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Recent advances of fungal diagnostics and application in Asian laboratories

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Recent advances of fungal diagnostics and application in Asian laboratories

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PRESENTED AT MMTN CONFERENCE, KL 2017
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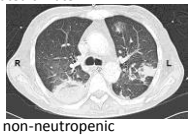
- **Mortality** due to invasive fungal infection
  - 97-100% if not treated
  - ~50% even after proper treatment
  - Why so poor outcome despite antifungal?
- **Management 'dictum'** – early diagnosis & prompt therapy
- **Dilemma** – In absence of diagnosis, **Which** patient has fungal infection?
- **Clinical symptoms & signs not specific**
  - Occult in immunosuppressed patients, attenuated till late
  - How to distinguish from bacterial sepsis?
- **Imaging**
  - Findings subtle
  - Halo sign, air-crescent signs are absent in non-neutropenic



EMERGING INFECTIOUS DISEASES PERSPECTIVE Volume 23, Number 2—February 2017 P. 179

Delivering on Antimicrobial Resistance Agenda Not Possible without Improving Fungal Diagnostic Capabilities

David W. Denning, David S. Perlin, Eavan G. Muldoon, Arnaldo Lopes Colombo, Arunaloke Chakrabarti, Malcolm D. Richardson, Tania C. Sorrell

4 common clinical situations:

1. inaccurate diagnosis of **fungal sepsis** - resulting in inappropriate use of broad-spectrum antibacterial drugs
2. failure to diagnose **chronic pulmonary aspergillosis** in smear-negative pulmonary tuberculosis – use of second line antitubercular drugs
3. misdiagnosis of **fungal asthma & invasive aspergillosis in COPD** - resulting in unnecessary antibacterial drugs
4. overtreatment and undertreatment of ***Pneumocystis* pneumonia** in HIV-positive patients.

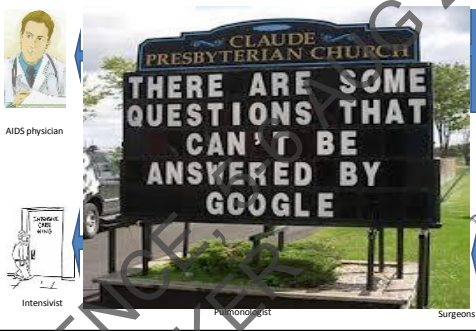
Access to advanced fungal diagnostics would benefit clinical outcome, antimicrobial stewardship, & control of antimicrobial resistance

It is easy to advice - diagnose & then treat!

(*Candida* sepsis in ICUs)

- Blood culture **positivity ~50%**
- **Candida score, colonization index** – sampling for all colonization sites daily, impractical in clinical situation, not cost effective
- Indian study - **97% patients were colonized** with *Candida* species at any point of time during ICU stay
- **Ostrosky's rule** – easier to implement, but only 10% of those patients will develop proven or probable IC
- Do you know, **which patients to be treated with antifungal when predictive rules, candida score, blood culture fail**?

You can't get answer always



AIDS physician

Intensivist

Pulmonologist

Surgeons

When patient has no specific symptom, how to diagnose?

- How to diagnose intra-abdominal candidiasis?
- When antifungal required?

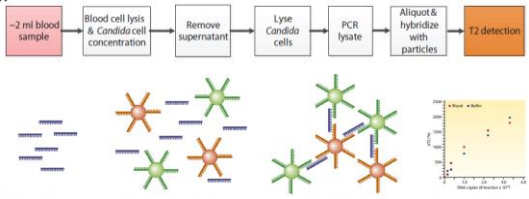
Laboratory diagnosis – some success

- Sample collection –
  - Difficult to avoid colonizers & to collect from deep tissue
  - Improvement in invasive procedure (FNAC/lung biopsy)
- Direct microscopy, culture & Histopathology –
  - Insensitive, slow, difficult to distinguish from colonizer
  - Very important (especially PJP), can see mycelial fungi, takes few minutes
- Identification – important, as you can choose the drug
  - Phenotypic method – time consuming & need expertise
  - MALDI & sequencing – revolutionized
- Ab detection – does not help in immunosuppressed hosts
- Ag detection – excellent in Cryptococcus, Histoplasma (urine – 80-90% positive)

T2 Magnetic Resonance Enables Nanoparticle-Mediated Rapid Detection of Candidemia in Whole Blood

www.ScienceTranslationalMedicine.org 24 April 2013 Vol 5 Issue 182 182ra54

Lori A. Neely,[1] Mark Audeh,[1] Nu Ai Phung,[1] Michael Min,[1] Adam Suchocki,[1] Daniella Plourde,[1]



- **Detection limit – 1-10CFU/ml compared to Multiplex PCR - >30CFU/ml**
- **Improve the time to detect – BACTEC – 2.6d, T2 – 3-4h**
- Detect only five common *Candida* species (95%); chance of contamination
- No antifungal susceptibility test performed & cannot replace blood culture

Beyda ND, *et al.* Diagn Microbiol Infect Dis 2013; 77: 324

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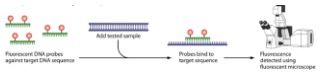
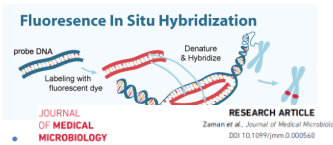
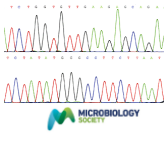
Identification of fungus in tissue

- Immunohistochemistry
- Extraction of DNA from tissue & sequencing







JOURNAL OF MEDICAL MICROBIOLOGY

RESEARCH ARTICLE

Zaman et al., Journal of Medical Microbiology

DOI:10.1099/jmm.0.000568

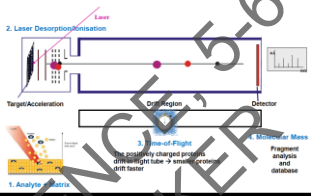
MICROBIOLOGY SOCIETY

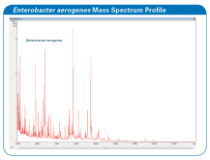
Molecular diagnosis of rhino-orbito-cerebral mucormycosis from fresh tissue samples

Kamran Zaman,[1] Shivaprakash Mandya Rudramurthy,[1] Ashim Das,[2] Naresh Panda,[3] Prasanna Honnavar,[1] Harsimran Kaur[1] and Arunaloke Chakrabarti[1,*]

Identification – proteomic based approach

- **MALDI**
  - Identification of bacteria & fungi within few minutes
  - Susceptibility testing
  - Molecular typing





Matrix-assisted laser desorption ionization time-of-flight mass spectrometry for the rapid identification of yeasts causing bloodstream infections

A. K. Ghosh, S. Paul, P. Sood, S. M. Rudramurthy, A. Rajbanshi, J. J. Jillwin and A. Chakrabarti

Clin Microbiol Infect 2015; **21**: 372–378

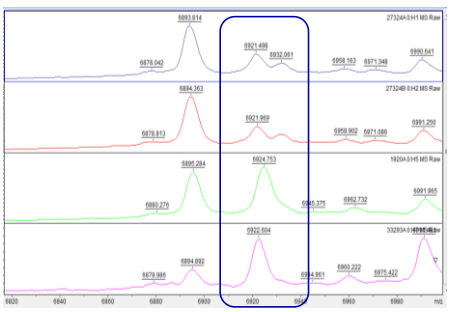
- 354 sequence yeast (standardization)
- 367 blind clinical yeast (validation)
- Database updated for *Candida auris, C. viswanathii, Kodamaea ohmeri* etc.

MALDI-TOF correctly identified 98.9% as compared to PCR-sequencing

Rapid detection of fluconazole resistance in *Candida tropicalis* by MALDI-TOF MS

Saikat Paul, Pankaj Singh, Shamanth A S, Shivaprakash M. Rudramurthy, Arunaloke Chakrabarti and Anup K Ghosh*

Medical Mycology, 2017, 0, 1–8
doi: 10.1093/mmy/myx042



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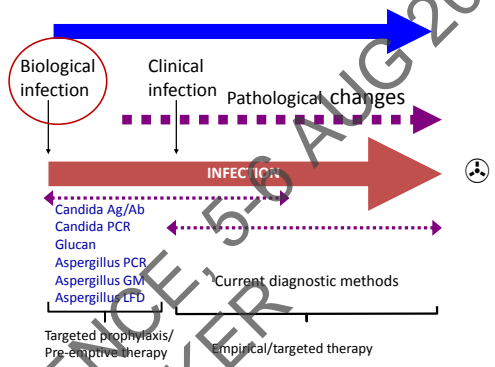
"Okay—who put my lunch through the mass spectrometer..?"

http://www.lab-initio.com/250dpi/nz025.jpg

But what would be real success?



Culture independent methods – proteomic vs. genomic approach

- Detection in clinical sample – promising, but success limited
- Limitation
  - presence of biomarker in pg
  - No scope of prior amplification before detection
- Pre-amplification possible
- Higher sensitivity & specificity
- Low turn around time
- GM released in active growth, PCR better in prophylaxis

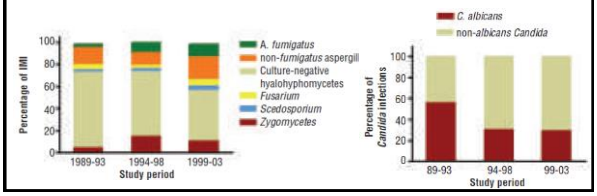
But real challenge diagnosis in clinical samples

Haematologica. 2006 Jul;91(7):986-9.

Invasive fungal infections in patients with hematologic malignancies in a tertiary care cancer center: an autopsy study over a 15-year period (1989-2003)

Chamilos G[1], Luna M, Lewis RE, Bodey GP, Chemaly R, Tarrand JJ, Safdar A, Raad II, Kontoyiannis DP

- 1,017 patients with haematological malignancies autopsied
  - 31% were found to have invasive fungal infections
  - **75% were not diagnosed before death**



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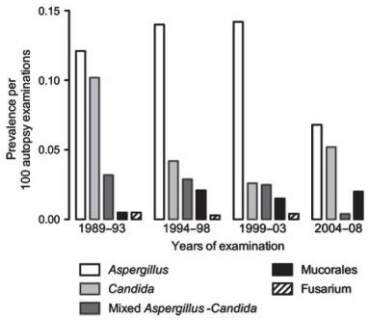
Improvement in diagnosis
(MD Anderson autopsy data on haematological malignancy)

- 84% of IFI were diagnosed post-mortem during 1989-93
- 49% of IFI were diagnosed post-mortem during 2004-08
- Improvement in aspergillosis diagnosis due to pre-emptive approach or introduction of molecular tests



Lewis RE *et al.* Mycoses 2013; 56: 638

Biomarker tests

Existing benchmark tests

- CRP & Procalcitonin ?
- Serum galactomannan
- BAL galactomannan
- Serum Beta-D gulcan

(Caution: may need 'expert' interpretation)

New biomarkers

- Aspergillus PCR
- Aspergillus GM + PCR
- Aspergillus Lateral flow
- BAL Beta-D glucan
- Mucorales PCR from blood
- Breath Volatile metabolites
- Many potential POCT

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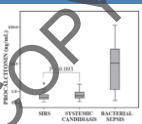
Procalcitonin, C-reactive protein and serum lactate dehydrogenase in the diagnosis of bacterial sepsis in SIRS and systemic candidiasis

Fabio Miglietta[1], Maria Letizia Faneschi[2], Giambattista Lobreglio[2], Claudio Palumbo[1], Adriana Rizzo[1], Marco Cucurachi[3], Geroiamo Portaccio[3], Francesco Guerra[3], Maria Pizzolante[3]

Le Infezioni in Medicina, n. 3, 230-237, 2013

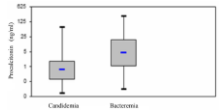


Variables	All patients (n=145)	SIRS (n=42)	P	Bacterial sepsis (n=70)	P	Systemic candidiasis (n=33)
PCT (ng/mL)						
day 0	0.5 (0.4-9.4)	0.38 (0.26-0.64)	<0.001	10.2 (1.2825.3)	<0.001	0.55 (0.360.9)
day 2	0.6 (0.3-4.9)	0.28 (0.12- 0.5)	<0.001	4.9 (0.711.9)	0.001	0.5 (0.20.6)
CRP (mg/L)						
day 0	74.7 (55.7164)	68.6 (48.5139)	<0.001	128.6 (77-254.7)	<0.001	60.5 (54.4-96.5)
day 2	69.8 (52.3117)	58.5 (47.183)	0.001	99.9 (58-180.2)	0.046	67.4 (50-78.8)

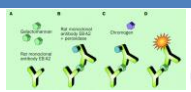
Intern Emerg Med
DOI 10.1007/s11739-017-1627-7
Published online: 04 February 2017

Usefulness of procalcitonin in differentiating *Candida* and bacterial blood stream infections in critically ill septic patients outside the intensive care unit

Filippo Pieralli[1] · Loremzo Corbo[2] · Arianna Torrigiani[2] · Dario Mannini[2] · Elisa Antonielli[2] · Antonio Mancini[2] · Francesco Corradi[2] · Fabio Arena[2] · Alberto Meggi Pignone[2] · Alessandro Morettini[2] · Carlo Nozzoli[2] · Gian Maria Rossolini[3,4,5]



Galactomannan



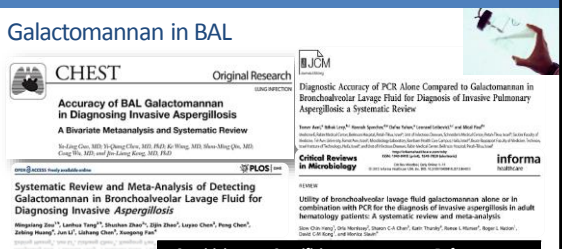
- Galactomannan (GM) testing has been reviewed in several meta-analyses[1–2]. Different cut-offs to define
- Better performance in patients undergoing intensive chemotherapy compared to solid-organ transplant patients

Patients	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Haematological malignancy	58 (52–64)	95 (94–96)
HSCT	65 (60–78)	65 (44–83)
Solid organ transplant	41 (21–64)	85 (80–89)

- **Diagnosis-driven strategy**: GM monitoring every 3–4 days combined with clinical and microbiological evaluation and high-resolution CT imaging (**A II recommendation**)

1. Mennink-Kersten MA, et al. *Lancet Infect Dis* 2004;4:349–57;
2. Leeflang MM, et al. *Cochrane Database Syst Rev* 2008;8:CD007394.

Galactomannan in BAL



	Sensitivity	Specificity	Ref.
	90	94	Guo, *Chest* 2010
	90	96.4	Avni, *JCM* 2011;4:665-70
Cut-off of 0.5	87	94	Zou, *PlosOne* 2012; 7:e52833
	92	98	Heng, *Crit Rev Microbiol* 2015;41:124-34 (haematological patients)

False positive & negative results

False positive results	
Host-related	Renal failure, mucositis, food intake of galactofuranose, gut colonization & possible translocation of *Bifidobacterium*, ganstrointestinal microflora of neonates
Iatrogenic	Blood derivatives, intravenous solution containing gluconate, treatment of antibiotics derived from the fermentation of *Penicillium* (piperacillin-tazobactam, amoxicillin-clavulanic acid)
Sample collection	Cotton swab & cardboard
Environmental	Presence of non-*Aspergillus* fungi, e.g. *Penicillium, Aletnaria, Paecilomyces, Geotrichum, Histoplasma,* rarely *Cryptococcus*
Food	Pasta & yoghurt
False-negative results	
Host conditions	Chronic granulomatous disease
Iatrogenic	Treatment with antifungals
Sample collection	Long-term storage

Lackner M, Lass-Flörl C. Methods Mol Biol. 2017; 1508: 85

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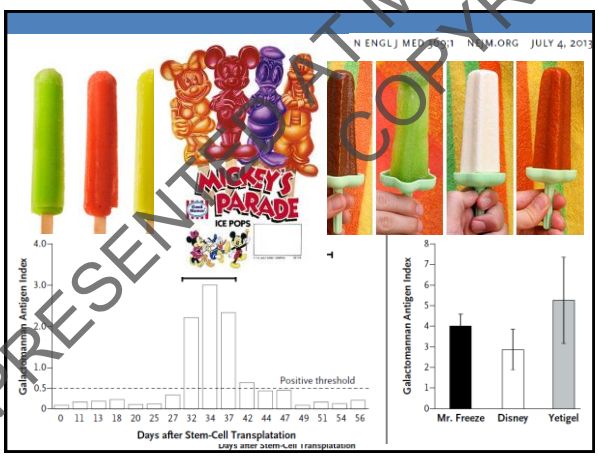


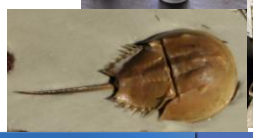
Pros & Cons of GM test

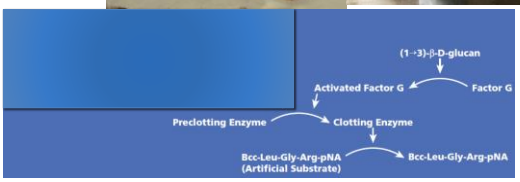
- FDA approved GM test in serum & BAL
- Detectable GM precedes clinical infection
- BAL GM precedes serum GM
- Good positive & negative predictive value in Haematology-Oncology

- Not yet standardized in ICU patients
- Limitation
  - Cross-reaction with some fungi (*Geotrichum, Penicillium, Histoplasma* etc.)
  - Variable turnaround time depending of number of specimens
  - False positive tests
  - Well-equipped laboratories & trained staff to perform the test

Amsden JR. Curr Fung Infect Rep 2015; 9:111

1,3-β-D-glucan detection

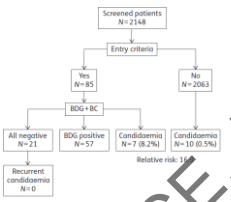




J Antimicrob Chemother 2016; **71**: 2628–2633

Discontinuation of empirical antifungal therapy in ICU patients using 1,3-β-D-glucan

Marcio Nucci[1]*, Simone A. Nouér[1], Patricia Esteves[2], Thais Guimarães[3], Giovanni Breda[4], Bianca Grassi de Miranda[3], Flavio Queiroz-Telles[4] and Arnaldo L. Colombo[2]



Factors related to false-positive BDG	Positive biomarker cohort (N = 57), n (%)	Negative biomarker cohort (N = 21), n (%)	P
Bacteraemia	11 (19.3)	6 (28.6)	0.38
Gram-positive	5 (8.7)	3 (14.3)	0.67
Gram-negative	5 (8.7)	3 (14.3)	0.67
Anaerobe	1 (1.7)	0 (0)	1.0
Use of piperacillin/tazobactam	49 (86.0)	19 (90.5)	0.72
Infusion of albumin	7 (12.3)	1 (4.8)	0.44
Surgery	13 (22.8)	4 (19.0)	1.00

All 21 patients with baseline negative BDG discontinued anidulafungin on day 4. None developed candidaemia until day 30.

Conclusions: Early discontinuation of empirical echinocandin therapy in high-risk ICU patients based on consecutive negative BDG tests may be a reasonable strategy, with great potential to reduce the overuse of echinocandins in ICU patients.

The performance of BDG as per meta-analysis

References	Guidelines	Patients	Type of infection	Strength of recommendation
Marchetti et al. BMT 2012	The third European Conference on Infections in Leukemia (ECIL-3)	Hemato-oncological patients	Invasive fungal infections	B II
Ruhnke et al. Annals of Oncology	Infectious Diseases Working Party of the German Society for Hematology and Oncology (AGIHO)	Hemato-oncological patients	Invasive fungal infections	B
Cuenca-Estrella et al. Clin Microbiol Infect 2012	European Society of Clinical Microbiology and Infectious Diseases (ESCMID)	ICU patients	Invasive candidiasis	II
Dellinger et al. Crit Care Med 2013	Surviving Sepsis Campaign for ICU patients	ICU patients	Invasive candidiasis	B II

Furfaro E, *et al*. Curr Fung Infect Rep 2015; 9: 292

- Pan-fungal marker except Mucor & possibly Cryptococcosis
- Positive before clinical symptoms; Helps to monitor therapy
- Good performance in suspected *Pneumocystis* & *Candida* infection
- False positivity, difficulty to test, cost

Nucleic acid detection - Real challenge in clinical sample

- PCR based detection assay - Real time PCR or qPCR
- Large number of PCR protocols published over 20 years, but absence of consensus standardized technique
- PCR is not included in EORTC/MSG guideline

Comparison with virology

- Different protocol published for viruses, but this does not hamper acceptance of PCR in diagnostic virology
- For viruses – we deal with >10^3

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Challenges in fungal PCR

- Too few fungal DNA in sample
- PCR inhibitors – heparin, haemoglobin, lactoferrin
- Contamination is a big issue - environment
  - 10-20% tube may have *Aspergillus* DNA contamination
  - 18% commercial tubes with anticoagulant have fungal DNA

Recommendation EAPCRI

- Serum may be used, plasma best – blood volume >3ml
  - Elution in small volume
  - Mechanical lysis better than enzymatic lysis of cell wall
  - Internal control, ITS target

Diagnosis of aspergillosis – comparison GM/BDG/PCR

White PL *et al.* Clin Infect Dis 2015; 61: 1293

Characteristic	GM-EIA	B-D-glucan	PCR
Methodological recommendation	Single commercial assay with SOP: **Platelia Aspergillus antigen** (BioRad)	5 commercial assays: **Fungitell** (Associates of Cape Cod) **Fungitec G-Test MK** (Seikagaku Corporation) **B-G Star** (Maruha Corporation **B-Glucan Test Wako** (Wako Pure Chemicals) **Dynamiker Fungus** (1–3)-B-D-Glucan Assay (Dynamiker Biotechnology Co, Ltd)	**Pathonostics Aspergenius, Roche Septifast, Myconostica MycAssay, Ademtech Mycogenie, Renishaw Fungiplex,** Procedural recommendations for DNA extraction **(EAPCRI)**
Quality control	Internal – BioRad Proficiency panel	No	Independent – QCMD & EAPCRI Panels
Sensitivity %	Blood: 79.3 BAL: 83.6–85.7	Blood: IA: 56.8–77.1	Blood: 84–88 BAL: 76.8–79.6
Specificity %	Blood: 80.5–86.3 BAL: 89.0–89.4	Blood: 81.3–97.0	Blood: 75–76 BAL: 93.7–94.5
False positive	Yes	Yes	Yes
False negative	Yes	Yes	Yes
Clinical utility	Yes	Limited	yes

Interpretation of non-culture diagnostic tests

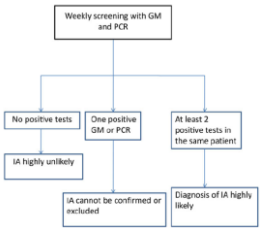
- If blood culture is negative due to low level of candidemia, beta-glucan & PCR assays unlikely to make diagnosis reliably
- If a patient in low-risk group (ICU admission), positive result does not help, but negative result excludes the disease
- If a patient in high-risk group (repeated ileal leak or pancreatitis), a positive result increases the likelihood of invasive candidiasis
- Temptation – shorter turn around time & early therapy
  - We tend to believe - non-culture diagnostic tests can identify blood culture negative primary or secondary deep-seated candidiasis
- Two high positive results are compelling
- Similarly multiple negative results are compelling

Galactomannan and Polymerase Chain Reaction–Based Screening for Invasive Aspergillosis Among High-Risk Hematology Patients: A Diagnostic Meta-analysis

Clin Infect Dis 2015; 61: 1263

Marios Arvanitis,[1,2,3] Theodora Anagnostou,[1,2] and Eleftherios Mylonakis[1,2]

Test	Sensitivity, % (95% CI)	Specificity, % (95% CI)
PCR	84 (71–92)	76 (64–85)
2 PCRs	57 (40–72)	93 (87–97)
GM	92 (83–96)	90 (81–95)
2 GMs	62 (48–74)	95 (91–97)
GM or PCR	99 (96–100)	64 (49–77)
GM and PCR	68 (54–80)	98 (94–100)



Pre-emptive approach can (i) direct antifungal therapy (reduce empiric therapy); (ii) allow earlier detection of IA

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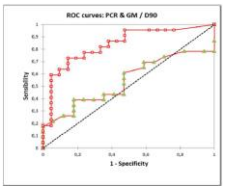
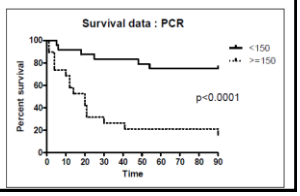
GM + PCR better than GM alone

- 941 patients, 5146 serum samples
- 51 patients – proven/probable IA
- PCR – 66.7% sens., 98.7% spec.
- GM – 78.4% sens., 87.5% spec.
- PCR+GM – 88.2% sens.

Imbert *et al.* Clin Microbiol Infect 2016, Feb 16 (on line)

Aspergillus PCR is highly predictive of 90d mortality





Current diagnostics: consensus

Infection	Culture/ Histo	Biomarker (Ab)	Biomarker (Ag)	Response to Rx
Aspergillosis	Yes -invasive	No	GM/BDG/PCR	Increasing evidence
Cryptococcosis	Routine	No	Ag/PCR	Yes (CSF Ag)
Histoplasmosis	Culture - delay	Limited	Ag	Yes (Ag)
Mucormycosis	Yes - invasive	No	Investigational	No
Other moulds	Yes –invasive	No	Investigational	No
Candidaisis	Routine	Investigational (anti-mannan)	PCR/mannan/BDG	No

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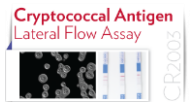
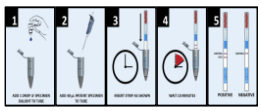
New techniques

POCT tests

Cryptococcal meningitis



- CrAg Lateral flow assay (Immy, Norman)
- No equipped lab or skill staff required
- Can identify disease before symptoms
- Temperature stable, rare cross-reaction
- Takes 10 minutes; Costs $2, cost-effective
- Cannot monitor therapy – clearance slow



Study in Uganda, Suspected cryptococcal meningitis

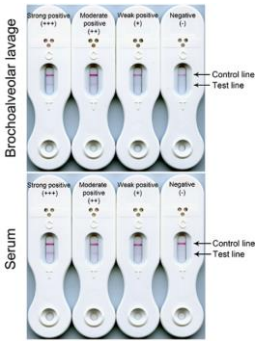
Diagnostic test	Number	Number positive/number tested (%)			
		Sensitivity	Specificity	PPV	NPV
CSF culture	806	459/510 (90.0)	296/296 (100.0)	459/459 (100.0)	296/347 (85.3)
100-µL volume	524	309/328 (94.2)	196/196 (100.0)	309/309 (100.0)	196/215 (91.2)
10-µL volume	282	150/182 (82.4)	100/100 (100.0)	150/150 (100.0)	100/132 (75.8)
India ink microscopy	805	438/509 (86.1)	288/296 (97.3)	438/446 (98.2)	288/359 (80.2)
CrAg LFA	666	435/438 (99.3)	226/228 (99.1)	435/437 (99.5)	226/229 (98.7)
CrAg latex (Meridian)	279	176/180 (97.8)	85/99 (85.9)	176/190 (92.6)	85/89 (95.5)
CrAg latex (IMMY)	749	452/466 (97.0)	283/283 (100.0)	452/452 (100.0)	283/297 (95.3)

Nalintya E, *et al.* Curr Fungal Infect Rep 2016; 10: 62

Detection of Invasive Pulmonary Aspergillosis in Haematological Malignancy Patients by using Lateral-flow Technology

Christopher Thornton[1], Gemma Johnson[2], Samir Agrawal[3]

J. Vis. Exp. (61), e3721, DOI : 10.3791/3721 (2012).



- *Aspergillus* specific extracellular glycoprotein Ag
- Secreted during active growth of fungi
- Mab (JF5) developed
- Lateral-flow device (point of care)
- Useful in BAL
- Lot of variability in sensitivity & specificity among the laboratories

Serum specificity tests

Aspergillosis diagnosis – BALF *Aspergillus* LFD

Serum showed less promising results cf. BAL fluid

Study	Risk group	Sample size (*n* of patients)	Specimen	Sensitivity	Specificity
Hoenigl 2012	HM	29	BALF	100	81.8
Micol 2015	HM	7	BALF	100	83
Prattes 2015	HM	72	BALF	71	76
Johnson 2012	HM and non-HM	32	BALF	100	80
Hoenigl 2012	SOT	10	BALF	100	80
Wiederhold 2014	SOT	47	BALF	91	83
Eigl 2015	ICU	133	BALF	80	81
Prattes 2014	Respiratory Disease	221	BALF	77	92
Held 2013	HSCT	101	Serum	40[a] 20[b]	86.8[a] 97.8[b]
White 2013	HM	103	Serum	81.8[a] 59.1[b]	84.8[a] 98[b]

Patient group	Sensitivity	Specificity	PPV	NPV
Solid organ transplantation	94 % (15/16)	92 % (89/97)	65 % (15/23)	99 % (89/90)
Intensive care unit	79 % (26/33)	85 % (176/206)	57 % (26/46)	96 % (176/183)
Respiratory diseases	77 % (24/31)	92 % (195/211)	60 % (24/40)	97 % (195/202)
Hematological malignancies	65 % (30/47)	89 % (88/99)	73 % (30/41)	84 % (88/105)

Prattes J, *et al.* Curr Fungal Infect Rep 2016; 10: 43

Aspergillus LFA: current status

- Use of test with BAL fluid >> serum
- Most promising in non-neutropenic patients (no data on serum LFA in this group)
- Use in combination with PCR +/- GM
- Non-specific binding evident even with the "CE marked" strips observed in some countries
- Till more data, for now, small but potential role in IA diagnostics

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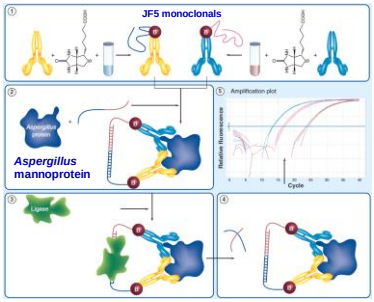
Proximity ligation assay for the early detection of invasive aspergillosis

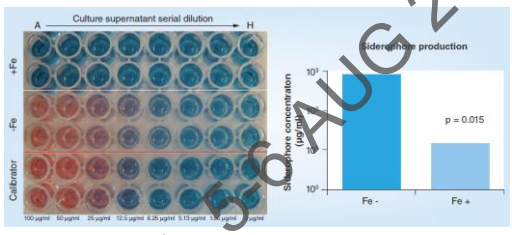
G. Johnson[1], M. Shannon[1], C. Thornton[1], S. Agrawal[2], C. Lass-Flörl[3], W. Mutschlechner[3], S. Bustin[1]

- PLA 10-100 fold higher sensitivity to GM
- 1000 fold higher sensitivity to lateral flow assay (LFD)
- No cross reaction with other fungal species



Biomark Med 2014; 8: 429-51; 25th ECCMID congress, Copenhagen, 2015

Siderophore production by *Aspergillus*



- Fuscarinine C (FsC) & triacetylfusarinine C (TAFC) – major siderophore of *A. fumigatus* released after spore germination
- Not validated yet in clinical samples

Johnson *et al.* Biomark Med 2014; 8: 429-51

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Electronic Nose Cyranose ®

Electronic Nose Technology for Detection of Invasive Pulmonary Aspergillosis in Prolonged Chemotherapy-Induced Neutropenia: a Proof-of-Principle Study

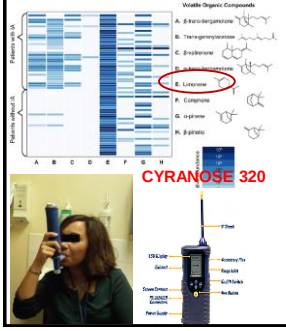
Highly effective in invasive aspergillosis in neutropenic patients

Sensitivity 100%
Specificity 83%

De Heer K. *J.Clin.Microb.* 2013;51:1490-5

A Breath Fungal Secondary Metabolite Signature to Diagnose Invasive Aspergillosis

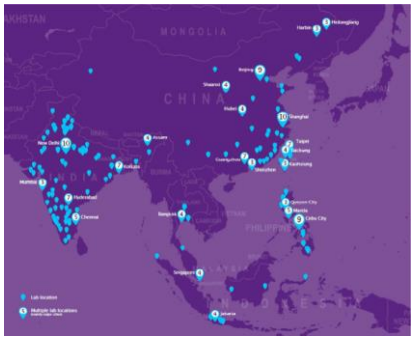
Sophia Koo,[1,2,3,a] Horatio R. Thomas,[1,2,3,a] S. David Daniels,[1] Robert C. Lynch,[1] Sean M. Fortier,[1] Margaret M. Shea,[1] Preshious Rearden,[4] James C. Comolli,[4] Lindsey R. Baden,[1,2,3] and Francisco M. Marty[1,2,3]



Clinical Infectious Diseases® 2014;59(12):1733–40

Parameter	Invasive Aspergillosis®	Other Pneumonia	Total Patients
Aspergillus metabolite signature® +	32	2	34
Aspergillus metabolite signature –	2©	28	30
Total patients	34	30	64
Test parameters			
Sensitivity (95% CI)	0.94 (.81–.98)		
Specificity (95% CI)	0.93 (.79–.98)		
Positive likelihood ratio (95% CI)	14.1 (3.69–54.0)		
Negative likelihood ratio (95% CI)	0.063 (.02–.24)		

Present scenario in Asian countries; 241 laboratories surveyed



Chindamporn *et al.* Med Mycol 2017 (accepted)

Present scenario in Asian countries

Tests	Overall n=241 (%)	China n=71 (%)	India n=104 (%)	Indonesia n=11 (%)	Philippines n=26 (%)	Singapore n=4 (%)	Taiwan n=18 (%)	Thailand n=7 (%)
Crypto Ag	65.2	66.7	58.3	50.0	75.0	100	100	50.0
Histo Ag	2.6	5.0	2.7	0	0	0	0	0
Candida Ag	14.8	43.8	7.1	22.2	0	0	0	0
GM	**22.8**	25.4	26.9	9.1	11.5	25.0	27.8	14.3
BDG	**10.0**	25.4	3.8	0	3.8	0	0	14.3
PCR	**37.8**	43.8	46.2	0	1 lab	0	0	0
TDM	**38.1**	58.3	16.7	0	0	0	0	0

Almost no access biomarker tests in Indonesia, Philippines, Thailand

Chindamporn *et al.* Med Mycol 2017 (accepted)

Summary

- Areas of interest – detection of fungi in blood & tissue, rapid identification of fungi & antifungal drug resistance in clinical samples
- Proteomic approach – MALDI, biomarkers - promising
- Genomic approach – more promising, but majority are in house & not standardized
- EAPCRI is a bold initiative, but commercial closed system required
- New initiatives – genetic susceptibility, POCT (lateral flow, proximity ligation assay, microarray, nano technology, T2)
- **Asian laboratories** – investment required, LFA – cheaper option, need to develop reference lab with availability of all biomarker tests

Thank you!

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