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Prognostic Features of Galactomannan Antigenemia in Galactomannan-Positive Invasive Aspergillosis▽

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Prognostic features of serum galactomannan (GM) remain poorly defined in patients with GM-positive invasive aspergillosis (GPA). We identified 93 patients with proven or probable invasive aspergillosis (IA) and GM values of ≥0.50 from January 2005 to March 2009. We used Cox modeling of time to 6- and 12-week mortality for the GM level at the time of diagnosis (GM_0), GM decay in the week following diagnosis in 72 patients with ≥2 GM values, other predictors of mortality, and antifungal use during the week following diagnosis. Six-week mortality was 55% in the whole cohort and 43% in patients with ≥2 GM determinations. The hazard ratio (HR) of GM_0 per unit increase and 1-week GM decay per unit decline per week were 1.25 (95% confidence interval [CI], 1.01 to 1.54; $P = 0.04$) and 0.78 (95% CI, 0.63 to 0.96; $P = 0.02$), respectively, adjusting for other predictors of IA mortality; these values remained stable after adjusting for antifungal use and were predictive of all-cause mortality at 12 weeks with similar adjusted HR values. We conclude that the combination of GM_0 and 1-week GM decay is predictive of all-cause mortality in patients with GPA, independent of other traditional risk factors for mortality and antifungal exposure, supporting GM decay as a potential surrogate endpoint for future antifungal therapeutic trials.

Galactomannan (GM) is a cell wall polysaccharide released by growing *Aspergillus* hyphae (14, 20). In experimental animal models of pulmonary invasive aspergillosis (IA), serum GM antigenemia correlates with tissue fungal burden, increasing with progressive disease and declining with effective antifungal therapy (1, 2, 6, 12, 16, 17, 24). In animal models, rising GM antigenemia has been associated with mortality, while clearance of antigenemia has been associated with survival (2, 12, 16, 17).

A similar relationship has been observed empirically in humans with IA. Soon after the development of serum GM testing, patients who died of IA were often noted to have progressively rising GM levels, while patients who survived IA gradually cleared their antigenemia (3, 4, 10, 11, 21, 23). It has also been observed that the use of mold-active antifungal therapy blunts GM diagnostic sensitivity in this setting, as antigenemia declines below the diagnostic threshold with effective therapy (12, 13).

Recently, two studies proposed a binarized GM outcome as a possible surrogate outcome measure for IA, based on a strong κ correlation between GM outcome and poor clinical outcomes in hematologic malignancy and hematopoietic stem cell transplantation (HSCT) patients (9, 27). Success was defined in these studies as a repeatedly negative serum GM in the absence of new extrapulmonary lesions and failure as a persistently positive GM level or death within 2 weeks of GM normalization unless autopsy failed to show evidence of IA. A review of 27 studies of serial GM screening for the diagnosis of IA in hematologic malignancy and HSCT patients also found a correlation between GM levels in the week preceding IA outcome and clinical outcome (15). A simple correlation, however, is insufficient for establishing surrogacy; measurements that correlate with the outcome of interest are not useful surrogates unless they also capture the net effects of treatment on outcome (19, 25). These studies also stratified patients by GM features available late in the course of IA, just proximal to the clinical outcome of interest, rather than by baseline and early GM features.

We hypothesized that early GM features, namely, the height of the initial GM at the time of diagnosis and the subsequent rate of GM decay within the initial week following diagnosis, were important factors in predicting clinical outcome, and we sought to further refine the relationship between GM kinetics and mortality, including the effect of antifungal therapy on this relationship.

MATERIALS AND METHODS

Patient selection and data collection. We reviewed the results of all GM values from 1 January 2005 to 31 March 2009 at Brigham & Women's Hospital/Dana-Farber Cancer Institute. All patients with proven or probable IA by 2008 European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) classification criteria (5) and at least one serum GM value of ≥0.50 were included in this analysis. Demographic data, baseline diagnoses, reasons for GM testing, details of immunosuppressive and systemic antifungal therapy, and results of relevant laboratory, microbiology, radiology, and pathology studies were recorded. We recorded the results of all GM values following the first value of ≥0.50. Mortality and cause of death were recorded at 6 weeks, after which mortality attributable to IA wanes (22, 26), and at 12 weeks, recommended as a secondary time point for IA outcome assessment by the recent EORTC/MSG therapeutic response and outcome consensus statement (22).

GM testing. All serum GM assessments were performed with the Platelia *Aspergillus* enzyme immunoassay (EIA) (Bio-Rad Laboratories, Hercules, CA) according to the manufacturer's standard protocol. GM testing was performed at the discretion of clinical care teams.

Definitions. The GM level at the time of diagnosis (GM_0) was defined as the first GM value of ≥0.5 in the setting of appropriate EORTC/MSG host factors, clinical criteria, and mycologic criteria (5). Patients who did not otherwise meet

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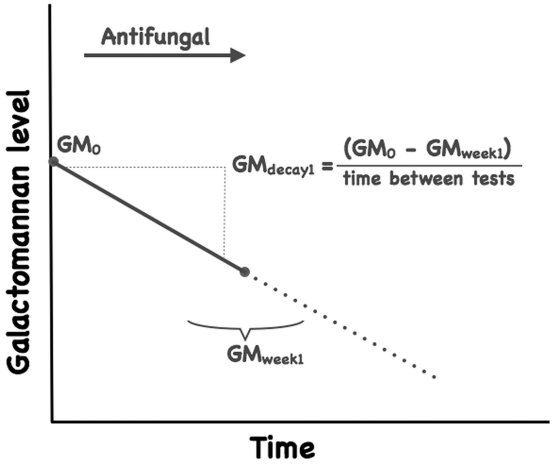

FIG. 1. Schematic diagram of GM_0 and determination of 1-week GM decay for a patient with GM-positive IA (GM_{decay1}). GM_{week1}, GM measurement obtained around 1 week after GM_0.

criteria for proven or probable IA were not included. No patients received piperacillin-tazobactam or any other parenteral β-lactam/β-lactamase combinations.

For patients with ≥2 serum GM values, a daily GM decay value was calculated by dividing the difference between GM_0 and a GM measurement obtained around 1 week after GM_0 by the number of days between the tests (Fig. 1). If a day 7 GM was unavailable, the GM value soonest after day 7 was preferentially used for the calculation, dividing by the actual number of days between tests. Daily GM decay values were multiplied by 7 to yield a 1-week GM decay value in EIA units per week.

Statistical methods. Wilcoxon rank-sum tests were used to compare medians. We used the method of Kaplan and Meier to estimate all-cause survival at 6 and 12 weeks for the whole cohort and for the subset of patients with ≥2 GM values.

Cox regression modeling was used to generate unadjusted hazard ratios (HRs) for GM_0, 1-week GM decay, and other potential predictors of mortality, including age, gender, and EORTC/MSG-defined host risk factors (Fig. 2). GM_0, 1-week GM decay, and age were modeled as continuous covariates. Univariate HRs were also generated for voriconazole, liposomal amphotericin B, and echinocandin use during the 1 week following GM_0 as daily time-dependent covariates.

Cox proportional hazards modeling was used to generate adjusted HRs of time to all-cause mortality at 6 and 12 weeks. Possible predictors of mortality were included in the multivariable Cox regression model if they were associated with this outcome in the univariable analysis or previously identified in the literature as significant risk factors. We assessed the impact of the inclusion of an interaction term between GM_0 and 1-week GM decay. We also assessed the impact of adjusting for time-dependent daily voriconazole, liposomal amphotericin B, and echinocandin (caspofungin or micafungin) use on our multivariable regression model.

All analyses were performed using STATA version 10 (STATA Corporation, College Station, TX). The hospital's Human Research Committee approved this study.

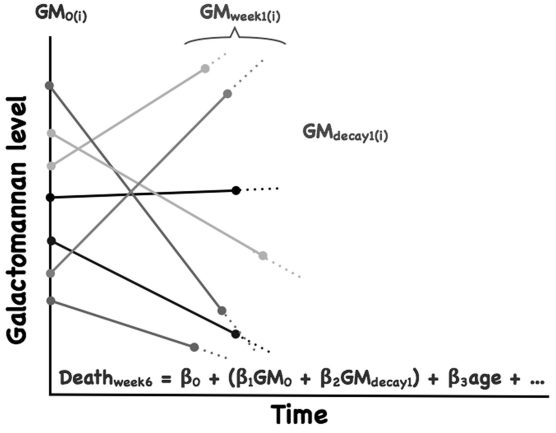

FIG. 2. Schema of the derivation of the Cox proportional hazards model for GM_0, 1-week GM decay, and other predictors on the probability of death at 6 weeks following the diagnosis of GM-positive IA. Each line represents a patient (i) with a specific GM_0 and 1-week GM decay slope.

TABLE 1. Baseline characteristics

Characteristic	Value (%) for:	
	All patients	Patients with ≥2 GM values
Total no.	93	72
Age (yr)	55 (42–63, 17–93)[a]	53 (41–62, 17–78)[a]
Female	42 (45.2)	37 (51.4)
Solid organ transplant	11 (11.8)	9 (12.5)
Malignancy	66 (71.0)	53 (73.6)
Hematologic malignancy	58 (62.4)	49 (68.1)
Allogeneic HSCT[b]	34 (36.6)	33 (45.8)
Acute grade III to IV GVHD	5 (5.4)	5 (6.9)
High-risk neutropenia[c]	35 (37.6)	30 (41.7)
Duration of high-risk neutropenia in 60-day period prior to GM_0 (days)[c]	35 (23–60, 13–60)[a]	37 (27–60, 13–60)[a]
Prolonged corticosteroid use within 90 days of GM_0[d]	37 (39.8)	29 (40.3)
T-cell immunosuppressants within 90 days of GM_0[e]	45 (48.4)	39 (54.2)

[a] Median, IQR, and range.
[b] There were no autologous HSCT patients in this cohort.
[c] High-risk neutropenia was defined according to the 2008 EORTC/MSG criteria for IFD classification as a recent history of neutropenia ($<0.5 \times 10^9$ neutrophils/liter for >10 days) temporally related to the onset of fungal disease.
[d] Prolonged corticosteroid use was defined according to 2008 EORTC/MSG IFD classification criteria as a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for >3 weeks.
[e] T-cell immunosuppressants were defined according to 2008 EORTC/MSG IFD classification criteria as recognized T-cell immunosuppressants, such as cyclosporine, tumor necrosis factor alpha blockers, specific monoclonal antibodies such as alemtuzumab, or nucleoside analogues.

RESULTS

Patient characteristics. We identified 93 patients with GM-positive IA (GPA) during the study period; 23 patients had proven IA, and 70 had probable IA. Baseline characteristics are presented in Table 1. While most patients had at least one traditional EORTC/MSG host factor, there were cases of proven IA in patients who were exposed to corticosteroids and other immunosuppressants who did not meet the dosing or duration definitions of the current classification criteria (5).

GM testing was triggered by a pneumonic syndrome in 66 patients (71.0%), febrile neutropenia in 17 patients (18.3%), sepsis in four patients (4.3%), skin nodules in two patients (2.2%), sinus or ear symptoms in two patients (2.2%), and microbiologic findings in two patients (2.2%).

Only one patient with GPA had isolated sinus disease. The remaining 92 patients had pulmonary IA at minimum, and eight of these patients had multifocal disseminated IA.

Forty-three patients (46.2%) had definitive microbiologic

TABLE 2. Cox proportional hazards model for GM_0, 1-week GM decay, and other potential predictors of 6-week mortality

Covariate	Univariate HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
GM_0 (per EIA unit increase)	1.27 (1.08–1.49)	0.005	1.25 (1.01–1.54)	0.039
1-wk GM decay (per EIA unit/week decline)[a]	0.82 (0.66–1.02)	0.075	0.78 (0.63–0.96)	0.020
Age, per decade	1.16 (0.91–1.48)	0.230	1.06 (0.83–1.35)	0.625
Allogeneic HSCT[b]	0.64 (0.31–1.31)	0.225	0.59 (0.26–1.33)	0.200
Acute grade III to IV GVHD	1.95 (0.59–6.41)	0.274		
High-risk neutropenia[c]	0.79 (0.39–1.62)	0.521	1.84 (0.71–4.75)	0.211
Prolonged corticosteroids within 90 days of GM_0[d]	3.27 (1.61–6.65)	0.001	3.53 (1.40–8.94)	0.008
T-cell immunosuppressants within 90 days of GM_0[e]	0.45 (0.22–0.91)	0.026		

[a] Negative GM decay values reflect an increase in GM EIA a week from GM_0; the inverse of the HR (1/0.78 = 1.28) should be used to calculate the HR in those cases.

[b] There were no autologous HSCT patients in this cohort.

[c] High-risk neutropenia was defined according to the 2008 EORTC/MSG criteria for IFD classification as a recent history of neutropenia ($<0.5 \times 10^9$ neutrophils/liter for >10 days) temporally related to the onset of fungal disease.

[d] Prolonged corticosteroid use was defined according to 2008 EORTC/MSG IFD classification criteria as a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for >3 weeks.

[e] T-cell immunosuppressants were defined according to 2008 EORTC/MSG IFD classification criteria as recognized T-cell immunosuppressants, such as cyclosporine, tumor necrosis factor alpha blockers, specific monoclonal antibodies such as alemtuzumab, or nucleoside analogues.

identification of their causative *Aspergillus* species; 33 grew *A. fumigatus*, six *A. flavus*, two *A. niger*, and two *A. terreus*.

Antifungal therapy. Ninety patients (96.8%) received systemic antifungal therapy. Forty-three patients (46.2%) were receiving antifungal therapy at the time of GM_0 for a median of 7 days (interquartile range [IQR], 2 to 17; range, 1 to 60) prior to GM_0; 24 (55.8%) were receiving echinocandins, 11 (25.6%) voriconazole, seven (16.3%) liposomal amphotericin B, and one (2.3%) itraconazole. These antifungals were prescribed for empirical treatment of febrile neutropenia or pulmonary syndromes. Of the 24 patients receiving echinocandins on the day of GM_0, 21 (87.5%) were switched to voriconazole during the week following GM_0, while the other three patients remained on echinocandin therapy.

Forty-three additional patients (46.2%) started antifungal therapy during the week following GM_0, 18 (41.9%) on the day of GM_0 and 11 (25.6%) the day following GM_0. Of these patients, 18 (41.9%) received voriconazole, 17 (39.5%) echinocandins, and eight (18.6%) liposomal amphotericin B as initial antifungal therapy. There were numerous antifungal therapeutic changes in the days following GM_0.

Three patients started voriconazole therapy 8, 9, and 10 days following GM_0, and one patient with slowly eroding pulmonary mycetomas started voriconazole therapy 33 days after GM_0. The three patients who did not receive systemic antifungal therapy died 1, 4, and 7 days after GM_0.

GM test use. Of the 93 GPA patients, 72 had ≥2 GM values during the 6 weeks following GM_0. Patients in this subset had a median of four GM values during this period (IQR, 2 to 7; range, 2 to 17). HSCT recipients had significantly more GM values than did non-HSCT patients, with a median of six (IQR, 3 to 9; range, 2 to 17) compared to four (IQR, 2 to 5; range, 2 to 11) values.

Of the 72 GPA patients with ≥2 GM values, 22 (30.6%) had 1-week GM drawn on day 7, and 11 (15.3%) had GM drawn on day 8. The median number of days between GM_0 and 1-week GM was 7 (IQR, 7 to 9; range, 1 to 40), and the distribution was positively skewed, with a skewness of +3.2.

GM parameters. The median GM_0 for all patients was 1.02 (IQR, 0.72 to 2.04; range, 0.50 to 8.45). The median GM_0 for the 72 patients with ≥2 GM values was 1.01 (IQR, 0.72 to 1.95; range, 0.50 to 8.45).

Median GM decay was 0.32 EIA units per week (IQR, −0.12 to 0.95; range, −9.73 to 6.94). A negative number indicates an increase in GM in the week following GM_0.

Outcomes. Actuarial all-cause mortality was 0.55 (95% confidence interval [CI], 0.45 to 0.65) at 6 weeks and 0.62 (95% CI, 0.52 to 0.72) at 12 weeks in the whole cohort, and 0.44 (95% CI, 0.34 to 0.57) at 6 weeks and 0.54 (95% CI, 0.43 to 0.66) at 12 weeks in the 72 patients with ≥2 GM values.

Of the 51 patients who died during the 6 weeks following GM_0, 9 (17.6%) underwent autopsy, with confirmation of IA in all cases. There were no autopsies performed in the additional seven patients who died 6 to 12 weeks after GM_0.

Cox proportional hazards models at 6 weeks. Among all 93 patients with GPA, the crude HR for GM_0 for time to mortality at 6 weeks was 1.23 (95% CI, 1.07 to 1.40; $P = 0.003$) per unit increase in EIA. Adjusting for age, allogeneic HSCT, prolonged corticosteroid use, and high-risk neutropenia, the adjusted HR for GM_0 for the full cohort of 93 GPA patients was 1.13 (95% CI, 0.97 to 1.32; $P = 0.11$) per unit increase in EIA.

Unadjusted and adjusted HR values for GM_0, 1-week GM decay, and other potential predictors of time to 6-week mortality are presented in Table 2 for the 72 GPA patients with ≥2 GM values. The adjusted HR for GM_0 for time to mortality at 6 weeks was 1.25 (95% CI, 1.01 to 1.54; $P = 0.04$) per unit increase in EIA. The adjusted HR for 1-week GM decay was 0.78 (95% CI, 0.63 to 0.96; $P = 0.02$) per EIA unit decline over the week following GM_0. There was no evidence of confounding of the combination of GM_0 and 1-week GM decay in the adjusted model. Grade III to IV acute graft-versus-host disease (GVHD) was excluded from the adjusted proportional hazards model because of the small number of observations in our cohort. T-cell immunosuppressants were also excluded from the adjusted proportional hazards model because the model became overspecified with the addition of this covariate, and there was colinearity between T-cell immunosuppressants and HSCT. There were no significant changes in the adjusted HR estimates of the covariates that remained in the final model

TABLE 3. Cox proportional hazards model for GM_0 and 1-week GM decay, adjusting for antifungal exposure in the week following GM_0 as time-dependent covariates

Characteristic	HR (95% CI)	*P* value
Unadjusted antifungal drug exposure of:		
Voriconazole[a]	0.40 (0.22–0.70)	0.002
Liposomal amphotericin B	1.59 (0.58–4.35)	0.364
Echinocandins[b]	1.45 (0.75–2.83)	0.273
Effect of adjusting multivariable model for voriconazole use on[c]:		
GM_0 (EIA, per unit increase)	1.30 (1.06–1.59)	0.011
1-wk GM decay (EIA units/week, per EIA unit/week decline)	0.76 (0.60–0.96)	0.019
Voriconazole[a]	0.42 (0.20–0.87)	0.020
Effect of adjusting multivariable model for liposomal amphotericin B use on[b]:		
GM_0 (EIA, per unit increase)	1.27 (1.03–1.58)	0.027
1-wk GM decay (EIA units/week, per EIA unit/week decline)	0.76 (0.61–0.94)	0.012
Liposomal amphotericin B	2.49 (0.49–12.79)	0.274
Effect of adjusting multivariable model for echinocandin use on[b]:		
GM_0 (EIA, per unit increase)	1.23 (0.99–1.53)	0.062
1-wk GM decay (EIA units/week, per EIA unit/week decline)	0.80 (0.64–1.01)	0.057
Echinocandins	1.57 (0.59–4.17)	0.367

[a] One patient in the voriconazole analysis received itraconazole rather than voriconazole.
[b] Caspofungin was used until November 2007; micafungin was used thereafter.
[c] Also adjusting for age, allogeneic HSCT, high-risk neutropenia, and prolonged corticosteroid use (individual adjusted HR not shown; see Table 2).

with the addition of T-cell immunosuppressants as an additional variable. Baseline renal dysfunction (modeled as continuous glomerular filtration rate at IA diagnosis) was not a significant predictor of 6-week mortality alone or when added to the multivariable model. There were no significant changes in the adjusted HR estimates with the inclusion of a $GM_0 \times$ 1-week GM decay interaction term.

Assessment of effect of antifungal therapy. Unadjusted HRs for antifungal therapy with azoles, liposomal amphotericin B, and echinocandins in the week following GM_0 for 6-week all-cause mortality are presented in Table 3. The impact of adjusting for daily administration of each systemic antifungal agent on the multivariable Cox proportional hazards model developed above is summarized in Table 3. Adjusting for systemic voriconazole, liposomal amphotericin B, or echinocandin use during the week following GM_0, controlling for age, allogeneic HSCT, high-risk neutropenia, and prolonged corticosteroid use had minimal effect on HR estimates for GM_0 or 1-week GM decay. Voriconazole use was protective against mortality at 6 weeks in the adjusted model, and while liposomal amphotericin B and echinocandins were associated with elevated HRs for mortality at 6 weeks, they did not reach statistical significance.

There was no evidence of confounding or effect modification by the receipt of empirical antifungal therapy prior to GM_0 when this covariate was included in the model.

Secondary analysis of 12-week outcome. GM_0 and 1-week GM decay were also predictive of outcome at 12 weeks. In patients with ≥2 GM values, the crude HR was 1.19 (95% CI, 1.04 to 1.37; $P = 0.011$) for GM_0 and 0.79 (95% CI, 0.64 to 0.96; $P = 0.020$) for 1-week GM decay for 12-week all-cause mortality. In the multivariable model, the adjusted HR was 1.27 (95% CI, 1.03 to 1.55; $P = 0.024$) per rise in EIA unit for GM_0 and 0.75 (95% CI, 0.61 to 0.92; $P = 0.006$) per EIA unit decline per week for 1-week GM decay.

DISCUSSION

We analyzed early GM prognostic features in all patients with GPA at our institution and found both GM_0 and 1-week GM decay to be predictive of time to all-cause mortality at 6 and 12 weeks, after adjusting for other traditional risk factors for mortality. Each EIA unit increase in GM_0 increased the hazard of time to all-cause mortality at 6 weeks by 25%, while each GM EIA unit decline in the week following GM_0 decreased the risk of time to all-cause mortality at 6 weeks by 22%.

In an unadjusted analysis, the colinear covariates HSCT and T-cell immunosuppressant use decreased the hazard of time to mortality, possibly because of a higher clinical index of suspicion and more-intensive serum GM surveillance in this subgroup, with a lower threshold for initiation of systemic antifungal therapy, but these factors were not predictive of time to mortality in either the 6- or 12-week multivariable model. In our adjusted Cox proportional hazards model, only GM_0, 1-week GM decay, and prolonged exposure to corticosteroids within the preceding 60 days predicted time to mortality at 6 and 12 weeks. These hazard ratios remained stable even after adjusting for receipt of systemic antifungal therapy with voriconazole, liposomal amphotericin B, and echinocandins in the week following GM_0.

Strengths of this study include its relatively large and unselected sample of all patients with GPA at our institution over 4 years and its nuanced assessment of early GM kinetic features in predicting time to mortality. A significant limitation of our study was the irregularity of GM monitoring after GM_0, given its retrospective nature and GM testing at the discretion of clinical care teams. For 1-week GM, we preferentially considered the GM value soonest after day 7 if a day 7 GM was unavailable, evident in the positively skewed distribution of the number of days between GM_0 and 1-week GM, and likely

underestimated true 1-week GM decay in patients who survived past 1 week, thus underestimating the protective effect of 1-week GM decay on all-cause mortality. Our autopsy rates were also relatively low, which limited our ability to analyze GM prognostic features for IA-specific mortality.

An ideal surrogate outcome marker meets the following criteria: (i) replaces a comparatively remote but most clinically meaningful "true" endpoint with one more proximate in time to the study intervention; (ii) is convincingly related to the hazard rate for the true endpoint; and (iii) mediates at least a substantial portion of treatment effect on the true endpoint (18, 19, 25). Proving surrogacy is a challenging endeavor, due to the tremendous biological complexity of the relationship between the surrogate candidate, the true outcome, and the effects of various therapeutic measures on both of these parameters. In the subset of IA patients with GPA, for example, serum GM is a product of numerous factors, including the virulence of the *Aspergillus* species, infecting inoculum, location of the infection, timeliness of diagnosis, immune status of the host, the effectiveness of host hepatic and renal metabolism in clearing fungal mannans from the bloodstream, and the effectiveness of various antifungal therapy regimens, among many others (14). In addition, patients with IA are usually at risk of death due to their underlying conditions, aggressive treatments and their toxicities, and other potentially fatal nonfungal infections.

Many empirical experimental and clinical observations indirectly support serum GM as a surrogate outcome marker in GPA. Serum GM is standardized, reproducible, continuous, and highly specific for IA in the absence of certain parenteral β-lactam antibiotics and other products industrially produced in *Aspergillus* species (8). GM correlates closely with fungal burden in *in vivo* models and appears to be inextricably linked to *Aspergillus* pathogenesis; in an elegant alveolar epithelial-endothelial cell bilayer model, the first appearance of GM in the endothelial compartment occurred as hyphae invaded the endothelial compartment (7). Prior studies have described a correlative relationship between failure to clear GM and poor clinical outcomes (9, 27) and a correlative relationship between elevated GM values the week prior to IA outcome and poor clinical outcomes (15). One study from the prevoriconazole era found that a rise in GM of 1.0 EIA units above baseline during the first week of each treatment episode was a marker of therapeutic failure, with a sensitivity of 44%, specificity of 87%, and positive predictive value of 94% (3).

We propose that the simple, early parameter of 1-week GM decay, accounting for GM_0, has value as a surrogate endpoint candidate; it has prognostic value for the true endpoint of mortality at 6 and 12 weeks and appears to be stably predictive of the true endpoint even after adjusting for treatment with distinct antifungal therapies, including voriconazole, liposomal amphotericin B, or echinocandins, during the initial week. Our findings will need validation in other data sets of patients who underwent more systematic GM testing.

IA has a wide spectrum of disease manifestations, and the subset of IA patients with elevated GM values at diagnosis may represent a biologically distinct stratum of patients that can be studied separately, analogous to the stratification of acute coronary syndrome patients by troponin and creatine phosphokinase biomarkers to unstable angina and non-heat-stable enterotoxin (non-ST) elevation myocardial infarction cohorts for the purposes of clinical trials. If the relationship between GM decay and IA outcome is confirmed in other data sets, using a surrogate endpoint of a difference in 1-week GM decay, accounting for GM_0, has the potential to accelerate development of future antifungal therapies by sharply reducing trial duration and sample size in GPA patients.

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