Serum β -D-glucan (BDG) as a biomarker for, or exclusion of, IFD in haematology and ICU patients – a pilot study

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Introduction

Australian patients undergoing haematopoietic stem cell transplant (HSCT) for haematologic malignancies experience invasive fungal disease (IFD) (~15.2%). Delayed treatment initiation due to insufficiently sensitive and specific diagnostic tests contributes to mortality of 40-90%. Standardised *Aspergillus* PCR based tests have a role in directing pre-emptive antifungal therapy in haematology patients, but have not been translated into the Intensive Care Unit (ICU) where IFD risks are less well defined. β -D-glucan (BDG) is a panfungal marker of IFD. Data indicate that serum BDG testing is useful in: (i) informing pre-emptive treatment, or (ii) excluding IFD in ICU and haematology patients.

Objectives: Determine the clinical utility of serum BDG testing in the early detection (or exclusion) of invasive candidiasis (IC) or other IFD in:

i) ICU patients; and ii) high-risk haematology patients

Methods

Twice weekly serum (n=110) from at-risk haematology patients was tested prospectively for 30 days for both BDG (Fungitell® assay) & *Aspergillus* galactomannan (Platelia™ *Aspergillus* EIA). For ICU patients, serum (n=135) was collected daily for the first 3 days in those with medium-to-high IFD risk. BDG results were not used in clinical management. Patients were assessed for IFD with EORTC/MSG criteria.

Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were calculated for the BDG test in both study populations and for *Aspergillus* galactomannan in haematology patients.

Results

Haematology patients (28 sampling episodes, 25 patients)

The frequency of probable/proven IFD was 25%.

Of the 3 cases of proven *A. fumigatus*; invasive sinusitis (2), invasive pulmonary aspergillosis (1).

Results (cont'd)

ICU patients (49 sampling episodes, 49 patients)

The frequency of probable/proven was 10.2%

Only 3 cases of IC occurred in this cohort (6%). Two patients had equivocal results for BDG and were excluded.

IFD Status	BDG	
	Negative	Positive
No (33)	21	12
Possible (9)	0	9
Probable (2)	0	2
Proven (3)	2	1
TOTAL (49)	NPV: 0.91	PPV: 0.13
	Sens: 0.6	Spec: 0.5

False +ve Results: No concurrent factors, e.g. other antimicrobial use/GVHD, associated with a higher chance of false positive BDG

False -ve Results

Infection	Result
Invasive sinusitis, <i>A. fumigatus</i> , haematology	Serial negative BDG
Invasive pulmonary <i>A. fumigatus</i> , haematology	Serial negative BDG
<i>C. tropicalis</i> fungaemia, ICU	Serial negative BDG with temporal inconsistency, final BDG collected 4 d prior to onset.
<i>C. glabrata</i> fungaemia, ICU	Serial negative BDG until 4 days after first positive BC, then became positive.

Conclusions

Testing of a larger cohort of patients is essential.

Haematology Population

- The NPV of BDG (0.8) was comparable to galactomannan.
- 8 of 9 'possible' IFD would have been considered as 'probable' infections if serum BDG was utilised as a mycological criterion (EORTC-MSG).
- Regarding false negatives, we hypothesise the fungal burden may not yet have become angio-invasive, and thus circulating BDG remained at normal physiological levels. This finding emphasises the utility of serum BDG as an adjunct rather than absolute diagnostic aid.

ICU Population

- The importance of interpretation of serial rather than single results is highlighted.
- Patients with consistently negative BDG are unlikely to have IFD and support cessation of antifungal prophylaxis.

IFD Status (n)	BDG		GM	
	Negative	Positive	Negative	Positive
No (12)	7	5	11	1
Possible (9)	1	8	9	0
Probable (4)	0	4	2	2
Proven (3)	2	1	2	1
TOTAL (28)	NPV: 0.80	PPV: 0.28	NPV: 0.83	PPV: 0.75
	Sens: 0.71	Spec: 0.38	Sens: 0.43	Spec: 0.95