Diagnostiek van schimmelinfecties

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Which tests can the lab offer to you?

Conventional Tests
- Histopathology
- Direct Microscopy
- Culture
- Mass Spectrometry (MALDI-TOF)

Biomarker Tests
- Galactomannan (GM)
- 1,3 β-D-glucan (BDG)
- PCR
- Lateral Flow Assays
DIAGNOSIS OF INVASIVE CANDIDIASIS
Culture of blood

Useful only for the diagnosis of yeast infections (and Fusarium infections)

Sensitivity of blood culture for invasive candidiasis is +/- 50%
Identification of yeasts
Mannan: immunodominant surface antigen of the Candida cell wall, that is released during infection

B. Sendid et al., JCM, 1999, 1510-1517

Mannan detection is inversely correlated to the presence of anti-mannan antibodies

-●- anti-mannan
-○- mannan

B. Sendid et al., JCM, 1999, 1510-1517
Mannan and anti-mannan in patients undergoing myeloablative chemotherapy

- Mannan is predominantly detected in patients who develop invasive candidiasis during their 1st cycle of chemotherapy (< 15 days of neutropenia)
- Anti-*Candida* antibody is predominantly detected in patients who developed invasive candidiasis after undergoing multiple cycles of chemotherapy (BG remains detectable, mannan not)


Diagnostic potential of surrogate markers is determined by the phase of treatment of the underlying disease (reflected by the number of days of neutropenia)
### Platelia *Candida* Ag Plus and Platelia *Candida* Ab Plus (BioRad)

<table>
<thead>
<tr>
<th>Days of neutropenia</th>
<th>Assay</th>
<th>Sn</th>
<th>Sp</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 15</td>
<td>Ag-Plus</td>
<td>7/10 (70%)</td>
<td>2/5 (40%)</td>
</tr>
<tr>
<td></td>
<td>Ab-Plus</td>
<td>3/10 (30%)</td>
<td>3/5 (60%)</td>
</tr>
<tr>
<td></td>
<td>BG</td>
<td>5/9 (55%)</td>
<td>4/5 (80%)</td>
</tr>
<tr>
<td>&gt;15</td>
<td>Ag-Plus</td>
<td>6/11 (55%)</td>
<td>11/25 (44%)</td>
</tr>
<tr>
<td></td>
<td>Ab-Plus</td>
<td>7/11 (64%)</td>
<td>23/25 (92%)</td>
</tr>
<tr>
<td></td>
<td>BG</td>
<td>7/11 (64%)</td>
<td>23/25 (92%)</td>
</tr>
</tbody>
</table>

Significant correlation between presence of superficial candidiasis (oropharyngeal and oesophagitis) and positive *Candida* Ag Plus and Ab Plus

No difference in levels of circulating mannan between superficial infected controls and systemic patients.

Detection of *Candida* DNA on whole blood

**Systematic review and meta-analysis**

- 54 studies with 4,694 patients, 963 proven/probable or possible IC
- 100% sens/spec for candidemia versus healthy controls
- PCR positivity rates in patients with proven/probable IC 85% versus 38% for blood cultures
- Attractive method for early diagnosis of *Candida* spp.
- Effect on clinical outcomes should be investigated

DIAGNOSIS OF CRYPTOCOCCOSIS
CAPSULAR POLYSACCHARIDE ANTIGEN
Cryptococcal antigen

- Detection in serum/CSF
- Latex-agglutination/Lateral flow assay
- “One of the most useful serologic tests in mycology”
• Correlation with # yeast cells
• Highly sensitive and specific
  – **False positive** results possible in serum by rheumatoid factor if no pretreatment with pronase or in case of infection with *Trichosporon asahii*
  – **False negatives:**
    • Prozone effect
    • Organism load is low or organisms not well encapsulated
• Usefulness limited for therapeutic monitoring

Detecting cryptococcal antigen in CSF or serum is **rapid, specific, noninvasive and virtually diagnostic** of meningoencephalitic or disseminated cryptococcosis.
DIAGNOSIS OF INVASIVE ASPERGILLOSIS
Aspergillus lentulus sp. nov., a New Sibling Species of A. fumigatus

S. Arunmozhi Balajee, Jennifer L. Gribskov, Edward Hanley, David Nickle and Kieren A. Marr

Aspergillus calidoustus sp. nov., Causative Agent of Human Infections Previously Assigned to Aspergillus ustus

János Varga, Jos Houbraken, Henrich A. L. Van Der Lee, Paul E. Verweij and Robert A. Samson

Mistaken Identity: Neosartorya pseudofischeri and Its Anamorph Masquerading as Aspergillus fumigatus

S. Arunmozhi Balajee, Jennifer Gribskov, Mary Brandt, James Ito, Annette Fothergill and Kieren A. Marr
Susceptibility testing \textit{A. niger} (N=10)

![Graph showing susceptibility results](http://atlasmicologia.blogspot.be/2011/05/aspergillus-niger.html)
Galactomannan (GM) detection (Platelia™)

- Heat stable hetero-polysaccharide present in the cell wall of most *Aspergillus* spp., release during growth (cross reactivity *Penicillium*, *Paecilomyces*, *Cryptococcus*, *Histoplasma*)

- Commercial kit: Platelia® Sandwich ELISA (BioRad)
Galactomannan detection in blood: screening of neutropenic haematology patients

<table>
<thead>
<tr>
<th>OD index cutoff value, episode classification</th>
<th>No. of episodes with positive results/no. of episodes tested</th>
<th>Sensitivity, % (95% CI)</th>
<th>No. of episodes with negative results/no. of episodes tested</th>
<th>Specificity, % (95% CI)</th>
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<tbody>
<tr>
<td>OD index ≥1.5</td>
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</tr>
<tr>
<td>Proven IA</td>
<td>19/19</td>
<td>100 (85.4–100)</td>
<td>...</td>
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<tr>
<td>Probable IA</td>
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<td>52.6 (28.9–75.5)</td>
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<td>...</td>
</tr>
<tr>
<td>Overall</td>
<td>29/38</td>
<td>76.3 (59.8–88.6)</td>
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<td>...</td>
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<tr>
<td>Control group</td>
<td>...</td>
<td>...</td>
<td>196/201</td>
<td>97.5 (94.3–99.2)</td>
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<tr>
<td>OD index ≥1.0</td>
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<tr>
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<td>100 (85.4–100)</td>
<td>...</td>
<td>...</td>
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<tr>
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<tr>
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<td>81.6 (65.7–92.3)</td>
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<td>...</td>
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<tr>
<td>Control group</td>
<td>...</td>
<td>...</td>
<td>194/201</td>
<td>96.5 (93.0–98.6)</td>
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<tr>
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<tr>
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<td>19/19</td>
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<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Probable IA</td>
<td>18/19</td>
<td>94.7 (74.0–99.9)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Overall</td>
<td>37/38</td>
<td>97.4 (86.2–99.9)</td>
<td>...</td>
<td>...</td>
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<tr>
<td>Control group</td>
<td>...</td>
<td>...</td>
<td>182/201</td>
<td>90.5 (85.6–94.2)</td>
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<td>OD index ≥2 × 0.5</td>
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</tr>
<tr>
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<td>100 (85.4–100)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Probable IA</td>
<td>16/19</td>
<td>84.2 (60.4–96.6)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Overall</td>
<td>35/38</td>
<td>92.1 (78.6–98.3)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Control group</td>
<td>...</td>
<td>...</td>
<td>196/201</td>
<td>97.5 (94.3–99.2)</td>
</tr>
</tbody>
</table>
### Galactomannan detection in blood: diagnosis of IA in ICU patients

**BAL culture/microscopy and serum GM remained negative in 11/26 (42%) proven cases**

<table>
<thead>
<tr>
<th>OD index cut-off:</th>
<th>1.5</th>
<th>1.0</th>
<th>0.7</th>
<th>0.5</th>
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<tbody>
<tr>
<td><strong>serum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>23</td>
<td>27</td>
<td>31</td>
<td>42</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>100</td>
<td>98</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>100</td>
<td>88</td>
<td>89</td>
<td>85</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>68</td>
<td>69</td>
<td>70</td>
<td>74</td>
</tr>
</tbody>
</table>

Galactomannan detection in blood: clear influence of neutrophil counts

False positive galactomannan results: no problem anymore with Tazocin™

Piperacillin/tazobactam (Tazocin™) seems to be no longer responsible for false-positive results of the galactomannan assay.

Mikulska M, Furfaro E, Del Bono V, Raiola AM, Ratto S, Bacigalupo A, Viscoli C.
Division of Infectious Diseases, San Martino University Hospital and University of Genoa, Genoa, Italy. m.mikulska@unige.it

<table>
<thead>
<tr>
<th>NO PIP-TAZO</th>
<th>PIP-TAZO THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>25/1606 (1.6 %) sera GM positive</td>
<td>10/394 (2.5 %) sera GM positive</td>
</tr>
</tbody>
</table>

90 PIP-TAZO vials from 30 randomly selected batches: all GM negative

Since introduction of new brand, Tazocin EF™ (Pfizer) in 2006?

False positive galactomannan results: testing the sample twice improves specificity

Big difference between initial and retest result
False positive galactomannan test after ice-pop ingestion

Post HSCT in patient with severe gastrointestinal GVHD

Galactomannan Indexes in the Patient and in Three Brands of Ice Pops.
## Galactomannan detection in BAL: diagnosis of IA in ICU patients

<table>
<thead>
<tr>
<th>OD index cut-off:</th>
<th>1,5</th>
<th>1,0</th>
<th>0,7</th>
<th>0,5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BAL</td>
<td>serum</td>
<td>BAL</td>
<td>serum</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>81</td>
<td>23</td>
<td>81</td>
<td>27</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>96</td>
<td>100</td>
<td>93</td>
<td>98</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>81</td>
<td>100</td>
<td>79</td>
<td>88</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>89</td>
<td>68</td>
<td>89</td>
<td>69</td>
</tr>
</tbody>
</table>
Clear influence of neutropenia on serum GM but not on BAL GM value

Jan 2005 – Sept 2008
58 proven/probable IA
41 controls


<table>
<thead>
<tr>
<th></th>
<th>Neutropenic</th>
<th>non-Neutropenic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAL, 1.0</td>
<td>100%</td>
<td>94.7%</td>
<td>0.99</td>
</tr>
<tr>
<td>Serum, 0.5</td>
<td>90%</td>
<td>36.8%</td>
<td>0.008</td>
</tr>
</tbody>
</table>
Galactomannan detection in BAL: optical density index cut-off value

The ROC curve identified 0.8 as the most appropriate cut-off value; the area under the curve was 0.94 (95% CI, 0.90-0.98)

Galactomannan detection in BAL: pre-analytical variables that impact sensitivity

- Trend for mold-active antifungal use to decrease sensitivity ($p=0.07$): pooled sensitivity decreased from 0.91 to 0.76 (meta-analysis in adult hematology patients).

- Single center retrospective study in hematology patients (28 episodes proven/probable IA, 71% of patients mold-active antifungals at time of BAL):
  - Time effect: sensitivity of GM detection decreased when antifungal treatment lasted \( \geq 2 \) days at the time of bronchoscopy.
  - Detection of GM in the alveolar samples better sensitivity than in bronchial sample (first aliquot returned).
  - No significant relationship between the amount of administered solution and the GM assay, trend towards a higher volume of aspirated fluid in GM-negative BAL ($p=0.093$).

- Pre-treatment of samples with Sputasol® lowers GM levels and alters the LFD results (discolors the LFD and control lines).

Serum galactomannan testing is a useful tool to screen for invasive aspergillosis ...

A. In patients receiving remission-induction chemotherapy for AML

B. In patients receiving remission-induction chemotherapy for AML and posaconazole prophylaxis

C. In alloHSCT recipients with GVHD

D. In alloHSCT recipients with GVHD receiving posaconazole prophylaxis
Points to consider

• Incidence of disease in target population
  *In a setting with:*
  - Incidence of IA of 2%
  - Performance GM test: sensitivity: 90%, specificity: 90%
  - Positive predictive value = 15%
  - For each true positive result → 6 false positive test results
  - To detect one IA case, you’ll need to screen > 50 patients

• Poor sensitivity of serum GM test in non-neutropenic patients

• Influence of posaconazole prophylaxis on GM OD index?
HIGH RISK PATIENTS
Neutropenic patients and HSCT recipients
NOT IF ON MOLD
ACTIVE PROPHYLAXIS
SCREEN BAL samples

DIAGNOSIS: BAL samples
(and other: blood, CSV)

LOW OR INTERMEDIATE RISK PATIENTS
Neutropenic patients, HSCT recipients,
solid organ transplant recipients and ICU patients
Mold active antifungal prophylaxis: huge impact on PPV of serum GM test!

262 unselected consecutive high-risk episodes, prospectively managed with posaconazole primary prophylaxis, biweekly serum GM testing.

Performance of serum galactomannan assay in high-risk patients receiving effective anti-mold prophylaxis

- **GM screening of all cases** (incidence < 2%)
  - NPV: 100%
  - PPV: 12%

- **Diagnosis of IFD suspicion only** (incidence > 50%)
  - NPV: 100%
  - PPV: 90%

- nearly 9/10 serum GM is false positive!
FAILRE OR SUCCESS??

Baseline
Prolonged neutropenic fever

2 Weeks therapy

Neutrophils: 0 /µL
Serum GM: 1.59

Neutrophils: 12,500/µL
Serum GM: 0.23
GM detection in blood is a reliable test to monitor treatment response and predict outcome

- Clinical outcome may be anticipated by charting early GM index trends during the first two weeks of antifungal therapy
- GM index at baseline ≥ 0.5 and reduction >35% between baseline and week 1 predicts satisfactory clinical response
- GM index at baseline < 0.5 and rise to > 0.5 at week 2 despite antifungals predicts poor outcome

1, 3 β-D-Glucan detection

• ‘Panfungal’:
  • *Aspergillus*, *Candida*, many other fungi
  • **NO detection of Mucorales and Cryptococcus**

• Several commercial kits available (different cut-off values): Fungitell™, Glucatell™ in US and Europe

• Approved for serum testing only. Lower specificity than GM detection in BAL (frequent Candida colonization of respiratory tract)

• Test not really user-friendly

• Many cause for false positivity β-lactam antibiotics
  – Hemodialysis/hemofiltration
  – Blood components: immunoglobulin preparations
  – Surgical gauzes
  – Bacterial infections
1, 3 β-D-Glucan Assay

A. Lysate source: horseshoe crab

B. Clinical specimen

C. Limus Amebocyte Lysate (LAL) Pathway

D. Synthetic peptide chromogenic substrate

E. Reaction Assay

- Endotoxin (LPS)
- Factor C (activated)
- Factor B (activated)
- Factor G (activated)
- Pro-clotting enzyme
- Clotting enzyme
- Yellow artificial substrate
- Absorbance 405 nm
(1→3)-β-D-glucan in patients with haematological malignancies

- Different BG assays have similar accuracy
- Two consecutive positive antigenemia assays: very high specificity, PPV and NPV
- Test needs to be combined with clinical, radiological and microbiological findings

Strong suspicion of invasive fungal infection while all (other) test remain negative or inconclusive

Inability to perform bronchoalveolar lavage in a patient with suspicion of *Pneumocystis jirovecii* pneumonia
• Murine MAb JF5: IgG₃ immunoglobulin
• Recognizes an extracellular, constitutive, glycoprotein antigen
• Antigen is secreted during active growth of hyphae and is not produced by dead or quiescent spores
• Displays superior specificity to rat MAb EB-A2 (Bio-Rad Platelia GM-EIA)
• Used to develop a rapid, user-friendly, diagnostic test for detection of IA


1 Cryptococcus neoformans
2 Candida albicans
3 Fusarium solani
4 Rhizopus oryzae
5 Aspergillus fumigatus
The lateral flow device

Monoclonal antibody: Mab JF-5
Antibody source: mouse

Pretreatment of serum samples necessary, not of BAL samples

Step 1

Step 2

Step 3

Positive reaction

Negative reaction

Clinical specimen

Capillary flow

Sample pad

Capture zone

Test line

Control line

(mAb) (anti-mouse IgG)

Aspergillus lateral flow assay

Capture zone

Clinical specimen

Sample pad

Test line

Control line

(mAb) (anti-mouse IgG)

Capture zone

Clinical specimen

Sample pad

Test line

Control line

(mAb) (anti-mouse IgG)
Localisation of JF5 antigen

Expert Review of Clinical Immunology (2014)

Current Fungal Infection Reports (2013) 7: 244-251.
Commercialisation of the Aspergillus LFD
• European *Aspergillus* PCR Initiative (2006)

• Commercial and in house assays  
  → lack of standardization… but we’re on our way!

• DNA load in many samples close to the detection limit of even highly sensitive PCR protocols

• *Aspergillus* PCR in blood mainly evaluated in hematology patients

• Not yet included in international guidelines…

Detection of *Aspergillus* DNA: serum versus whole blood

Case (n = 47) – control (n = 31) study

- alloSCT + chemotherapy for AML
- Blood (PCR) and serum (PCR and GM) twice weekly (803 samples)
- PCR following EAPCRI guidelines

- No significant difference between WB and serum for PCR
- Trend for WB to be more sensitive and positive earlier than serum
- BUT serum: lower false positivity and suited for GM testing

Combination of GM and PCR on WB or serum best diagnostic utility
**Combined assay performance for blood screening in high risk hematology patients**

Case-control design: 22 proven/probable IA versus 59 controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Positivity threshold</th>
<th>Assay combination&lt;sup&gt;a&lt;/sup&gt;</th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PCR or LFD</td>
<td>PCR and LFD</td>
<td>PCR or GM</td>
<td>PCR and GM</td>
<td>GM or LFD</td>
<td>GM and LFD</td>
</tr>
<tr>
<td>% sensitivity (95% CI)</td>
<td>Single</td>
<td>100 (85.1–100)</td>
<td>77.3 (56.6–89.9)</td>
<td>95.5 (78.2–99.2)</td>
<td>77.3 (56.6–89.9)</td>
<td>86.4 (66.7–95.3)</td>
<td>72.7 (51.9–86.9)</td>
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<tr>
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<td>Multiple</td>
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<td>40.9 (23.3–61.3)</td>
<td>90.9 (72.2–97.5)</td>
<td>45.5 (26.9–65.3)</td>
<td>77.3 (56.6–89.9)</td>
<td>50.0 (30.7–69.3)</td>
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<tr>
<td>% specificity (95% CI)</td>
<td>Single</td>
<td>57.6 (44.9–69.4)</td>
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<td>54.2 (41.7–66.3)</td>
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<td>72.9 (60.4–82.6)</td>
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<td>100 (93.9–100)</td>
<td>88.1 (77.5–94.1)</td>
<td>100 (93.9–100)</td>
<td>91.5 (81.7–96.3)</td>
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<td>% PPV (95% CI)</td>
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<td>43.8 (30.7–57.7)</td>
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<td>54.3 (38.2–69.5)</td>
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<td>100 (70.1–100)</td>
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<td>100 (72.3–100)</td>
<td>77.3 (56.6–89.9)</td>
<td>91.7 (64.6–98.5)</td>
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<tr>
<td>% NPV (95% CI)</td>
<td>Single</td>
<td>100 (89.9–100)</td>
<td>92.2 (83.0–96.6)</td>
<td>97.0 (84.7–99.5)</td>
<td>92.2 (83.0–96.6)</td>
<td>94.4 (82.5–97.8)</td>
<td>90.2 (80.2–95.4)</td>
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<td>81.9 (71.5–89.1)</td>
<td>96.3 (87.5–99.0)</td>
<td>83.1 (72.7–90.1)</td>
<td>91.5 (81.7–96.3)</td>
<td>84.1 (73.7–90.9)</td>
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<td>Positive likelihood ratio</td>
<td>Single</td>
<td>2.4</td>
<td>&gt;772.7</td>
<td>2.1</td>
<td>&gt;772.7</td>
<td>3.2</td>
<td>10.7</td>
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<td></td>
<td>Multiple</td>
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<td>7.7</td>
<td>&gt;454.5</td>
<td>9.1</td>
<td>29.6</td>
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<td>Negative likelihood ratio</td>
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<td>&lt;0.0017</td>
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<td>0.08</td>
<td>0.23</td>
<td>0.19</td>
<td>0.29</td>
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<td>0.10</td>
<td>0.55</td>
<td>0.25</td>
<td>0.51</td>
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<tr>
<td>DOR</td>
<td>Single</td>
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<td>&gt;3,359.6</td>
<td>26.1</td>
<td>&gt;3,359.6</td>
<td>16.7</td>
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<td>&gt;693.4</td>
<td>76.7</td>
<td>&gt;826.4</td>
<td>36.5</td>
<td>58.0</td>
</tr>
</tbody>
</table>
Novel tests for diagnosis of IA in patients with underlying respiratory disease

- 286 BAL from 221 patients with underlying respiratory diseases (without hematological malignancy or SOT)
- 14% proven/probable IPA
- 02/2012 – 05/2014, Graz, Austria

<table>
<thead>
<tr>
<th>Test Methods</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>DOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAL GM &gt; 0.5 ODI</td>
<td>97 (30/31)</td>
<td>81 (170/211)</td>
<td>42 (30/71)</td>
<td>99 (170/171)</td>
<td>124.4 (16.5–938.9)</td>
</tr>
<tr>
<td>BAL GM &gt; 1.0 ODI</td>
<td>97 (30/31)</td>
<td>93 (197/211)</td>
<td>68 (30/44)</td>
<td>99 (197/198)</td>
<td>422.1 (53.5–3,328)</td>
</tr>
<tr>
<td>BAL GM &gt; 3.0 ODI</td>
<td>61 (19/31)</td>
<td>99 (208/211)</td>
<td>86 (19/22)</td>
<td>95 (208/220)</td>
<td>109.8 (28.5–423.3)</td>
</tr>
<tr>
<td>BDG &gt; 80 pg/ml</td>
<td>90 (27/30)</td>
<td>42 (84/199)</td>
<td>19 (27/142)</td>
<td>96 (84/87)</td>
<td>6.6 (1.9–22.4)</td>
</tr>
<tr>
<td>BDG &gt; 200 pg/ml</td>
<td>70 (21/30)</td>
<td>61 (122/199)</td>
<td>21 (21/98)</td>
<td>93 (122/131)</td>
<td>3.7 (1.6–8.5)</td>
</tr>
<tr>
<td>LFD</td>
<td>77 (24/31)</td>
<td>92 (195/211)</td>
<td>60 (24/40)</td>
<td>97 (195/202)</td>
<td>41.8 (15.6–111.8)</td>
</tr>
<tr>
<td>Conventional culture</td>
<td>29 (9/31)</td>
<td>97 (205/211)</td>
<td>60 (9/15)</td>
<td>90 (205/227)</td>
<td>14 (4.5–43)</td>
</tr>
<tr>
<td>BAL GM &gt; 3.0 ODI and/or positive LFD</td>
<td>100 (31/31)</td>
<td>91 (192/211)</td>
<td>62 (31/50)</td>
<td>100 (192/192)</td>
<td>621.9 (36.6–10,563)</td>
</tr>
</tbody>
</table>
Antifungal strategies for patients at risk of invasive fungal disease (IFD)

Population at risk for IFD

Preventative strategy

No prophylaxis
- Empirical
- Diagnostics-driven

Fluconazole prophylaxis
- Empirical
- Diagnostics-driven

Mould-active prophylaxis
- Empirical
- Diagnostics-driven

Until results of diagnostic tests are available and IFD is confirmed or excluded

High risk of IFD: screening with biomarkers

“Of course I will need to run some tests, but offhand I’d say it’s some sort of fungus infection”