β-(1,5)-galactofuranose (Gal*f*) oligomers in the side chains of the galactomannan molecule. Other moulds including *Penicillium* and *Paecilomyces* also release

antigens containing that epitope. The fungus *Penicillium* is used in the production process of certain β-lactam antibiotics, mainly piperacillin/tazobactam and amoxicillin/clavulanic acid, which explains the false positive reactivity of GM assays in the serum of patients receiving these antibiotics [38]. However, due to improvement of the manufacturing process, some currently available brand piperacillin/tazobactam preparations manufactured in the US no longer seem responsible for false-positive GM results [39, 40]. Galactoxylomannan released by *Cryptococcus neoformans* also cross-reacts with EB-A2 antibodies [38]. ELISA reactivity was also shown to be associated with bacterial lipoglycans containing a beta-1,5-galactofuranosyl chain in certain bacteria, most notably bifidobacteria. Since bifidobacteria are abundant in the human gut, especially in infants and neonates [41], these bacteria or the excreted lipoglycan may cause false serum GM reactivity [42]. False positive reactivity has also been reported with gluconate-containing intravenous solutions [43] and infant milk formulas thickened with carob bean gum [44].

3.2 GM Kinetics and Elimination

Elimination of serum GM occurs via three different routes that include uptake by the kupffer cells in the liver, excretion in urine, and finally uptake by the neutrophils. The latter would explain the higher sensitivity of serum GM detection in neutropenic patients compared to non-neutropenic patients [36]. Aubry et al. [45] analyzed the kinetics of the decrease of GM in adult and pediatric patients with hematologic malignancies and bone marrow transplant recipients in whom an invasive aspergillosis was ruled out and source of GM reactivity deemed to be secondary to GM containing beta-lactam antibiotics. After discontinuation of implicated antibiotics, the average time to negative antigen was 5.5 days (95% CI, 4.1 to 7.0), with an estimated half-life of elimination of GM of 2.4 days (95% CI, 1.8 to 3.0).

3.3 Performance of GM as a Screening and a Diagnostic Tool in Pediatric Bone Marrow Transplant Recipients for Detection of Invasive Fungal Infections

A recent systematic review [46] of studies enrolling 184 patients with proven/probable IFD evaluated serum GM in the pediatric cancer and HSCT setting when used as a screening tool during immunosuppression or as a diagnostic test in patients presenting with symptoms potentially suggestive of an invasive fungal infection. Overall, the prevalence of IFD ranged from 0% to 30.8% in individual studies. Among the 10 studies in which GM was used for screening in patients with neutropenia or post-HSCT, wide ranges were observed as follows: sensitivity 0%-100%, specificity 50%-100%, PPV 0%-100%, and NPV 85%-100%. According to the authors, only 5 studies were appropriate for pooled analysis (used EORTC/MSG criteria, used proven or probable IFD as a case, and used a GM index ≥0.5 once or twice, or ≥0.7 once as a threshold for positive test). The pooled sensitivity and specificity for GM as a screening tool were 68% (95% CI, 51%–81%) and 91% (95% CI, 86%–94%) which calculates a positive likelihood ratio (LR) of 7.56 (95% CI, 3.64-13) and a negative LR of 0.35 (95% CI, 0.2-0.57) [46]. Eight studies including a total of 84 patients evaluated GM as a diagnostic test with the following reported ranges: sensitivity 14%–100%, specificity 35%–100%, PPV 0%–100%, and NPV 70%–100%. The pooled sensitivity and specificity of five studies were 89% (95% CI, 79%–95%) and 85% (95% CI, 51%–97%), respectively, which calculates a positive likelihood ratio (LR) of 5.93 (95% CI, 1.61- 32) and a negative LR of 0.13 (95%

CI, 0.05-0.41) [46]. Combining the results of both settings (diagnosis and screening) demonstrated a pooled sensitivity of 81% (95% CI, 69%–89%), pooled specificity of 88% (95% CI, 75%–95%), pooled positive likelihood ratio 6.75 (95% CI, 2.76- 18) and pooled negative likelihood ratio 0.22 (95% CI, 0.12- 0.41) [46]. For a pretest probability of 7% for invasive aspergillosis, a positive GM will raise the posttest probability to 36% (which may be enough of an increase to prompt additional diagnostic tests or initiation of antifungal therapy) and a negative GM will decrease the posttest probability to 1%.

3.4 GM as a Prognostic Marker of Response to Treatment in Invasive Fungal Disease

It has been demonstrated in animal models that GM serum level was significantly associated with the degree of fungal burden of *Aspergillus* species in the lung. Receipt of appropriate antifungal therapy was associated with a decrease in GM levels and an increase in the survival rate [47]. Persistently positive serum GM despite antifungal therapy has been shown to correlate with persisting fungal burden and continuous fungal infection. Changes in GM from the time of diagnosis appear to significantly correlate with outcome [48], specifically, reduction in serum GM in the early phase of antifungal therapy, especially during the first one or two weeks, was reported to be associated with improved prognosis [48-51]. One study enrolling 45 pediatric patients with hematologic/oncologic diseases who were diagnosed with proven or probable invasive aspergillosis found that a serum GM > 1.50 at 1 week after initiation of therapy exhibited a sensitivity and specificity of 61.5% and 89.3%, respectively, in predicting mortality within 12 weeks after antifungal therapy [47]. Another study that enrolled adult and pediatric patients with proven or probable invasive aspergillosis, including allogeneic bone marrow transplant recipients, found that each GM EIA unit decline in the week following diagnosis decreased the risk of time to all-cause mortality at 6 weeks by 22% [49]. Similarly, an increase in the GM value of 1.0 above the baseline value during the first week of treatment was predictive of treatment failure with a sensitivity of 44%, a specificity of 87%, and a positive predictive value of 94% in allogeneic HSCT recipients during treatment and suggests need for modification of treatment [50]. A systematic review of studies including adult and pediatric patients with hematologic malignancies including those undergoing allogeneic HSCT reported a very strong correlation between GM (measured one week before outcome) and survival with a k correlation coefficient of 0.8737 (95% CI, 0.8140–0.9333; $P < 0.001$). Comparable results were demonstrated among the subgroups of studies evaluating adults, children, or a combination of both and among studies that included allogeneic HSCT recipients [51].

4. Conclusions

Given limited evidence, strong recommendations for routine use of BDG and GM in HSCT cannot be made. For surveillance in the early post HSCT period, BDG and GM seem to have a PPV less than 30% and 50%, respectively, assuming a prevalence of 10% of IFD. While they may help identify invasive fungal infections in less than a half of the patients with a positive value, they may lead to unnecessary extensive workup in the other majority. Data for the use of BDG in pediatric HSCT recipients who are already exhibiting symptoms suggestive of IFD is lacking. Only a very small number of HSCT patients was included in the already published studies as discussed above and specific recommendations for its use cannot be made based on the limited available evidence.

This population of patients may be different from other patients with hematologic malignancies in regards to the risk of IFD, receipt of prophylactic antifungal agents, and presence of factors associated with positive BDG in the absence of IFD, such as IVIG. All of these factors are significant determinants of the diagnostic performance of BDG as previously discussed. Overall, fungal cell markers, if used in symptomatic patients, should be interpreted in combination with the clinical and radiologic findings. Further research is needed to determine the value of using these markers in this specific group of patients.

Author Contributions

These authors contributed equally to this work.

Competing Interests

The authors have declared that no competing interests exist.

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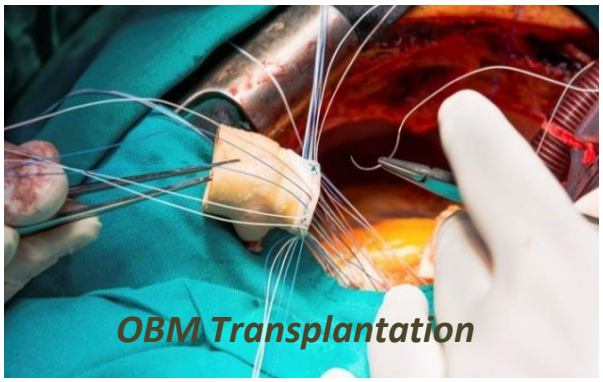

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