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Galactomannan Antigenemia in Pediatric Oncology Patients With Invasive Aspergillosis

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Abstract

Background: Diagnosing invasive aspergillosis is difficult but might be improved by detection of circulating galactomannan. Although galactomannan antigenemia has been well studied in the detection of invasive aspergillosis in adult patients, little is known about the expression of circulating galactomannan in immunocompromised children with invasive aspergillosis.

Methods: We studied the expression of galactomannan antigen by enzyme immunoassay (EIA) in 990 serum samples from 56 pediatric oncology patients (ages 3 months to 18 years) of whom 17 had proven or probable invasive aspergillosis defined by the European Organization for Research and Treatment of Cancer-Mycoses Study Group criteria. Any sample with a galactomannan EIA Galactomannan index value of ≥0.5 was considered positive.

Results: At least 1 serum sample was positive for 11 of 17 pediatric oncology patients (65.7% sensitivity, 95% confidence interval: 38.3–85.7) with invasive aspergillosis. Galactomannan EIA was positive in 99 of 304 samples from patients with proven or probable invasive aspergillosis, and 7 of 686 (1.0%) samples from 39 control subjects resulted in a positive galactomannan EIA result. At least 1 sample tested positive in 5 of the 39 controls (12.8%, 95% confidence interval: 4.3–27.4). No significant association between accuracy and patient age was observed. Among the 7 evaluable galactomannan-positive patients with IA, the galactomannan EIA produced a positive result before clinical or radiographic evidence of infection in 6 cases, with a lead-time to diagnosis ranging from 1 day to 34 days (median: 10 days). In the remaining case, a positive galactomannan was observed on the same day as diagnosis by non-EIA methods.

Conclusions: The presence of circulating galactomannan is predictive of invasive aspergillosis in most pediatric oncology patients. Galactomannan antigenemia may precede clinical, microbiologic, or radiographic evidence of invasive aspergillosis.

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Keywords

aspergillosis; galactomannan; pediatric oncology

Invasive aspergillosis is an important cause of morbidity and mortality in immunocompromised pediatric patients, including patients with hematologic malignancies, hematopoietic stem cell transplant recipients, solid organ transplant recipients, and those with primary or acquired immunodeficiencies.[1–7] Several new antifungal agents offer hope for improved outcome in treating many of these infections.[8–13] Such therapies are often initiated after infection has become deeply invasive, thus reducing the chances for successful recovery from the primary infection while increasing the risk of complications and other comorbidities. Prompt therapy for invasive aspergillosis improves outcome.[14] Thus, methods allowing more rapid and sensitive detection of invasive aspergillosis are needed.

Lack of rapid, early, and accurate diagnosis of invasive fungal infections, particularly invasive aspergillosis, is a major limitation in treatment of these infections.[15,16] Traditional culture-based methods of detection lack sensitivity and often require invasive procedures for diagnosis of invasive aspergillosis.[17] Although histopathology has a high degree of specificity, it has limited sensitivity, requires the removal of tissue (sometimes not possible in critically ill patients) and may not be helpful in the early stages of infection.[18]

Recent efforts have focused on the use of nucleic acid amplification techniques.[19,20] The results of studies of nucleic acid amplification vary depending on platform, primer sequences, and study design. Nucleic acid amplification testing for detection of invasive aspergillosis is technically demanding and a single system has not been standardized and validated in a large number of centers.

Galactomannan is a major heteropolysaccharide of the cell wall of *Aspergillus* spp. During the course of infection, this carbohydrate antigen is expressed in tissue, the circulation, and the tracheobronchial tree.[21–27] The most recent and widely used platform for detection of galactomannan antigen in serum is an enzyme immunoassay (EIA) that uses the EB-A2 rat monoclonal antibodies.[28] Most clinical studies of the expression of serum galactomannan have been performed in adult patients.[15,21,22,24,26,29–32] The patterns of expression of serum galactomannan in pediatric patients are not well understood.[32–35] We therefore studied expression of serum galactomannan in pediatric oncology patients with invasive aspergillosis.

MATERIALS AND METHODS

Patients and Experimental Design.

This study included 990 serum samples from 56 pediatric oncology patients (age ≤18 years) from St. Jude Children's Research Hospital and the Pediatric Oncology Branch, National Cancer Institute. The demographic characteristics of this population are described in Table 1. We studied 686 serum samples from 39 patients without evidence of invasive aspergillosis (control patients), and 304 serum samples from 17 patients with proven or probable invasive aspergillosis. Among these 686 samples, blinded, retrospective galactomannan testing was

performed on 536 frozen, excess, serum samples from 36 patients, remaining after routine diagnostic testing; the remaining 150 samples from 3 patients were tested prospectively, for patient care purposes, with results reviewed retrospectively. Samples were collected at least once weekly during the period of neutropenic or immunosuppressive risk. Review of the medical record was performed to categorize patients according to EORTC/IFICG (European Organization for Research and Treatment of Cancer/Invasive Fungal Infection Cooperative Group) and NIAID/MSG (National Institute of Allergy and Infectious Disease/Mycoses Study Group) criteria as having proven, probable or possible aspergillosis, or as having no evidence of aspergillosis.[37] Chart review was conducted in a blinded manner without awareness of patients' galactomannan antigen data. Analysis for serum galactomannan, data collection, and data analysis were performed after institutional review board approval. As the study posed no risk to patients, signed informed consent was not required.

Antigen Determination.

All assays were conducted using the Platelia *Aspergillus* EIA test (Bio-Rad Laboratories, Marnes, France). Reagents and test kits were provided by Bio-Rad. Testing was performed at the 2 study locations using identical methodology, as outlined in the manufacturer's instructions.

Galactomannan index (GMI) value was calculated for the positive and negative controls, as well as for each patient specimen (a mean GMI value was calculated for samples run in duplicate). GMI values were calculated by dividing the optical density of the sample by the mean optical density of the 2 cutoff control replicates. The positive control was expected to have a GMI value of greater than 2 for a run to be considered valid. Negative control samples were expected to have a GMI value of <0.4, and the cutoff control values were acceptable when ≥ 0.3 and ≤ 0.8. Patient samples with a calculated GMI value of ≥ 0.5 were considered positive for galactomannan.

Statistical Analysis.

The binomial distribution was used to compute confidence intervals for the proportion of patients having at least one positive result and for the proportion of patients with a positive result that was achieved before clinical diagnosis. Fisher exact test was used to compare sensitivity of the assay across the 2 institutions. Classic logistic regression[38] was used to explore the association of age with having at least one positive sample. Logistic regression based on generalized estimating equations was used in separate univariate models to explore the association of a positive result with age or antifungal therapy. The generalized estimating equation model treated multiple samples from the same subject as exchangeable repeated measurements.

RESULTS

Galactomannan Antigen Expression in Control Patients.

Seven (1.0%) of 686 samples from 39 control subjects produced a positive galactomannan EIA result (Table 2). All serum samples tested negative in 34 of 39 control subjects, giving a subject-level specificity of 87.2% [95% confidence interval (CI), 72.5–95.7]. Based on the

probability of a control subject having at least 1 positive sample, age was not associated with false positive results ($P = 0.9580$). Figure 1 shows the distribution of GMI values in samples from control patients. The 7 false-positive tests among the 5 patients gave a GMI value of ≤0.8, with 3 values above 0.6. Most values in the control group (98.4%) were ≤0.4 and 95.5% were ≤0.3.

Galactomannan Antigen Expression in Patients With Proven or Probable Invasive Aspergillosis.

At least 1 serum sample was positive in 11 of 17 pediatric oncology patients (65.7% subject-level sensitivity, 95% CI: 38.3–85.8) with invasive aspergillosis. Galactomannan EIA was positive in 99 of 304 samples from these patients with proven or probable invasive aspergillosis. Piperacillin-tazobactam was not used in the patients in this study.

Fifteen (88%) of 17 patients in this study had proven aspergillosis and 2 (12%) had probable invasive aspergillosis. Ten (67%) of 15 patients with proven invasive aspergillosis tested positive for galactomannan (95% CI: 38.3–88.2). Positive results were obtained in 98 of 283 (34.6%) samples taken from these patients. One of 2 patients with probable invasive aspergillosis yielded positive galactomannan results with 1 (4.8%) of 21 of samples in these subjects testing positive.

Dates of clinical and radiographic diagnosis and sample collection were available for 7 of 11 patients testing positive for galactomannan. A positive result on or before the date of clinical diagnosis was present in all 7 (100%; 95% CI: 59.0–100) of those patients. Galactomannan was detected a median of 10 days before clinical diagnosis. Among 6 of these patients, the positive result occurred 34, 25, 12, 9, 6, and 1 days before the date of clinical diagnosis. In 1 patient, the positive result was obtained on the date of diagnosis.

Galactomannan antigen expression was assessed in relationship to patient age, history of transplantation, and the use of antifungal therapy, including prophylactic and empirical usage. There was no statistically significant association of age with the probability of detecting galactomannan in at least 1 sample for a subject with proven or probable invasive aspergillosis ($P = 0.23$). The probability of testing positive in at least 1 sample was not significantly associated with history of hematopoietic stem cell transplant among subjects with proven or probable aspergillosis ($P = 0.24$) or among control subjects ($P = 0.67$). A positive result was obtained in at least 1 sample for 4 of 9 (44.4%) subjects receiving antifungal therapy and in 7 of 8 (87.5%) of subjects who did not receive such therapy ($P = 0.13$).

DISCUSSION

This study found that serum galactomannan is frequently expressed in pediatric oncology patients with invasive aspergillosis and infrequently detected above interpretative cut-off points in control populations. The sensitivity and specificity of this assay were comparable with that seen in several adult studies and with that reported in a recent meta-analysis.[21,22,24,29–32] In addition, a positive signal was obtained in most cases before clinical or radiographic evidence of infection.

Few studies have evaluated the use of galactomannan for detection of invasive aspergillosis in pediatric patients. Some studies have suggested a much lower degree of specificity of galactomannan in children.[24,39–42] These earlier studies consisted of small numbers of pediatric patients, including low-birth-weight infants who are not usually considered to be patients at high risk for invasive aspergillosis. Whether these earlier studies considered the effects of antimicrobial agents in causing false-positive results is not apparent.[43–46] Recent studies suggest that mannoproteins from milk or lipoglycans from some enteric bacteria, such as *Bifidobacterium* spp., may contribute to falsely positive serum galactomannan values.[40,41] The specificity observed in this study is comparable to that of a recent report of serum galactomannan in children.[48]

When the specimen-based false-positive rate is closely examined, the levels of the GMI were only slightly elevated above the interpretive cutoff point of 0.5. Given the relatively large number of samples, these slightly elevated values are compatible with the analytic variability expected around this value.

The sensitivity demonstrated in the current study is in accordance with some reports from the adult literature,[24,31] but it is also somewhat lower compared with that of some early reports.[29,48] However, these studies detected galactomannan in serum of adult patients with advanced and fatal invasive aspergillosis. Studies in experimental invasive pulmonary aspergillosis demonstrate that expression of galactomannan in serum varies directly with the tissue burden in lungs, histologic extent of infection, and mortality.[23] Laboratory animal studies and clinical data also demonstrate that concomitant use of antifungal agents reduces serum galactomannan levels.[49–51]

Finally, several studies in immunocompromised adult patients have demonstrated the potential value of prospective screening for expression of serum galactomannan for early diagnosis of invasive aspergillosis at times before clinical, radiographic, or microbiologic findings.[30,33,36,47,49,52] The findings presented here demonstrate the utility of serum galactomannan as a biologic marker that complements existing diagnostic modalities for early detection of invasive aspergillosis in immunocompromised pediatric oncology patients.

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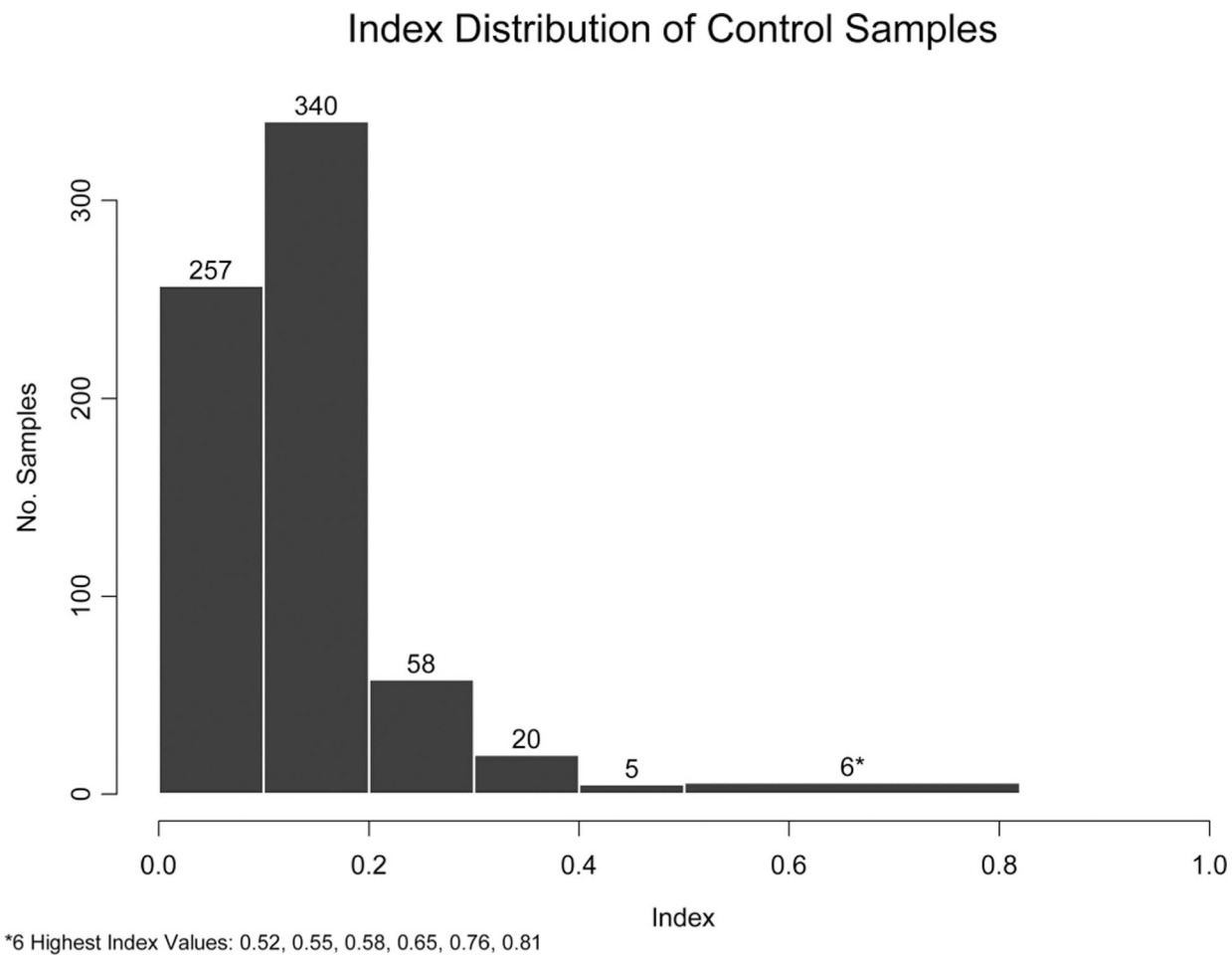

FIGURE 1.

Distribution of galactomannan indices from 686 samples among 39 pediatric oncology patients without clinically overt invasive aspergillosis. Seven (1.0%) of 686 samples expressed a positive galactomannan index. Numbers located at the top of each column indicate the number of samples within each index group.

TABLE 1.

Demographic Characteristics of Patients

Demographic Variable	Aspergillosis (n = 17)*	Controls† (n = 39)	Total (n = 56)
Age			
Mean	10.0	8.0	8.3
Range	1.0–17.0	0.3–18.0	0.3–18.0
Primary diagnosis			
Leukemia/MDS‡	14	22	36
Lymphoma	3	6	9
Solid tumor	1	10	11
Hematopoietic stem cell transplant recipients	8	14	22
Treatment with antifungal agents§	10	17	27

*Proven or probable aspergillosis by EORTC/IFICG and NIAID/MSG criteria.

†No clinical or laboratory evidence of aspergillosis.

‡Myelodysplastic syndrome.

§Antifungal agents included treatment for proven or probable aspergillosis, empirical therapy, or for prophylaxis.

TABLE 2.

Expression of Serum Galactomannan Antigen

	Aspergillosis*	Controls	Total
Patients			
Positive	11	5	16
Negative	6	34	40
Total	17	39	56
Samples			
Positive	99	7	106
Negative	205	679	884
Total	304	686	990

Patient-level sensitivity = 65%; Patient-level specificity = 87%; Specimen-level sensitivity = 33% (not all specimens are expected to be positive early in the course of infection); Specimen-level specificity = 99%; As the study was not designed to determine prevalence of invasive aspergillosis, positive and negative predictive values are not calculated.

*Proven or probable invasive aspergillosis by EORTC-BAMSG criteria.[37]