MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

How do I interpret …
Serum beta-D-glucan?

Dr Atul Patel, MD, FIDSA
Chief Consultant and Director
Infectious Diseases Clinic
Vedanta Institute of Medical Sciences
Ahmedabad, India

ASIA FUNGAL WORKING GROUP
an ISHAM working group

How I Interpret Beta D Glucan

ATUL K PATEL MD, FIDSA
Ahmedabad, India

Why we need fungal biomarker?

- IFI is a significant cause of Morbidity and mortality
- Early diagnosis of IFI might be useful to reduce mortality
- Culture based methods are time consuming with poor sensitivity
- Antibody based tests lacks specificity
- Detection of fungal antigens in body fluids, including cryptococcus capsular polysaccharide, histoplasma antigen, galactomannan, and -D-glucan, : clinically useful for at least the presumptive diagnosis
- The EORTC/MSG guidelines included a positive BDG result as meeting their criteria for mycological evidence of infection

- BDG is found in broad range of fungal pathogens
- Mainly Candida, PJP, Aspergillus
- Except mucormycosis, cryptococcus, and Blastomyces dermatitidis: produce BDG at minimal level

Variable	Fungitec G-Test MK	β-glucan Test Wako	B-G Star	Fungitell
Manufacturer	Seikagaku Corporation	Wako Pure Chemical	Maruha Corporation	Associates of Cape Cod
Country	Japan	Japan	Japan	USA
Approval year	1995	1996	2001	2004
Assay method	Kinetic chromogenic	Kinetic turbidimetry	Endopoint chromogenic	Kinetic chromogenic
Sample	Serum or plasma	Serum or plasma	Serum or plasma	Serum
Pretreatment	Alkali	Dilution and heating	Dilution and heating	Alkali
Standard β-glucan	Pachyman	Carboxymethyl-curdlan	Lentinan	Pachyman
Origin of lysate	*Tachypleus tridentatus*	*Limulus polyphemus*	*Tachypleus tridentatus*	*Limulus polyphemus*
Cutoff value, pg/mL	20	11	11	60 or 80
Measurable range, pg/mL	3.9–500	6–600	1.2–120	31.25–500
Turn-around time, min	30	90	30	40

False positive BDG:

1. Semi-synthetic beta-lactam antibiotics
2. Human blood products, including immunoglobulins, albumin, plasma, coagulation factor infusions, filtered through cellulose membranes
3. Cellulose hemodialysis/hemofiltration membranes
4. Exposure to (surgical) gauze
5. Bacterial bloodstream infections

Elitza S. Theel, Journal of Clinical Microbiology p. 3478–3483; Nov 2013

Advantages of using BDG

- Easily available specimen source in sick patients: i.e. Serum compared to BAL, biopsy, CSF etc
- Serial BDG monitoring is possible
- Sensitivity and specificity values, regardless of the invasive organism, can range from 38% to 100% and 45% to 99%, respectively, and positive predictive value (PPV; 30% to 89%) and negative predictive value (NPV; 73% to 97%)

Pickering JW,. J. Clin. Microbiol. 43:5957–5962. 2005
Odabasi Z,. Clin. Infect. Dis. 39:199–205; 2004
Ellis M, J. Med. Microbiol. 57:287–295; 2008
Karageorgopoulos DE,. Clin. Infect. Dis. 52:750–770; 2011

BDG in Hematology Setting:

- Serial BDG antigenemia testing (at least biweekly) in haematology patients; specificity (76% to 99%) and NPVs (87% to 96%) for the presence of proven or probable IFI than single-time-point testing
- Unacceptably low sensitivity: Pooled sensitivity of 49.6%, a PPV and NPV of 83.5% and 94.6%, respectively
- Summary: Due to the consistently low sensitivity and despite the strong NPV, **a negative BDG result should not be used to exclude the possibility of IFI**

Serial BDG in Candidemia

- Serial BDG performed in 203 patients with proven invasive candidiasis on Anidulafungin
- Correlation of a negative slope in BDG levels from patients with a favourable treatment outcome (PPV of 90%) and a positive slope following treatment failure (NPV of 90%)
- In this study, only 16% achieved negative BDG in a patients who responded and have negative BDG slop
- This phenomena is due to lack of understanding of precise BDG kinetics; it's release and route of elimination
- Summary: **The presence or absence of BDG should not be used to guide cessation of therapy or as a "test of cure**

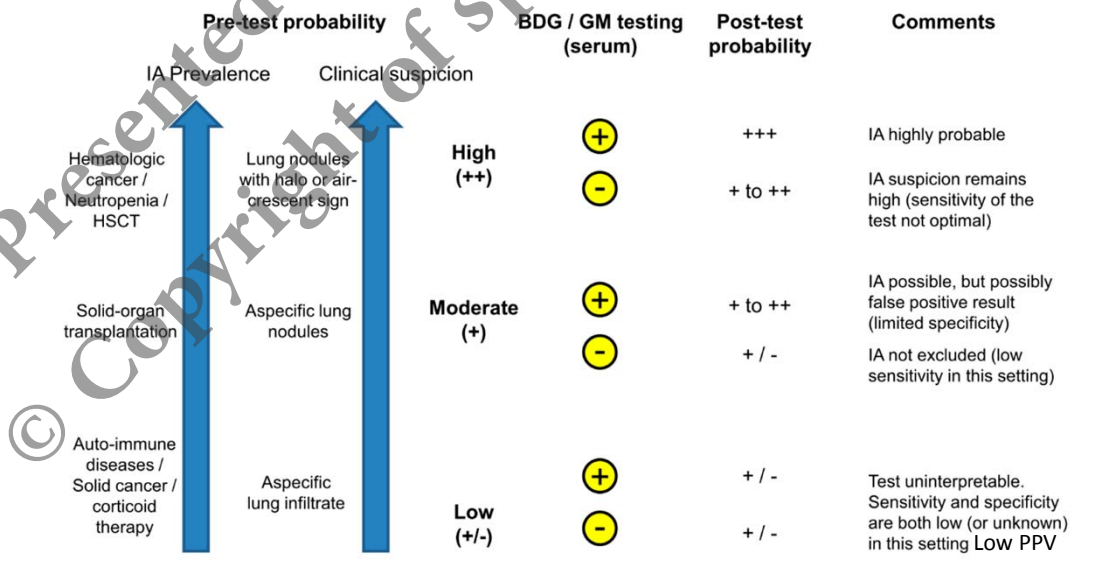
Jaijakul S, Clin. Infect. Dis. 55:521–526. 2012

BDG in PJP

- BDG is a major component of the *P. jirovecii* surface structure
- A meta-analysis evaluating 11 studies of patients with laboratory-confirmed PJP found a pooled sensitivity and specificity of 94.8% and 86.3%, respectively
- BDG has strong NPV (>95%)
- Summary:
  - Levels of BDG has no correlation with severity of PJP (PJP is a weak pathogen & Host immune response leads to lung injury)
  - Negative BDG suggest PJP is less likely

Karageorgopoulos DE, Clin. Microbiol. Infect. 19:39–49. 2013
Held J, Clin. Microbiol. Infect. 17:595–602; 2011

BDG/GM in diagnosis of Invasive Aspergillosis



Lamoth F. J. Fungi 2016, 2, 22; doi:10.3390/jof2030022

BDG in Clinical practice

1. This test is likely of value only for select patient populations (HSCT patients) or in the diagnosis of select infections, (P. jirovecii pneumonia)
2. Multiple positive results are best at predicting the presence of invasive fungal infections
3. Many potential sources of false positives, a single positive test is of limited value
4. The test has poor sensitivity, so it has no value as a screening test
5. A negative test cannot exclude the diagnosis of invasive fungal infection
6. Monitoring -D-glucan quantitative levels in patients being treated for invasive Candida infections has value

Summary

- Overall, BDG is a useful panfungal biomarker supporting clinical suspicion, allowing early antifungal therapy
- Patients with a high pre-test probability of an IFI, a single positive BDG test warrants close patient monitoring and antifungal treatment
- BDG should be targeted in a right population and right situation to get optimal information on IFI diagnosis