BRAZ J INFECT DIS 2017;xxx(xx):xxx–xxx

The Brazilian Journal of
INFECTIOUS DISEASES

www.elsevier.com/locate/bjid

Original article

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

Jeniffer S. dos Santos[a], Djuli M. Hermes[a], Alessandro C. Pasqualotto[b,c,*]

[a] Centro Universitário Ritter dos Reis (UniRitter), Porto Alegre, RS, Brazil
[b] Santa Casa de Misericórdia, Porto Alegre, RS, Brazil
[c] Universidade Federal de Ciências da Saúde, Porto Alegre, RS, Brazil

ARTICLE INFO

*Article history:*
Received 27 September 2017
Accepted 5 November 2017
Available online xxx

*Keywords:*
*Aspergillus*
Aspergillosis
Opportunistic infections
Diagnosis
Tomography
Neutropenia
Immunosuppressed

ABSTRACT

*Introduction:* Invasive aspergillosis (IA) is a condition associated with a high mortality rate due to difficulties in performing an early diagnosis. In recent years, galactomannan (GM) detection has markedly improved the diagnosis of IA, 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 GM 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 GM 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%). GM 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 GM testing is essential for an early diagnosis of IA, which may improve the prognosis of the disease. We demonstrated that clinicians usually ask for GM tests to confirm imaging findings, something that could be improved by medical education activities. We observed a low frequency of GM use for preemptive antifungal therapy (25.7%), which is worrying considering the well-known beneficial use of GM testing in this scenario.



* *Corresponding author.*
E-mail address: pasqualotto@santacasa.tche.br (A.C. Pasqualotto).

https://doi.org/10.1016/j.bjid.2017.11.002

## 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 increase 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 test request. 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 patient came from 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, 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



Please cite this article in press as: dos Santos JS, et al. Galactomannan use in clinical practice: providing free testing is not the answer. Braz J Infect Dis. 2017. https://doi.org/10.1016/j.bjid.2017.11.002