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Galactomannan use in clinical practice: providing free testing is not the full answer

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ABSTRACT

Introduction: Invasive aspergillosis is a condition associated with a high mortality rate mostly due to difficulties in performing an early diagnosis. In recent years, galactomannan detection has markedly improved the diagnosis of invasive aspergillosis, but very little is known on how physicians deal with this test in clinical practice.
Methods: This cross-sectional study aimed to analyze the indications for the use of serum galactomannan in a large Brazilian hospital, between 2015 and 2016. No specific protocol was in place for GM request. We reviewed the medical records of adult (>18 years-old) patients who were tested for galactomannan due to one the following indications: screening, diagnosis, or treatment follow-up. Additional variables included demographic data, underlying diseases, presence of neutropenia, and use of previous antifungal (anti-*Aspergillus*) drugs.
Results: The mean age of the patients was 51 years-old (sd ± 15.8), and 63.3% of patients were male. Patients with hematological malignancies accounted for 60.1% of the cases, mostly acute myeloid leukemia (19.6%). Galactomannan testing was positive in 12.2% of patients, including 1.6% of occasions in which the test was used for screening purposes, 13.2% for diagnosis, and 32.4% during follow-up. Median time for chest imaging request was two days before GM testing. Previous antifungal therapy was reported for 35.1% of patients, mostly amphotericin B (57.1%).
Conclusion: The correct use of galactomannan testing is essential for an early diagnosis of invasive aspergillosis, which may improve the prognosis of the disease. We demonstrated that clinicians usually ask for galactomannan tests to confirm imaging findings in patients who frequently were on antifungal drugs, something that could be improved by medical education. We observed a low frequency of galactomannan use for preemptive antifungal therapy (25.7%), which is worrying considering the well-known beneficial use of GM testing in this scenario.

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Introduction

Aspergillus species are opportunistic cosmopolitan fungi, being important causes of infection in immunosuppressed patients, mainly neutropenic individuals.[1,2] These filamentous fungi are also becoming increasingly common in non-neutropenic individuals,[3,4] in addition to being recognized as agents of a variety of clinical syndromes.[5] With the increase of treatments using immunosuppressants as well as of chronic diseases, an overall increment in the frequency of patients under high risk of opportunistic mycoses has been observed.[6]

Amongst the most common diseases caused by *Aspergillus* spp., we can highlight invasive aspergillosis (IA),[7] a condition responsible for high mortality rates, in which diagnosis is usually difficult and late.[8] Several techniques are used for diagnosing IA, in particular the detection of galactomannan (GM), a polysaccharide of the wall of *Aspergillus spp.* used as a microbiological substitute for IA diagnosis,[9] mostly in serum samples.[10] Positive tests would characterize the patient as having a probable IA, in combination with host factors and imaging tests.[1] As this technique has considerable specificity and allows for an early diagnosis, it is very useful for both the selection of patients needing therapy as well as monitoring of patients with IA.[11]

In Brazil galactomannan testing is provided free of charge by a pharmaceutical drug company to hospitals that consume their antifungal drug. Our institution has provided physicians with GM testing for many years in both serum and bronchoalveolar lavage samples, with no specific protocol for testing. In this context, we perceive the importance of characterizing the clinical scenarios in which GM serum testing has been used in clinical practice and how clinicians have correlated GM results with chest imaging findings.

Methods

Design, inclusion and exclusion criteria

This was a cross-sectional observational study carried out during the years 2015 and 2016 in a large (1200 beds) tertiary-care hospital. All medical records of adult (≥18 years) individuals tested for serum GM were considered for study, including outpatients and hospitalized patients. Patients were excluded if GM testing was not performed in the serum (e.g., bronchoalveolar lavage), if samples were obtained in another institution, and if medical records were not available or incomplete.

Variables and clinical groups

Clinical-demographic variables were studied and these were obtained from patient's medical records. These variables included: sex, age, result (optical index) of GM (considered positive if ≥0.5), underline diseases, immunosuppressive conditions, presence and duration of neutropenia and use of corticosteroids. We also obtained information on fungal culture request, in addition to previous (last week) use of anti-*Aspergillus* antifungal drugs. As per convention, neutropenia was defined as a neutrophil count equal or below 500 cells/mm^3.

GM serum requests were divided into the following groups: screening (individuals at risk of IA due to immunosuppression but with no evidence of disease); investigation for suspected IA (use for diagnostic purposes in individuals with signs and/or symptoms suggestive of IA); or use for therapeutic follow-up. In addition, it was evaluated whether the patient was treated because of the GM test result, and also if biopsies and/or imaging were performed temporally related to GM testing. Radiological findings (e.g., presence of nodules, halos or ground glass infiltrates) were also described.

Statistical analysis

Descriptive statistics were used to describe the data, and analysis of the results was performed using the statistical program SPSS® (version 24.0). Qualitative variables were compared by chi-square test or Fisher's test, as appropriate. Quantitative variables were assessed by the Student t test or Mann–Whitney test, depending on data distribution. *p*-Values ≤0.05 were considered statistically significant.

Ethical approval

The project was approved by the Ethics and Research Committees of the participant institutions, with no major comments on the study design.

Results

During the study period, 245 serum GM samples from 158 patients were evaluated, and 683 requests were excluded. There was a median of 1.5 samples per patient, ranging from 1–10 tests. Of the 158 tested patients, 43% were evaluated in 2015 and 57% in 2016. There was a predominance of male patients (63.3%), and the mean age was 51 years-old (standard deviation ± 15.8).

Regarding underlying diseases, 60.1% of patients had hematological malignancies, mainly acute myeloid leukemia (19.6%). In addition, 17.7% had non-Hodgkin's lymphoma and 8.2% acute lymphocytic leukemia. Still, 16.5% were recipients of solid organ transplants and 3.2% were HIV infected.

The majority of patients were tested for GM for diagnostic purposes (46.5%), followed by screening (preemptive use; 25.7%) and therapeutic follow-up (15.1%). Table 1 shows the distribution of underlying diseases according to GM indication (i.e., screening, diagnosis or follow-up).

Regarding the results of serum GM, the median of the optical indices was 0.14, ranging from 0.01 to 4.82. The overall frequency of GM positivity was 12.2% (30/245), ranging from 1.6% (screening) to 13.2% (diagnosis) and 32.4% (follow-up). Eighty-six samples (35.1%) were tested in the context of prior antifungal use, mainly amphotericin B (57.1% of the total), voriconazole (32.9%), posaconazole (4.3%), anidulafungin (4.3%), and itraconazole (1.4%). In only 20% (6/30) of the cases with positive GM results, GM testing triggered the onset of antifungal therapy.

The median time between a request for serum GM and the next test request was 26 days, ranging from 1 to 231 days; 46.9% (115/245) of the patients had only one request, being 44.0% in

Table 1 – Main underlying diseases and predisposing conditions for invasive aspergillosis, as stratified by the reason for serum galactomannan request.

	Hematological neoplasia *n* (%)	SOT *n* (%)	HIV *n* (%)	Neutropenia *n* (%)	Steroids *n* (%)	Positive GM *n* (%)	Total *n* (%)
Preemptive	51 (81.0)	3 (4.8)	1 (1.6)	37 (58.7)	44.4 (28)	1 (1.6)	63 (25.7)
Diagnosis	73 (64.0)	20 (17.5)	1 (0.9)	66 (57.9)	54.4 (62)	15 (13.2)	114 (46.5)
Follow-up	28 (75.7)	1 (2.7)	2 (5.4)	24 (64.9)	54.1 (20)	12 (32.4)	37 (15.1)

GM, galactomannan testing; HIV, human immunodeficiency virus; SOT, solid organ transplantation.

screening, 51.7% in diagnosis and 4.3% in the follow-up group. Regarding the presence and duration of neutropenia, mean duration was seven days in all groups.

Overall, chest imaging preceded GM request by a median of two days (range, 19 days before to seven days later). Chest imaging was requested before GM by a median of two days in both diagnostic and follow-up groups, and one day in the preemptive (screening) group. Regarding the imaging findings, there was a predominance of ground glass infiltrates and nodules, 49.0% (102/208) and 48.1% (100/208) respectively, whilst the halo signal was present in only 21.6% (45/208) of episodes of GM testing.

Discussion

Although the GM testing is widely used for diagnosing IA, little is known about how physicians use the test in clinical practice, particularly in the context of preemptive antifungal therapy. Until now, health care professionals' attitudes regarding the timing of the request for chest imaging tests in relation to the GM testing had not yet been documented in Brazil. Here we showed that most clinicians make inadequate use of the GM serum testing, including not asking for serial (i.e., 2–3 times weekly) testing, as well as and not using the test as a trigger for chest computed tomography (CT) request. Rather, physicians commonly ask for chest CT before GM testing. Until recently, empiric antifungal therapy was widely used for patients with prolonged neutropenia who remained febrile despite the use of broad-spectrum antimicrobials.[12] However, studies initiated by Maertens et al.[13] have shown that it is possible to markedly reduce antifungal use in these patients with the use of tests with high negative predictive value, such as GM, in the so-called preemptive antifungal therapy. However, the positive predictive value of the GM test is known to be low to moderate,[14] reinforcing the importance of testing in a new sample to increase the test prediction of disease. In our study, only 43 patients out of 158 had a repeated GM test, and GM positivity was only 1.6% in the clinical screening group, a surprisingly low frequency.

In our hospital, having free GM testing does not seem to help physicians making a proper diagnosis of IA. The frequency of a positive GM test was ridiculously low in the preemptive strategy, which may be related to a selection of patients with low pre-test probability of disease (unlikely) or (more likely) inadequate serial monitoring. GM testing was frequently used to diagnose patients with IA, but chest CT was (erroneously) usually requested before GM was tested, and many patients were testes after antifungal therapy had alredy been initiated. That clearly shows that advocacy for having GM testing in place is not enough to improve the outcome of patients infected with invasive fungal diseases – education of health care providers is also critical. Such training would involve education about the high negative predictive value of serum GM testing (particularly for the neutropenic patient), in addition to reinforcing the importance of GM use in the preemptive strategy. In that case, a positive serum GM result should led physicians to order a chest CT, in order to confirm the results obtained by GM in the serum.

Conflicts of interest

Dr. Pasqualotto has consulted and/or received research grants for Pfizer, Gilead, United Medical, MSD, and Astellas, all companies that produce or commercialize antifungal drugs.

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