

## New Developments and Challenges in Diagnostics of Invasive Fungal Infections

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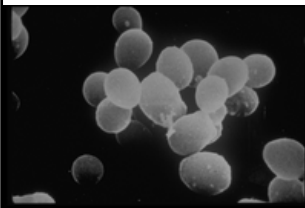
## Outline

### NEW DIAGNOSTIC TOOLS

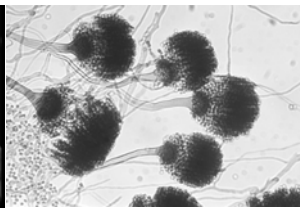
**WHY ?**  
**WHICH TESTS ?**  
**WHEN TO USE THEM ?**

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### Candida



### Aspergillus



70-90%	<u>HOSPITAL / ICU</u>	10-30%
30-60%	<u>NEUTROPENIA / TRANSPLANTATION</u>	30-60%

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### Clinical Profiles at Risk for Invasive Fungal Infections (IFI)

- Neutropenia, immunosuppressive agents : risk < 5% to > 30%
- ICU stay +/- mechanical ventilation > 3-5 days : risk 1% to 20%
  - Antibacterials, intravascular devices, hemodialysis/CVVHD, ....
- Recurrent GI leakage, acute necrotizing pancreatitis : risk 30-40%
- Fungal colonisation (> 2-3 sites, corrected colonization index > 0.4)
  - PPV 44 to 100%, NPV 68 to 100%
- Prediction rules : PPV low (down to 10%) and NPV high (up to 97%)
- LACK OF SPECIFICITY : Bacterial co-infections ! Utility in management ?
- EORTC-MSG criteria : for clinical trials only, not for patients' care

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### Conventional Diagnosis of IFI

MICROSCOPY / CULTURES KEY FOR IDENTIFICATION / SUSCEPTIBILITY

BLOOD CULTURES :

growth 2-7 d, sensitivity 20-50% invasive candidiasis, < 5% invasive aspergillosis

TISSUES CULTURES / HISTOPATHOLOGY :

often unfeasible (co-morbidity, bleeding); sensitivity 40-70% (empirical antifungals)

CULTURES AT NOT STERILE SITES :

BAL sensitivity for moulds 40-60% / Colonization URINE / BAL ?

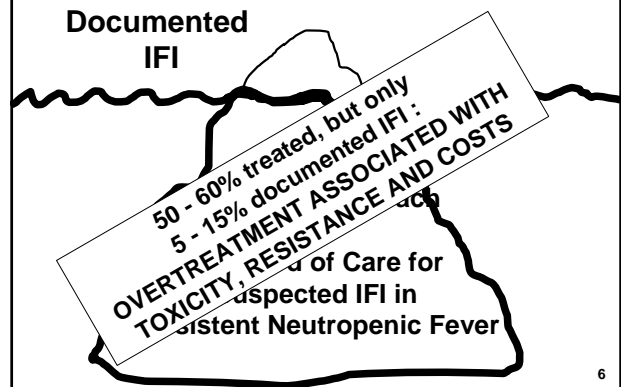
IMAGING : not specific, often delayed

LATE DOCUMENTATION (locally advanced or disseminated infection)  
→ MORTALITY CANDIDIASIS 30-60% - ASPERGILLOSIS 40-90% !

EARLY THERAPY PROGNOSTIC KEY  
→ 20 to 30% HIGHER RESPONSE / SURVIVAL RATES !

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### Documented IFI



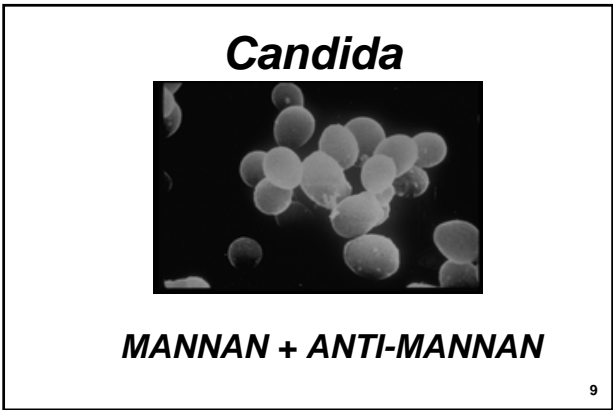
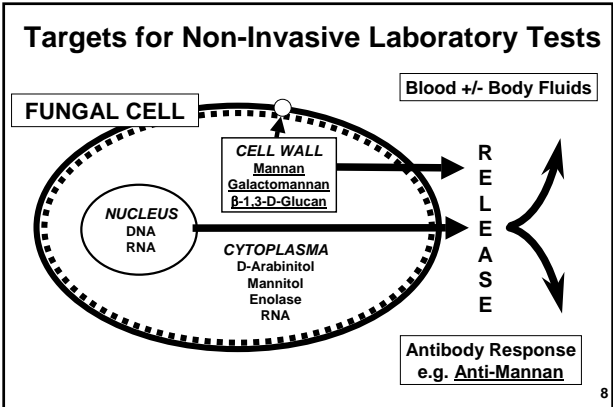
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**Outline**

**NEW DIAGNOSTIC TESTS**

**WHY ?**  
**WHICH TESTS ?**  
**WHEN TO USE THEM ?**

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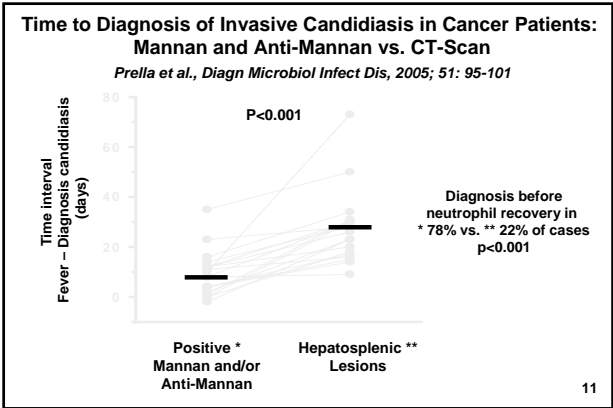


**Mannan Antigenemia and Anti-Mannan Antibodies for Diagnosis of Invasive Candidiasis**  
*Sendid et al., J Clin Microbiol, 1999; 37: 1510-7*  
*Prella et al., Diagn Microbiol Infect Dis, 2005; 51: 95-101*

	Sendid, 2 Hospitals, France	Prella, 1 Hospital, Switzerland
Setting	Non-Neutropenic n = 43 (+ 150)	Neutropenic n = 28 (+ 25)
Sampling	NOT systematic 1 to 11/pat	1x/week Median 7/pat (3 to 11)
Sensitivity	1x, Mn >0.5 / AMn >10 80%	2x, Mn >0.25 / AMn >5 89%
Specificity	93%	84%
PPV	78%	86%
NPV	93%	88%

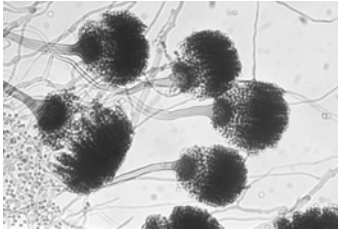
Sensitivity < 50% in *C. parapsilosis*, *krusei*, *kefyr* ?

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- Mannan / Anti-Mannan**
- Limited number of studies
    - Retrospective > prospective : ICU > hematological, NO HSCT
    - Healthy controls > high-risk cohorts
    - Candidemia > other types of invasive candidiasis
  - Best performance with combination of both test
    - Sensitivity mannan < anti-mannan
    - Specificity anti-mannan < mannan : impact of colonization ?
    - Cut-offs and number of positive samples to be redefined
  - Early positivity, before conventional diagnosis
  - New tests in the pipeline: improved sensitivity / lab procedures
  - 3<sup>rd</sup> European Conference on Infections in Leukemia (ECIL) 2009: grading of evidence and recommendation CII
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# Aspergillus



## GALACTOMANNAN

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### Galactomannan for Diagnosis of Invasive Aspergillosis: Meta-Analysis, 27 Studies

Pfeiffer et al., Clin Infect Dis, 2006; 42: 1417-27

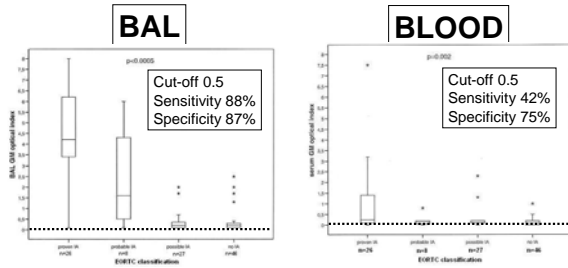
Clinical setting	Sample size	Sensitivity (95%CI)	Specificity (95%CI)
Hematological malignancies	2960	70% (62-77%)	92% (90-93%)
Allogeneic HSC transplant	903	82% (70-90%)	86% (83-88%)
Solid organ transplant	224	22% - 40% (3-60%)	84% (78-88%)

NEUTROPENIC VS. NON-NEUTROPENIC STATUS  
 → SYSTEMIC VS. LOCALIZED FUNGAL DISEASE  
 → DIFFERENT ANTIGENEMIA !?

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### Galactomannan in BAL for Diagnosis of Invasive Aspergillosis in ICU Patients

Meersseman et al. Am J Resp Crit Care Med, 2008; 177: 27-34



BAL CULTURE + DIRECT EXAMINATION :  
 sensitivity 60%, PPV LOW

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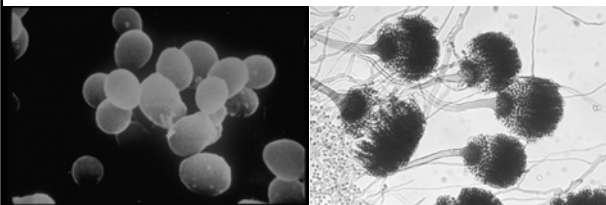
### Galactomannan

- BLOOD : solid data set
  - Cut-off 0.5 (vs. 1 or 1.5) : ↑ sensitivity, ↓ specificity, early diagnosis
  - 1 x positive or 2 x positive ?
- Different detection in neutropenic vs. non-neutropenic patients
- Ongoing antifungal therapy : ↓ sensitivity, delayed diagnosis
- False-positives: piperacillin/tazobactam, food, ....
- Follow-up : galactomannan ↓ if response / ↑ if therapy failing
- BAL : promising, further validation needed
- 3<sup>rd</sup> European Conference on Infections in Leukemia (ECIL) 2009 : grading of evidence and recommendation All

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# Candida

# Aspergillus



## 1,3-BETA-D-GLUCAN

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### Beta-Glucan Antigenemia for Diagnosis of IFI

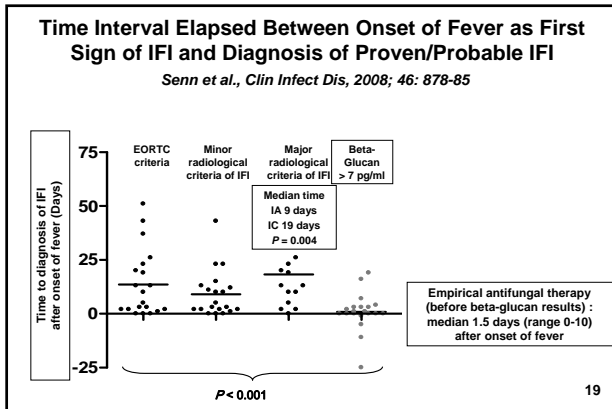
Ostrosky-Zeichner et al., Clin Infect Dis, 2005; 41: 654-9

Senn et al., Clin Infect Dis, 2008; 46: 878-85

	Ostrosky-Zeichner, 6 Hospitals, USA Fungitell, USA, 1x >60	Senn, 1 Hospital, Switzerland WAKO-Maruha, JP, 2x >7
Setting	Mainly candidiasis Non-Neutropenic n = 107 (+ 170)	Candidiasis + Aspergilliosis Neutropenic n = 30 (+ 113)
Sampling	Within 72h of Cultures 1/pat	2x/week Median 7/pat (3 to 11)
Sensitivity	81%	63%
Specificity	87%	96%
PPV	80%	79%
NPV	89%	91%

Performance similar in *C. albicans*, non-*albicans* *Candida* sp., *Aspergillus*

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- ### Beta-Glucan
- 3 different tests (2 Japan, 1 USA)
    - Variable quality of data : retrospective vs. prospective; heterogenous patients / controls vs. high-risk cohorts
  - Sensitivity 45-70% ; specificity, PPV, and NPV high
  - False-positives: bacteremia, antibiotics, pre- / analytical contaminations
  - Lacking data
    - Influence of ongoing antifungal prophylaxis - therapy
    - BAL, other moulds
    - Assessment of response to therapy
  - Costs, complex analytical procedures : automated assay in the pipeline
  - 3<sup>rd</sup> European Conference on Infections in Leukemia (ECIL) 2009 : [grading of evidence and recommendation BII](#)
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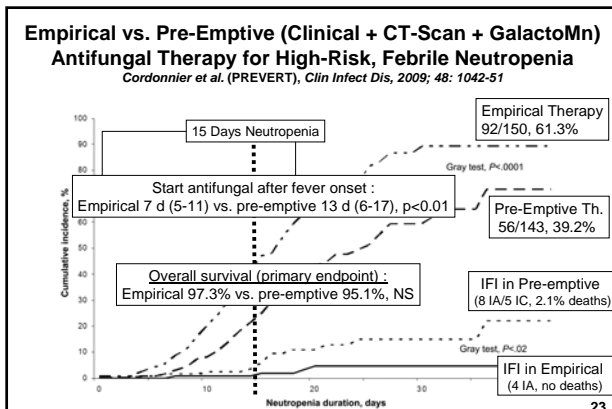
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### Fungal Monitoring in Cancer Patients ?

Selection criteria	Incidence IFI / « Number Needed to Test »	Monitoring
Neutropenia < 5-10 days including autologous HSCT	2 - 5% « NNT » 20 - 50	NO
Myeloablative chemotherapy for acute leukemia, neutropenia > 10-15 days	5 - 20% « NNT » 5 - 20	YES
Allogeneic HSCT	15 - 30% « NNT » 3 - 6	YES

**Straightforward clinical selection criteria**

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### Fungal Monitoring in ICU Patients ?

Selection criteria	% Candidiasis « Number Needed to Test »	Monitoring
Expected ICU stay > 2 d	1 - 2% « NNT » 50 - 100	NO
Mechanical ventilation > 2 d + ICU stay > 3 d and/or multiple risk factors or Composite Candida SCORES	5 - 15% « NNT » 7-20	YES ?
Corrected colonization index > 0.4 or Recurrent GI perforation/leakage	30 - 40% « NNT » 3	YES ?

**Intuitive selection criteria need to be clinically validated : Lacking data in non-candidemic invasive infections, e.g. peritonitis, CVC, ....**

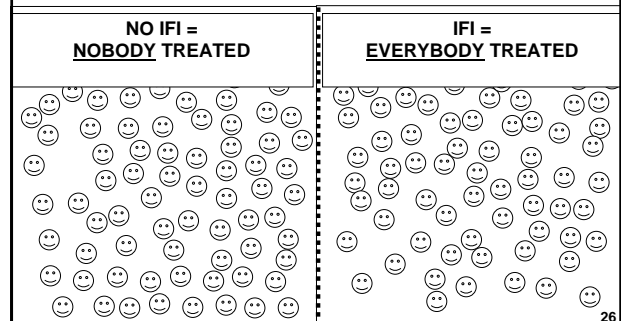
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### Challenges of Antifungal Strategies Based on New Diagnostic Tools

- **Reference gold standard**
  - Immunocompromised pts. : EORTC-MSG
  - ICU / surgical pts. : what beyond candidemia ?
- **Timing of blood sampling**
  - Monitoring 2-3x/week for risk period vs. clinically-driven (persistent fever, ...)
- **Diagnostic spectrum**
  - Combination of *Candida/Aspergillus*-specific and panfungal tests
- **Decision for start and/or reassessment of antifungal therapy combining fungal markers + conventional tools based on patients' risk profile**
  - Randomized prospective evaluation of clinical efficiency / safety
  - Global cost-effectiveness : lab, drugs, morbidity-mortality
  - Data in children needed

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### Future Goal of Pre-Emptive Antifungal Therapy ? Early and Focussed



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