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Post-diagnostic Kinetics of the (1→3)-β-D-Glucan Assay in Invasive Aspergillosis, Invasive Candidiasis, and *Pneumocystis jirovecii* Pneumonia

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Abstract

The kinetics of serum (1→3)-β-D-glucan (BG) following the diagnosis of invasive fungal disease and administration of antifungal therapy are poorly characterized. It is unknown whether early BG changes have prognostic implications. We assessed the post-diagnostic kinetics of BG in patients with an initial serum BG ≥80 pg/mL and at least one additional post-diagnostic BG value in the setting of invasive aspergillosis (IA, n=69), invasive candidiasis (IC, n=40), or *Pneumocystis jirovecii* pneumonia (PCP, n=18), treated with antifungal therapy. Clinical failure of antifungal therapy and mortality were assessed at 6 and 12 weeks, and Cox modeling was used to assess the hazard of initial BG and change in BG at 1 or 2 weeks for these outcomes. In patients with ≥2 BG values, median initial BG was >500 pg/mL (IQR (interquartile range) 168, >500; range 80, >500) in IA, 136 pg/mL (IQR 88, >500; range 31, >500) in IC, and >500 pg/mL (IQR 235, >500; range 86, >500) in PCP. In patients with ≥2 BG values through one week after diagnosis, overall one-week decline in BG was 0 pg/mL (IQR 0, 53) in IA, 0 (IQR −65, 12) in IC, and 17 (IQR 0, 82) in PCP. Most patients with BG values through 6 and 12 weeks had persistent levels >80 pg/mL. Initial BG and the early trajectory of BG were not predictive of 6 or 12-week clinical failure or mortality. While BG eventually declines in patients with IA, IC, and PCP, it lacks prognostic value within a clinically meaningful time frame.

Keywords

beta-glucan; invasive aspergillosis; candidiasis; *Pneumocystis jirovecii*; invasive fungal disease; galactomannan; kinetics

Background

While the diagnostic performance of serum (1→3)-β-D-glucan (BG) for invasive fungal disease (IFD) is fairly well-defined [1–4], its response to antifungal therapy is unknown. In a murine invasive aspergillosis (IA) model, animals receiving antifungal therapy had lower

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BG levels at censoring than untreated controls, and a decline in BG was associated with improved survival [5, 6]. In an analysis of its diagnostic performance in a large cohort at our institution, BG sensitivity did not decrease in patients treated with antifungal agents for over a week, suggesting relatively slow BG clearance [4]. We sought to determine whether BG declines within a clinically meaningful timeframe with antifungal therapy, and whether this decline has any prognostic value.

Methods

Patient population

We identified all Brigham and Women's Hospital/Dana-Farber Cancer Institute patients from January 2005-June 2009 fulfilling the following criteria: (A) proven or probable IA or invasive candidiasis (IC) per 2008 European Organization for Research and Treatment of Cancer–Mycoses Study Group (EORTC/MSG) IFD diagnostic criteria [7], independent of BG results; or *Pneumocystis jirovecii* pneumonia (PCP) based on host factors, a compatible clinical syndrome, and cysts in respiratory tract specimens; (B) BG ≥80 pg/mL at IFD diagnosis; and (C) receipt of antifungal therapy for IFD.

Patients with concurrent invasive mycoses and patients exposed to factors associated with elevated serum BG in the absence of IFD, such as intravenous immunoglobulin, albumin, or cellulose hemodialysis membranes, were excluded [4, 8]. No patients were bacteremic with *Pseudomonas aeruginosa*, *Alcaligenes faecalis*, or *Streptococcus pneumoniae*; *in vitro* culture supernatants of these organisms have been associated with elevated BG levels [9].

Demographic, IFD, and antifungal treatment details were recorded. IFD host factors were assessed per current EORTC/MSG definitions [7]. All BG values from IFD diagnosis were recorded.

BG testing

Serum BG levels were determined with the Fungitell assay (Associates of Cape Cod, East Falmouth, MA) by a reference laboratory without knowledge of patient IFD status. This assay is reported continuously for results between 31–500 pg/mL, and as >500 pg/mL for values above this range. A value ≥80 pg/mL is considered positive. BG testing was performed at the discretion of clinical care teams.

Outcome measures

Mortality and cause of death were assessed in all patients at 6 weeks, after which IFD-related mortality wanes [10], and 12 weeks, a recommended secondary time point for IA and IC outcome assessment by the 2008 EORTC/MSG therapeutic outcome consensus statement [11]. Patients were further classified as clinical 'successes' (complete or partial response) or clinical 'failures' (stable response, progression of disease, or death) at 6 and 12 weeks according to these consensus criteria for defining responses to antifungal therapy [11]. There is some controversy about whether to classify 'stable response' as clinical failure or success in these consensus criteria, so we assessed the endpoint of 'failure' according to the standard definition and made a separate assessment reclassifying the 6 stable response cases as 'successes' at 6 weeks.

Statistical methods

Change in BG at 1 and 2 weeks was calculated by linear interpolation from the two surrounding data points in patients with BG follow-up values extending through these time points. For the purposes of this analysis, 501 pg/mL was used for BG values reported as

>500 pg/mL. Time to BG <80 pg/mL was estimated using linear interpolation in patients with values that eventually declined below this threshold.

We used the Kaplan-Meier method to estimate clinical failure of antifungal therapy (as a binary outcome) 6 and 12 weeks and 6 and 12-week mortality. Cox modeling was used to generate unadjusted hazard ratios (HRs) for initial serum BG, change in BG after 1 and 2 weeks of antifungal therapy, and other potential predictors of mortality or clinical failure, including age, gender, and IFD risk factors. Cox modeling was also used to generate adjusted HRs for 6 and 12-week clinical failure and mortality.

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

Results

Invasive Aspergillosis

We identified 88 patients with IA; 69 had ≥2 post-diagnostic BG values and 53 had BG values at least one week after diagnosis. Key patient characteristics are outlined in Table 1[7].

Of 69 patients with ≥2 post-diagnostic BG values, 19 had proven and 50 probable IA. One patient had isolated sinus disease; the remaining 68 had pulmonary IA at minimum, and 6 had multifocal IA. Causative *Aspergillus* species was identified in 41 (59%) patients—32 *A. fumigatus*, 4 *A. flavus*, 4 *A. terreus*, and 1 *A. niger*. Sixty-five (94%) of 69 patients received voriconazole for treatment of IA during their BG follow-up period. The remaining 4 patients received amphotericin or echinocandin therapy.

Actuarial data on rates of patient mortality and failure to respond to antifungal therapy at 6 and 12 weeks are presented in Table 2. Eleven patients who were alive at 6 weeks had clinical outcomes discordant with their survival status – while alive, they were considered clinical failures because of either stable clinical response or evidence of progressive infection. Only two patients with progressive disease had clinical outcomes discordant with their survival status at 12 weeks.

Median initial BG was >500 pg/mL (IQR 169, >500; range 80, >500) overall and >500 pg/mL (IQR 168, >500; range 80, >500) in patients with ≥2 BG values. Patients with ≥2 BG values had 3 (IQR 2, 6; range 2, 20) values following IA diagnosis over 19 (IQR 7, 109; range 1, 964) days.

In the 53 patients with BG values extending through one week after IA diagnosis, BG decline was 0 pg/mL (IQR 0, 53; range −347, 160) at one week, with negative numbers representing an increase in BG levels. Table 3 summarizes changes in BG at one week by initial BG strata.

Twenty-seven patients had BG follow-up through 6 weeks after IA diagnosis: 22 (82%) had persistent BG elevations, with a median interpolated BG of 221 (IQR 116, >500; range <31, >501) pg/mL. Twenty-two had concurrent galactomannan (GM) elevations at IA diagnosis; only 3 (14%) patients had persistent GM >0.5 units at 6 weeks.

Twenty patients had BG follow-up 12 weeks after diagnosis; 12 (60%) had persistently elevated BG with a median interpolated BG of 249 (IQR 73, >500; range <31, >500) pg/mL. In contrast, 15 of these patients had concurrent GM elevations at IA diagnosis; none had persistent GM elevations >0.5 units at 12 weeks.

In 23 patients whose BG values eventually declined to <80 pg/mL, median time to this threshold was 7 days (IQR 3, 11; range 1, 162) in 11 patients with an initial BG <150 pg/mL, 17 days (IQR 10, 24; range 4, 76) in 5 patients with initial BG 150–500 pg/mL, and 78 days (69, 711; 54, 821) in 7 patients with initial BG >500 pg/mL.

In 9 lung transplant recipients with ≥2 BG values following IA diagnosis, 5 with pleural involvement, median initial BG was >500 (IQR >500, >500; range 229, >500) pg/mL. All 8 patients with BG follow-up values through 6 weeks and 7 patients with BG follow-up through 12 weeks had persistently elevated BG values. One patient's serum BG eventually declined to <80 pg/mL 2.6 years after IA diagnosis; the remaining 6 patients with BG follow-up past 12 weeks had persistently elevated BG values 0.4 – 1.8 years after diagnosis despite clinical IA resolution and in most patients, cessation of antifungal therapy.

In the whole cohort, initial BG was not predictive of 6-week mortality, either in 3 strata, <150, 151 – 500, and >500 pg/mL (HR 1.23; 95% CI 0.90, 1.74), or continuously (HR 1.11 per 100 pg/mL increase; 95% CI, 0.95, 1.28). In the 53 patients with BG values through at least one week after IA diagnosis, change in BG at 1 week (HR 0.99 per 10 pg/mL decline, 95% CI 0.95, 1.04) or 2 weeks (HR 0.99 per 10 pg/mL decline; 95% CI 0.92, 1.06) was not predictive of 6-week mortality, either alone or accounting for initial BG. Neither initial BG nor change in BG at 1 or 2 weeks was predictive of 12-week mortality, alone or adjusting for each other.

Initial BG did not predict clinical failure of antifungal therapy at 6 weeks (HR 1.10 per 100 pg/mL increase; 95% CI 0.94, 1.28) or 12 weeks (HR 1.12 per 100 pg/mL increase; 95% CI 0.95, 1.31) in the cohort overall. In the 53 patients with BG values at least one week following IA diagnosis, change in BG at 1 week (HR 1.00 per 10 pg/mL decline; 95% CI 0.96, 1.03) or 2 weeks (HR 1.00 per 10 pg/mL decline; 95% CI 0.95, 1.04) was not predictive of 6-week mortality, either alone or accounting for initial BG. These HR estimates remained unchanged when the 6 patients with a stable response at 6 weeks were classified as clinical 'successes' rather than clinical 'failures.' Neither initial BG nor change in BG at 1 or 2 weeks was predictive of clinical failure in response to antifungal therapy at 12 weeks, individually or adjusting for each other.Excluding patients with non-linear BG values (>500 pg/mL) within the first 1–2 weeks, initial BG and change in BG at 1 or 2 weeks were still not predictive of 6 or 12-week mortality or clinical failure, with similar HRs.

Invasive Candidiasis

We identified 75 IC patients, 40 with ≥2 BG values following IC diagnosis. Patient characteristics are outlined in Table 1.

Of patients with ≥2 post-diagnostic BG values, 36 had proven and 4 probable IC. Of the 36 proven IC cases, 19 were caused by *C. albicans*, 3 *C. glabrata*, 3 *C. tropicalis*, 2 *C. parapsilosis*, 2 *C. krusei*, 1 *C. guillermondii*, and 1 *Kodamaea (Pichia) omeri*. Three patients had concurrent Candidemia with more than one species—*C. albicans* and *C. tropicalis*, *C. albicans* and *C. glabrata*, and *C. tropicalis* and *C. parapsilosis*. Two patients had abundant yeast forms and pseudohyphae strongly suggestive of *Candida* species on visceral biopsy, with sterile biopsy specimen cultures.

Twenty-eight patients with ≥2 BG values received fluconazole, 8 an echinocandin, and 4 voriconazole maintenance therapy for IC treatment during their BG follow-up period.

All-cause mortality was 0.24 (95% CI 0.15, 0.35) at 6 weeks and 0.28 (95% CI 0.19, 0.40) at 12 weeks overall, and 0.13 (95% CI 0.06, 0.28) at 6 weeks and 0.21 (95% CI 0.11, 0.37) at

12 weeks in the 40 patients with ≥2 BG values. Clinical response at 6 and 12 weeks was perfectly concordant with survival status in all IC patients – all patients had either a complete or partial response or death at these time points.

Median initial BG was 212 pg/mL (IQR 119, >500; range <31, >500) overall and 136 pg/mL (IQR 88, >500; range 31, >500) in patients with ≥2 BG values. Patients with ≥2 BG values had 3 (IQR 2, 5; range 2, 9) values following IC diagnosis over 51 (IQR 24, 124; range 4, 832) days.

Median decline in BG one week after IC diagnosis was 0 (IQR −65, 12; range −365, 243) pg/mL in 39 patients with BG follow-up extending through this time point. Change in BG at one week by initial BG strata is summarized in Table 3.

Sixteen (70%) of 23 patients with BG follow-up values through 6 weeks had persistent BG elevations >80 pg/mL, with a median 6-week interpolated BG of 138 (IQR 82, 489; range 47, >501) pg/mL. Ten (63%) of 16 patients with BG follow-up through 12 weeks had values >80 pg/mL, with a median 12-week interpolated BG of 140 (IQR 70, 428; range 31, >500) pg/mL.

In the whole IC cohort, initial BG was not predictive of 6-week mortality or clinical outcome (HR 0.87 per 100 pg/mL increase; 95% CI 0.58, 1.30). In the 40 patients with BG values through at least one or two weeks after IC diagnosis, change in BG at 1 week (HR 1.00 per 10 pg/mL, 95% CI 0.96, 1.05) or 2 weeks (HR 0.99 per 10 pg/mL, 95% CI 0.95, 1.04) was also not predictive of 6-week mortality or clinical outcome, either alone or accounting for initial BG. Initial BG and change in BG at 1 or 2 weeks were also not predictive of 12-week mortality or clinical outcome, either alone or in combination.

Pneumocystis jirovecii Pneumonia

We identified 38 PCP patients, 18 with ≥2 postdiagnostic BG values. Twenty-eight (74%) had an underlying malignancy and 7 (18%) had HIV. Of patients with ≥2 BG values, 16 (89%) received trimethoprim-sulfamethoxazole, 1 atovaquone, and 1 primaquine and clindamycin for PCP treatment.

Median initial BG was >500 pg/mL (IQR 410, >500; range 86, >500) overall and >500 pg/mL (IQR 235, >500; range 86, >500) in patients with ≥2 BG values. Patients with ≥2 BG values had 2 (IQR 2, 3; range 2, 11) values over 22 (IQR 15, 115; range 1, 347) days of BG follow-up. Median decline in BG was 17 (IQR 0, 82; range −343, 205) pg/mL one week after PCP diagnosis in 16 patients with BG follow-up through this time point.

Five of 7 (71%) patients with BG values through 6 weeks and 4 of 6 (67%) patients with BG follow-up values through 12 weeks after PCP diagnosis had BG values >80 pg/mL at these time points.

All-cause mortality was 0.22 (95% CI 0.11, 0.39) at 6 weeks and 0.33 (95% CI 0.20, 0.51) at 12 weeks in all patients and 0.17 (95% CI 0.06, 0.43) at 6 weeks and 0.28 (95% CI 0.13, 0.54) at 12 weeks in patients with ≥2 BG values. Clinical response at 6 and 12 weeks was perfectly concordant with survival status in all PCP patients – all patients had either a complete response or death at these time points.

Neither initial BG (HR 1.05 per 100 pg/mL increase; 95% CI 0.77, 1.45) nor decline in BG at 1 week (HR 1.03 per 10 pg/mL, 95% CI 0.94, 1.13) or 2 weeks (HR 1.00 per 10 pg/mL, 95% CI 0.93, 1.06) was predictive of 6-week mortality or clinical outcome, alone or in combination. Neither initial BG nor decline in BG at 1 or 2 weeks was predictive of 12-week mortality or clinical outcome, alone or in combination.

Discussion

Serum BG declined slowly in most IA, IC, and PCP patients treated with appropriate antifungal therapy, and often persisted above the usual threshold for positivity long after clinical resolution of the original infection. Neither BG height at diagnosis nor early changes in BG levels were predictive of clinical outcome or mortality at 6 or 12 weeks.

The rise and fall of serum BG remains poorly characterized in human IFD and likely depends on a range of organism and host factors, including fungal species and burden, location of the infection, structure and molecular weights of BG released into the bloodstream, timeliness of IFD diagnosis, host immune status, rate of glomerular filtration of low molecular weight BG, and rate of hepatic degradation of higher molecular weight BG [8, 12, 13].

In mammalian IA and PCP models, BG parallels fungal burden and declines with effective therapy [5, 6, 14–16]. Data on post-diagnostic BG kinetics in humans are sparse, but the available data are concordant with our findings. One study of BG for IA diagnosis in neutropenic hematologic malignancy patients reported persistent BG elevations in patients not responding to antifungal therapy and eventual normalization in 5 IA patients who clinically responded to antifungal therapy, although BG declined to <80 pg/mL after 6 weeks in patients whose values did eventually normalize [17]. In 6 HSCT recipients with candidemia, median time between clearance of candidemia and decline of BG to less than the diagnostic threshold for positivity was 48 days [18]. In 35 of 42 AIDS patients with PCP, BG trajectory did not reflect the clinical course after 3 weeks of therapy, and BG actually increased in 9 patients despite clinical improvement [19]. The authors reported eventual normalization of BG values several months to years after treatment in all patients. In another recent retrospective study of BG in 17 AIDS patients with PCP, only 3 (18%) patients 4 weeks and 7 (41%) patients 6 weeks after PCP diagnosis had BG values less than the diagnostic threshold for positivity [20].

It is unclear why BG appears to behave differently in mammalian models than in human infection—it may reflect earlier initiation of antifungal therapy in experimental models, prior to the onset of extensive invasive disease, while in our cohort, BG testing was generally driven by a syndrome suggestive of IFD.

There are major caveats to consider when interpreting this study. Samples with values greater than the 500pg/mL upper threshold the Fungitell assay reports were not further characterized at the time of testing, and original serum samples were unavailable for further analysis. We were thus unable to explore the full impact of the rate of BG decay due to this artificial truncation of the assay's linear range, creating a ceiling effect. Initial BG and early BG changes were not predictive of clinical outcome when we restricted our analysis to values in the clinically reported linear range of the assay, and given the extremely slow clearance of BG in patients with initial values >500 pg/mL, often months to years after diagnosis, it is unlikely that these early incremental changes in BG would have provided useful prognostic information. Our study was also subject to the biases of nonsystematic testing, as BG values were obtained at the discretion of clinical care teams.

Post-diagnostic BG values have limited prognostic value—BG often lingers in the serum past the clinical outcome of interest, and its early trajectory does not appear to predict clinical outcome. Unlike serum GM in IA [21], BG is not clearly related to the hazard rate for mortality and does not capture the net effects of IFD treatment on clinical outcome; it is therefore unlikely to be a useful surrogate marker for successful response to antifungal therapy in IFD patients [22, 23]. While BG has no discernible prognostic value, it likely

retains its use as an IFD diagnostic test even after initiation of antifungal therapy, precisely because of its slow clearance.

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Table 1

Demographics and host factors in patients with ≥2 BG values.

	Invasive Aspergillosis N(%)	Invasive Candidiasis N(%)	*Pneumocystis jirovecii* Pneumonia N(%)
N	69	40	18
Age, years[a]	54 (53, 64; 19, 79)	54 (42, 63; 19, 67)	53 (46, 60; 23, 82)
Female	29 (42)	12 (30)	9 (50)
Prolonged corticosteroids[b]	33 (48)	6 (15)	6 (33)
T-cell immunosuppressants[b]	35 (51)	28 (70)	12 (67)
High-risk neutropenia[b]	24 (35)	18 (45)	0 (0)
Allogeneic HSCT[c]	25 (36)	6 (15)	2 (11)
Grade III-IV acute GVHD[d]	4 (6)	0 (0)	0 (0)

[a] Median, interquartile range, range

[b] As defined by EORTC/MSG IFD diagnostic criteria(7)

[c] HSCT: hematopoietic stem cell transplantation

[d] GVHD: graft-versus-host disease

Table 2

Clinical outcomes in patients with invasive aspergillosis at 6 and 12 weeks.

	6 weeks	12 weeks
All IA patients (n = 88)		
All-cause mortality (95% CI)[a]	0.51 (0.41, 0.62)	0.60 (0.50, 0.70)
Clinical failure in response to antifungal therapy (95% CI)[a,b]	0.64 (0.54, 0.74)[c]	0.62 (0.52, 0.72)[d]
Patients with ≥2 BG values (n = 69)		
All-cause mortality (95% CI)[a]	0.38 (0.27, 0.50)	0.49 (0.38, 0.62)
Clinical failure in response to antifungal therapy (95% CI)[a,b]	0.54 (0.42, 0.66)	0.51 (0.40, 0.63)

[a] 95% CI: 95% confidence interval

[b] As defined by 2008 EORTC/MSG consensus criteria for defining responses to antifungal therapy

[c] At 6 weeks, 32 patients were considered clinical ‘successes’ (3 complete clinical responses, 29 partial responses) and 56 were considered clinical ‘failures’ (6 stable responses, 5 progressive disease, and 45 deaths).

[d] At 12 weeks, 34 patients were considered clinical ‘successes’ (13 complete clinical responses, 21 partial responses) and 54 were considered clinical ‘failures’ (0 stable responses, 2 progressive disease, 52 deaths).

Table 3

Post-diagnostic kinetics of BG by initial BG strata in IA and IC patients with ≥2 values one week after IFD diagnosis.

	Invasive Aspergillosis		Invasive Candidiasis	
	N	**BG decline, pg/mL (IQR, range)[a]**	**N**	**BG decline, pg/mL (IQR, range)[a]**
All Patients	53	0 (0, 53; −347, 160)	39	0 (−65, 12; −365, 243)
Initial BG <150 pg/mL	14	11 (−17, 52; −129, 75)	20	−37 (−92, 3; −365, 33)
Initial BG 150–500 pg/mL	14	38 (−293, 104; −347, 153)	7	18 (0, 39; −264, 243)
Initial BG >500 pg/mL	25	0 (0, 0; 0, 160)	12	0 (0, 0; 0, 127)

[a]Negative numbers indicate an interval increase in BG.