The value of the serum *Aspergillus* galactomannan (GM) to diagnose invasive aspergillosis (IA) and invasive fungal infections (IFI) as defined by European Organization of Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) in recipients of hematopoietic stem cell transplants (HSCT).

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INTRODUCTION

- Detection of serum GM is widely used and is incorporated into the definitions proposed for diagnosis of IFI by the EORTC/MSG[1].
- Our center uses this as a diagnostic test to be done in patients suspected to have IFI and not as a periodic surveillance test.
- Wide variability in its sensitivity has been reported based on the population tested and cut-off used[2,3].
- **Goal**: To describe test performance characteristics and identify risk factors for positivity.

METHODS

- **Study design:** Retrospective analysis, chart review and review of institutional informatics database to ascertain diagnosis of IFI (includes host criteria, radiology, microbiology, pathology data).
- **Population**: All patients who had ≥1 GM after HSCT from December 2006 (since introduction of test) to September 2015.
- Cut-off of ≥0.5 optical density index was used to define a positive test as this is the value recommended to improve test accuracy parameters[3].
- **Exclusion criteria** for tests included invalidity of results, all tests for a patient after the first positive, duplicate negative tests after diagnosis of at least a possible IFI, and positive tests in patients who had insufficient data to ascertain whether they had IFI.
- We collected data for receipt of semisynthetic penicillins in the week prior to a positive test in order to rule out false positives related to this.
- **Data analysis**: Univariate analyses to compare baseline characteristics. Student t-test was used to compare continuous variables and χ^2 test and Fisher's exact test for categorical variables.

RESULTS

- **Baseline characteristics** of the 587 patients who had a GM after transplant were comparable except for patient source of HSCT (autologous versus allogeneic) .
- 1/125 patients with an autologous HSCT and 36/462 patients with an allogeneic HSCT had a positive test (p=0.003). (Table 1.)
- Allogeneic transplant recipients are at risk for IA. AML/MDS, diabetes and GVHD are also risk factors for IA, (Table 2.) but not for GM positivity.

Table 1. Characteristics of patients with and without positive galactomannan testing (n=587)

Patient characteristic	Patients with ever positive GM(n=37)	Patients with never positive GM (n=550)	P-value
Mean age at testing (years)	55.0	52.8	0.32
Male sex	24 (64.9%)	340 (61.8%)	0.71
White race	36 (97.3%)	502 (91.3%)	0.35
Primary malignancy AML or MDS	19 (51.4%)	239 (43.5%)	0.35
Allogeneic transplant	36 (97.3%)	426 (77.5%)	0.0028
Cardiovascular disease	8 (21.6%)	167 (30.4%)	0.26
Diabetes mellitus	21 (56.8%)	265 (48.2%)	0.31
Chronic kidney disease	15 (40.5%)	152 (27.6%)	0.09
Cirrhosis	1(2.7%)	31 (5.64%)	0.71
Chronic respiratory failure	18 (48.65%)	264 (48.0%)	0.94
Acute or chronic GVHD	22 (59.5%)	304 (55.3%)	0.62

Table 2. Characteristics of patients with and without at least possible invasive aspergillosis (n=587)

Patient characteristic	Patients ever diagnosed with at least possible IA (n=85)	Patients never diagnosed with at least possible IA (n=502)	P-value
Mean age at latest transplant (years)	51.9	52.2	0.85
Male sex	49 (57.7%)	315 (62.8%)	0.37
White race	78 (91.8%)	460 (91.6%)	0.97
Primary malignancy AML or MDS	49 (57.7%)	210 (41.8%)	0.0066
Allogeneic transplant	79 (92.9%)	383 (76.3%)	0.0005
Cardiovascular disease	23 (27.1%)	152 (30.3%)	0.55
Diabetes mellitus	51(60.0%)	235 (46.8%)	0.02
Chronic kidney disease	28 (33.0%)	139 (27.7%)	0.32
Cirrhosis	8 (9.4%)	24 (4.8%)	0.11
Chronic respiratory failure	48 (56.5%)	234 (46.6%)	0.09
Acute or chronic GVHD	56 (65.9%)	271 (54.0%)	0.04

GM = galactomannan, IA = invasive aspergillosis, AML= Acute myelogenous leukemia, MDS = Myelodysplastic syndrome, GVHD = Graft versus host disease

Table 3. Test results by diagnosis at time of testing in all patients (Table 3a; n=841) and those with only proven IFI (Table 3b; n=35)

3a	At least possible IA	No suspected IA	
GM +	28 (TP)	9 (FP)	37
GM -	46 (FN)	758 (TN)	804
	74	767	841

3b	Proven IA	No proven IA	
GM +	6 (TP)	6 (FP)	12
GM -	1 (FN)	22 (TN)	23
	7	28	35

TP = true positive, FP =false positive, TN = true negative, FN = false negative

- **Test performance**: 841 tests were performed in 587 patients.
- **Test positivity prevalence**: 37 /841(4.4%) (Table 3a.), 28/37 (75.7%) were true positives.
- **False positive rate**: 9/841 (1.1%); 6 of these were in patients infected with other molds. No patient with a positive test had received any semisynthetic penicillin within a week prior to the test.
- 758/841(90.1%) tests were negative in cases who did not satisfy criteria for at least possible IFI at the time of the test.
- **Sensitivity** of the assay to detect at least possible IA was 37.9% (26.8 – 49.9%); specificity was 98.8% (97.8 - 99.5%); positive predictive value was 75.7% (58.8 – 88.2%) and negative predictive value was 94.3% (92.4 - 95.8%). (Table 4.)
- In cases of proven IFI, sensitivity to detect proven IA rose to 85.7% (42.1- 99.6%).

Table 4. Test performance by diagnosis at time of testing in all patients and those with only proven IFI

Test statistic	For at least possible IA	Confidence interval	For proven IA	Confidence interval
Sensitivity (%)	26.5	18.2 – 36.1	85.7	42.1 – 99.6
Specificity (%)	99.0	98.3 – 99.6	78.6	59.1 – 91.7
Positive predictive value (%)	79.4	62.1 – 91.3	50.0	21.1 – 78.9
Negative predictive value (%)	90.6	88.4 – 92.6	95.7	78.1 – 98.9

CONCLUSIONS

- Serum GM was widely overused for diagnosis of IA at our institution.
- Limiting its use to patients with higher pre-test probability of an IFI increases its sensitivity.
- For HSCT recipients, we suggest performing the test only in allogeneic HSCT recipients who satisfy criteria for at least possible IFI per EORTC/MSG; this strategy would have missed only 1 positive test in our cohort and would have prevented >90% of the testing.

REFERENCES

1. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive. *Clin Infect Dis*. 2008;46(12):1813-1821. doi:10.1086/588660.Revised.
2. Miceli MH, Maertens J. Role of Non – Culture-Based Tests , with an Emphasis on Galactomannan Testing for the Diagnosis of Invasive Aspergillosis. 2015;1(212):650-661. doi:10.1055/s-0035-1562892.
3. Marr KA, Balajee SA, McLaughlin L, Tabouret M, Bentsen C, Walsh TJ. Detection of galactomannan antigenemia by enzyme immunoassay for the diagnosis of invasive aspergillosis: variables that affect performance. *J Infect Dis*. 2004;190(3):641-649. doi:10.1086/422009.