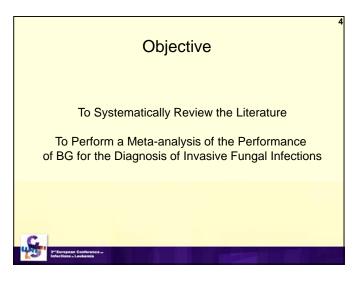




Kit product	Manufacturer	Availability	Horseshoe crab species	Photometric principle	Manufacturer Cut-off
Fungitell®	Associates of Cape Cod (ACC), Inc. (USA)	USA (FDA approved), Europe Kit 900 EUR	Limulus polyphemus	Chromogenic	60-80 pg/ml > 80 pg/ml
Fungitec G-MK®	Seikagaku Biobusiness (Japan)	Japan only, (collaboration with ACC)	Tachypleus tridentatus	Chromogenic	20 pg/ml *
β-Glucan Test®	Wako Pure Chemical Industries, Ltd (Japan)	Japan only	Tachypleus tridentatus	Turbidimetric	11 pg/ml *
β-Glucan Test	Maruha Corp. (Japan)	Japan only, collaboration with Wako	Tachypleus tridentatus	Chromogenic	11 pg/ml *



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Methods – Literature Search Criteria

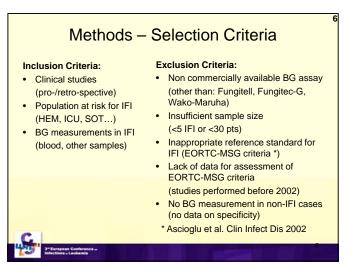
Keywords / MESH terms:

« beta-glucan » or « glucan »

- AND
- « fungal infections » or « mycoses » or « candidiasis » or
- « candidemia » or « aspergillosis »

Search tools:

- Pubmed
- Embase
- Abstracts presented at international meetings: ICAAC, ASM, ECCMID, EBMT, ASCO 2005-2009
- Reviews published in 2005-2009
- English language



Types of Studies

Study populations

- Patients with hematological malignancies (neutropenia, HSCT)
- Other patients at risk for IFI: ICU, SOT, HIV...

Study designs

- **Case control studies:** IFI vs controls (e.g. healthy blood donors, outpatients, inpatients not at risk of IFI,)
- Cohort studies: prospective screening of BG (consecutive sampling method) in a homogenous patients population at risk for IFI (e.g. hematological, ICU, SOT...)

Assessment of the methodological quality of the studies

 Recommendations of the Standards for Reporting of Diagnostic Accuracy (SRDA) using the QUADAS tool (14 items).

Study Selection

- · 861 studies were screened
- 29 Studies met inclusion criteria
- 6 were excluded:
 - 2 inappropriate standard reference for IFI
 - 2 lack of data for calculation of performance
 - 1 non validated BG test
 - 1 no English language
- 23 were selected for analysis:
 - 12 (+1) case control studies
 - 10 (+1) cohort studies

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Case Control Studies – BG Performance	
for Diagnosis of Proven/Probable IFI	

	Funci		a af Cana Ca	(لم	
Cut-off	Sensitivity	ell (Associate	PPV	NPV	Efficiency
Cut-on	Sensitivity	Specificity	PPV	NPV	Efficiency
60 pg/ml *	70	87	84	75	NA
80 pg/ml **	47 - 93	71 - 100	52 - 88	77 - 98	74 - 80
	I	Fungitec-G (Se	eikagaku)		
Cut-off	Sensitivity	Specificity	PPV	NPV	Efficiency
20 pg/ml ***	58 – 100	100	59 – 100	40 - 100	79 - 100
60 pg/ml ****	76 – 85	95 – 100	70 – 100	75 – 98	86 - 91
* Ostrosky-Zeichne		Pel Bono E	Efficiency: (true p	ositives + true n	egatives) / total

** Hachem, Persat, Alam, Pickering, Del Bono *** Obayashi (1995), Hossain, Miyazaki, Kondori **** Obayashi (2008), Kohno, Mitsutake

ng, Del Bono number of tests yazaki, Kondori sutake

Case Control Studies – Comments

- Major limitations in study design:
 - Heterogeneity of controls and IFI patients (HEM, ICU...)
 - Lack of data on sampling time (vs. diagnosis of IFI ?)
 - Most retrospective analyses: bias ?
- Limitations related to types of BG assays:
 - Different cut-offs used
 - Many studies performed in the 1990s (tests' evolution with multiple modifications in BG assay technique ?)
 - No studies with BG assays Wako / Maruha
- Variable performance
 - Sensitivity: 50-90%
 - Specificity: 70-100%
 - Efficiency: 75-90%

		Fungitell (/	Associates of	Cape Cod)			
Study	Cut-off tested	Optimal cut-off *	Sensitivity	Specificity	PPV	NPV	Efficiency
Ellis 2008	60-100 pg/ml	100 pg/ml	-	-	-	-	-
J Med Microbiol	(1 or 2 values)	(2 values)	(82)	(83)	(82)	(83)	(83)
Koo 2006	80 pg/ml	80 pg/ml	71	86	-	-	-
ICAAC (abstract)	(1 value)	(1 value)	(-)	(-)	(-)	(-)	(-)
Pazos 2006	120 pg/ml	120 pg/ml	83	90	63	96	89
Rev Ibero Micol	(1 value)	(1 value)	(-)	(-)	(-)	(-)	(-)
Pazos 2005	120 pg/ml	120 pg/ml	88	90	70	96	89
J Clin Microbiol	(1 value)	(1 value)	(73)	(90)	(73)	(90)	(85)
Odabasi 2004	60 pg/ml	60 pg/ml	60	100	100	97	97
Clin Infect Dis	(1,2,3 values)	(3 values)	(28)	(100)	(100)	(86)	(87)
Presterl 2009	40 pg/ml	40 pg/ml	50	76	46	79	68
Int J Infect Dis	(1 value)	(single)	(-)	(-)	(-)	(-)	(-)
Del Bono 2009	80 pg/ml	80 pg/ml	100	67	75	100	83
ICAAC (abstract)	(1 value)	(1 value)	(100)	(67)	(87)	(100)	(90)

		hort St /en/probat		-	-	-		12
1			Fung	itec-G (Seika	gaku)			
	Study	Cut-off tested	Optimal cut-off *	Sensitivity	Specificity	PPV	NPV	Efficiency
	Kami 2000 Hematologica	20 pg/ml (1 value)	20 pg/ml (1 value)	63 (60)	76 (76)	19 (29)	96 (92)	75 (74)
	Akamatsu 2007 Infection	40 pg/ml (1 value)	40 pg/ml (1 value)	63 (-)	83 (-)	32 (-)	95 (-)	81 (-)
			BG	(Wako / Maru	ıha)			
	Kawazu 2004 J Clin Microbiol	2 - 11 pg/ml (1 or 2 values)	11 pg/ml (2 values)	45 (25)	99 (99)	83 (71)	95 87)	95 (87)
	Senn 2008 Clin Infect Dis	3 - 11 pg/ml (1 or 2 values)	7 pg/ml (2 values)	63 (37)	96 (96)	79 (81)	91 (74)	89 (75)
1		ological popula 007 (solid-organ			* Cut-	off with b	est efficier	псу
	2"European Infections - D	Conference eukemia						

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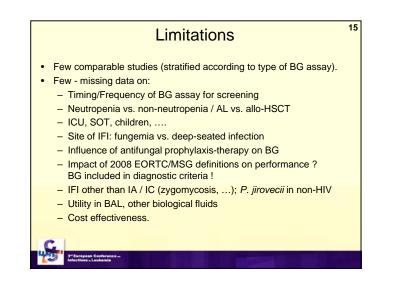
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	Proven+p	robable inv	asive asp	ergillosis	s (IA)	
BG Assay	Cut-off	Sensitivity	Specificity	PPV	NPV	Effic
Fungitell	60-120 pg/ml (1-3 values)	67 - 83 25 - 88	90 - 100 90 - 100	63 - 100 70 - 100	96 - 98 96 - 99	89 89
Fungitec-G	20-40 pg/ml (1 value)	<mark>50</mark> 63 – 100	<mark>83</mark> 76 – 83	<mark>21</mark> 16 – 19	<mark>95</mark> 96 – 100	75
Wako / Maruha	7-11 pg/ml (2 values)	<mark>59</mark> 45 - 60	<mark>96</mark> 96 – 99	67 64 - 83	94 95	91

Cohort Studies – Comments

- For each BG assay 1-2 high quality cohort studies with significant sample size in hematological patients :
 - Fungitell: Odabasi (CID 2004), Ellis (JMM 2008).
 - Fungitec-G: Kami (Hematologica 2000).
 - BG (Wako / Maruha): Kawazu (JCM 2004), Senn (CID 2008).
- Variable performance of BG for diagnosis of proven/probable IFI:
 - Sensitivity: 45 70% / Specificity: 75 100%
 - PPV: 80 100% / NPV: 90 95%
 - Efficiency: 75 95%.
- Similar performance of BG for the diagnosis of IA / IC.
- Global performance (efficiency) similar comparing one single and 2 or more consecutive positive values.





BG test Cut-off	Comparative test Cut-off	Sensitivity	Specificity	PPV	NPV	Efficiency
	В	eta-glucan / g	alactomanna	n		
Fungitell (3) ¹	Platelia	<mark>67 - 88</mark>	73 – 90	<mark>64 - 88</mark>	72 - 96	71 - 89
80-120 pg/ml	ODI=0.5-1.5	38 - 88	56 – 100	47 - 100	61 - 96	56 - 89
Wako/Marhua (2) ²	Platelia	<mark>45 - 60</mark>	<mark>96 - 99</mark>	<mark>64 - 83</mark>	<mark>95</mark>	<mark>91 - 95</mark>
7-11 pg/ml (2x)	ODI=1 (2x)	36 - 64	98 - 100	70 - 100	91 – 97	94 - 95
	Beta-glu	<mark>ican /</mark> mannai	n and/or anti-	mannan		
Fungitell (2) ³	M: 0.5 ng/ml or	52 - 87	70 - 100	100	55	70
80 pg/ml	AM: 10 AU/ml	48 - 81	73 - 100	100	76	88
Wako/Marhua (1) ⁴	M: 0.5 ng/ml or	60	96	64	95	<mark>91</mark>
7 pg/ml (2x)	AM: 10 AU/ml	69	95	64	96	92
		s 2005, Pers				

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Conclusions

- Beta-glucan is a screening test that may identify patients with invasive fungal infections, such as invasive aspergillosis and invasive candidiasis.
- Available data suggest that beta-glucan is a reliable test to estimate the diagnostic accuracy for these invasive fungal infections in adults only.
- A frequency of 2 tests per week which was performed in most studies seems an appropriate screening strategy.
- Results of the beta-glucan assay may complement clinical, radiological and laboratory criteria for the diagnosis of IFI.
- The threshold for positive results depends on the test which is used. Evidence from the available data suggest the following cut-off:
 - Fungitell: between 60 and 80 pg/ml.
 - Wako / Maruha: between 7 and 11 pg/ml
 - Fungitec-G: 20 pg/ml.
- The criteria of two consecutive specimens to define the test as positive increases the specificity but decreases the sensitivity.

Warnings

False positive results may be associated with:

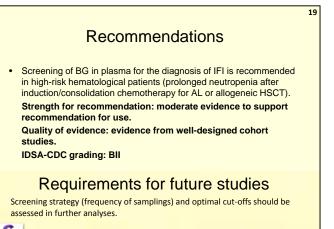
- · Concomitant antimicrobial therapy (beta-lactams)
- Bacteremias
- Hemodialysis patients (cellulose filters)
- Patients receiving coagulation factors / albumin / immunoglobulins
- Hemolyzed serum specimens
- Contaminated specimens (gauze for desinfection at the bedside / environmental dusts-organic wastes in the lab)

False negative results may be associated with:

- Zygomycosis, cryptococcosis, other fungal infections
- Antifungal therapy (?)

Attention should be paid to the technical complexity of the assay and the cost implications.

Server Conference --Infections - Landama



20 IDSA-United States Public Health Service Grading System for Ranking Recommendations

Quality of evidence	Strength of recommendation
I Evidence from ≥ 1 properly randomized, controlled trial	A Good evidence to support a recommendation for use
II Evidence from ≥ well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments	
III Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	C Poor evidence to support a recommendation