

**Fungal Biomarkers**

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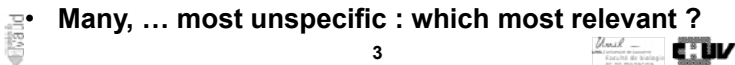
« Meet-The-Expert Session 10 »  
October 13, 2013 - Harlekin, 10:15 - 11:00

6th Trends in Medical Mycology  
Copenhagen - DK



**Risk Factors for IFI**


- Length of ICU stay
- Antibacterials (number, spectrum, duration)
- Intravascular devices / Hemodialysis / CRRT
- Abdominal surgery / Parenteral nutrition
- *Candida* colonization, ...
- Immunosuppression
  - Neutropenia (depth, duration, ...)
  - Chemotherapy-induced toxic mucositis
  - Underlying conditions : cancer, SOT, ...
  - Corticosteroids, cyclosporin, ...
- Many, ... most unspecific : which most relevant ?



**Disclosures**

Research, educational, and/or travel grants / speaker / advisor :

- Associates of Cape Code
- BioMérieux - Cepheid
- Bio-Rad / Wako / Roche Diagnostics
- Essex Schering-Plough / Gilead
- Merck, Sharp & Dohme-Chibret / Novartis / Pfizer
- ALLFUN FP7
- Foundation for the Advancement in Medical Microbiology and Infectious Diseases, FAMMID
- FUNGINOS
- Leenards Foundation



**Conventional Diagnosis of IFI**

MICROSCOPY / CULTURES KEY FOR IDENTIFICATION / SUSCEPTIBILITY

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

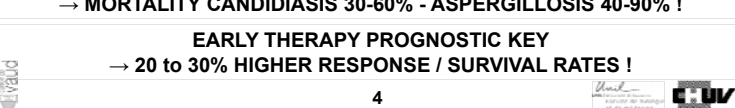
TISSUES CULTURES / HISTOPATHOLOGY :  
often unfeasible (co-morbidity, bleeding) ; sensitivity 40-70% (empirical antifungals)

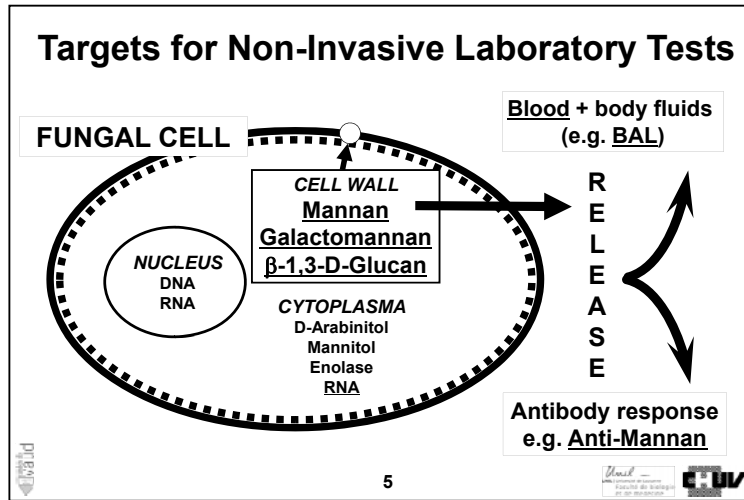
CULTURES AT NOT STERILE SITES :  
BAL sensitivity for moulds 40-60% / Colonization URINE / BAL ?

IMAGING : not specific, 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 !





### Clinical Case

- 45-year old patient, myelodysplastic syndrome with excess of blasts
- Induction chemotherapy, expected marrow aplasia > 28 days  
Posaconazole prophylaxis 200mg 3x/d per os
- Day 7, febrile neutropenia, diarrhea, abdominal cramps  
Empirical imipenem → resolution of fever, negative cultures
- Day 17, relapsing fever, tachypnea, hypoxemia  
ICU admission for non-invasive mechanical ventilation

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### Interactive Case Studies : ICU & Hemato-Oncology

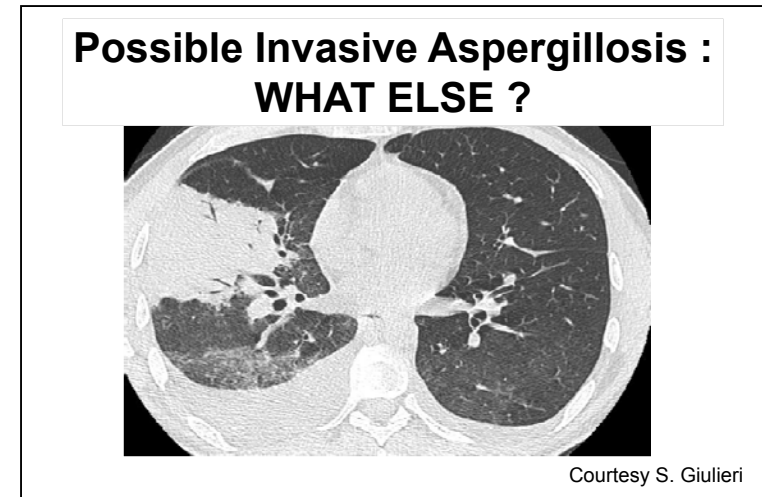
Mannan  
Anti-Mannan  
Beta-Glucan

**Candida**

GalactoMannan  
Beta-Glucan

**Aspergillus**

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## Boualem : Blood & BAL GalactoMannan in Invasive Aspergillosis

### Clinical Case

- 36-year old female patient with acute myeloblastic leukemia
- Induction chemotherapy
- Day 9, FUO : empirical cefepime, defervescence
- Day 16, relapsing fever, diarrhea, abdominal pain : imipenem
- Day 18, persistent fever, worsening abdominal status, *C. albicans* GI tract colonization, negative blood cultures, ... Empirical caspofungin
- Day 21, resolution of fever
- Day 27, neutrophils recovery, relapsing fever, upper right abdominal pain

### Possible Hepatosplenic Candidiasis : HOW TO GET CLOSE TO THE ETIOLOGY ?



Courtesy F. Lamothe

### Boualem : Mannan in Early Course and Anti-Mannan in Late Course of Invasive (Hepato-Splenic) Candidiasis

## Boualem : Summary GalactoMannan / Mn-AntiMn HEM & ICU Pts

### Clinical Case

- 55-year old patient, acute myocardial infarction
- Day 1 : cardiogenic shock, aortic balloon counter-pulsation, mechanical ventilation, CRRT
- Day 7 : nosocomial pneumonia, cefepime
- Day 12 : MRSA bacteremia (CVC infection), vancomycin
- Day 18 : candiduria (*C. albicans*)
- Day 21 : septic shock, no apparent focus of infection ...

#### • BLOOD CULTURES ...

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Proietti et al. Critical Care 2011, 15:R249  
http://ccforum.com/content/15/5/R249



RESEARCH

Open Access

### Early diagnosis of candidemia in intensive care unit patients with sepsis: a prospective comparison of (1→3)-β-D-glucan assay, *Candida* score, and colonization index

Brunella Postoraro<sup>1</sup>, Gennaro De Pascale<sup>2</sup>, Mario Turribardolo<sup>3\*</sup>, Riccardo Torelli<sup>1</sup>, Mariano Alberto Perrini<sup>4</sup>, Giuseppe Bello<sup>2</sup>, Riccardo Maviglia<sup>2</sup>, Giovanni Fadda<sup>1</sup>, Maurizio Sanguinetto<sup>1</sup> and Massimo Antonelli<sup>2</sup>

Ospedale Gemelli, Università Cattolica, Roma, Italy

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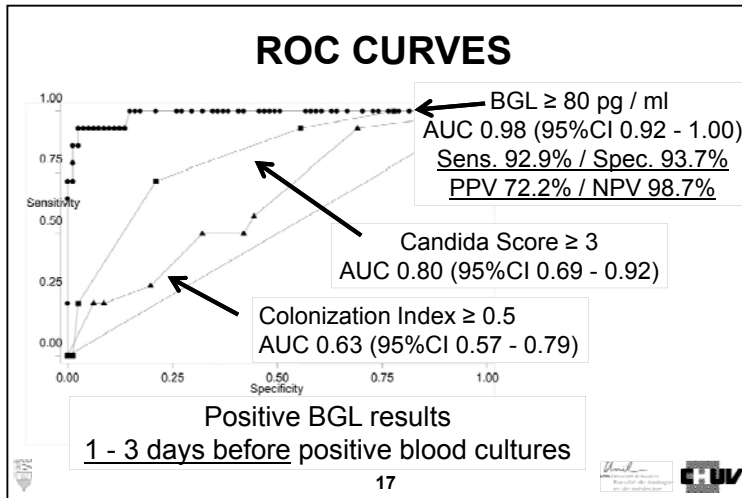
### METHODS

- Inclusion criteria (ALL fulfilled) :
  - Medical ICU admission with sepsis
  - Not neutropenic / No IFI at baseline
  - ICU stay > 5 days
- Diagnostic assessment at inclusion :
  - Blood cultures
  - Beta-glucan (≥ 80 pg / ml)
  - *Candida* score (≥ 3)
  - Colonization index (≥ 0.5)

95 patients included, 16 IFI :  
13 candidemias, 1 *Candida* mediastinitis,  
1 lung aspergillosis, 1 lung fusariosis

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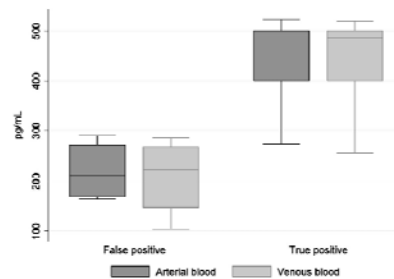




## Beta-Glucan in Candidemia

- Single BGL  $\geq 80$  pg / ml at onset of sepsis in medical patients with ICU stay > 5 days
- Accurate for EARLY diagnosis of candidemia
- Detection of all *Candida* species  
*Ostrosky-Zeichner et al., Clin Infect Dis, 2005; 41: 654-9*
- Practical : simple patients' selection and one single blood sample (catheter = venipuncture) !

## BGL IN BLOOD FROM ARTERIAL CATHETER VS. PERIPHERAL VENIPUNCTURE



## Clinical Case


- Hemicolectomy for colon cancer
- Day 1 surgical revision for haemorrhagic shock
  - Mechanical ventilation for ARDS
  - CVVHD for ARF
  - TPN, multiple vascular access devices
  - Cefepime + metronidazole
- Day 10 postoperative peritonitis with septic shock :
  - Surgical revision for anastomotic leakage
  - Imipenem, afebrile 48h, and then relapsing fever
- Intraoperative cultures NOT DONE ...

### Monitoring of 1,3-Beta-D-Glucan (BDG) in High-Risk Surgical ICU Patients for Early Diagnosis of Intra-Abdominal Candidiasis

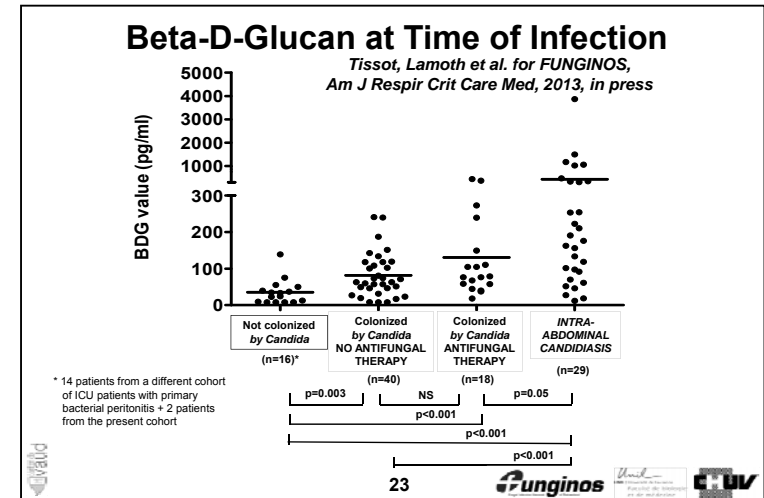
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#### a Prospective Cohort Study of the Fungal Infection Network of Switzerland (FUNGINOS)

*Tissot, Lamoth et al. for FUNGINOS,  
Am J Respir Crit Care Med, 2013, in press*




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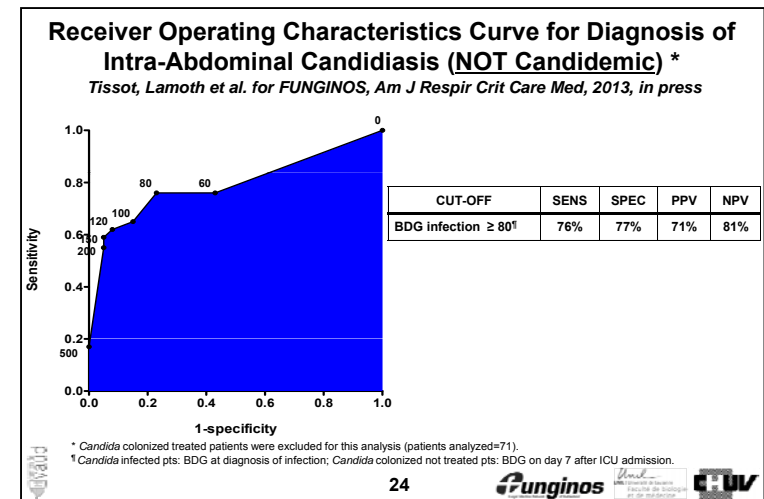
### CLINICAL CHARACTERISTICS (n = 89)

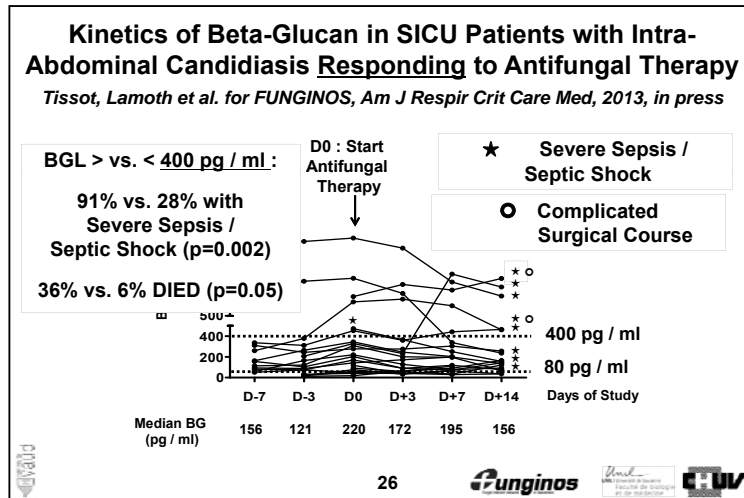
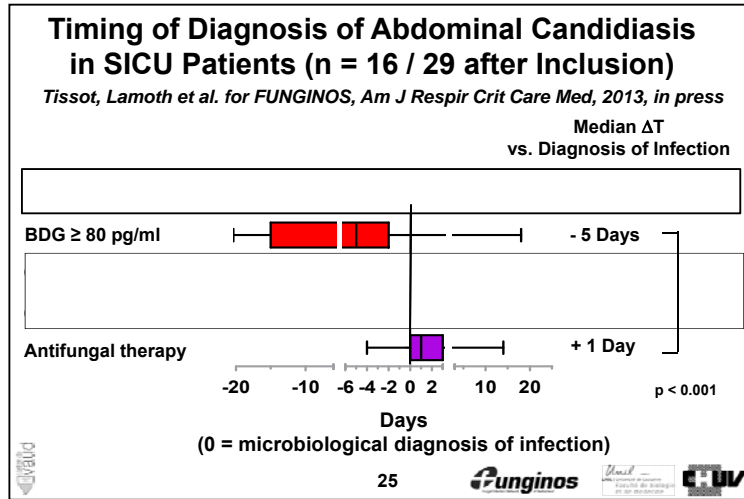
*Tissot, Lamoth et al. for FUNGINOS, Am J Respir Crit Care Med, 2013, in press*

<b>Surgical condition</b>	
Recurrent GI perforation/anastomotic leakage	68 (77%)
Acute necrotizing pancreatitis	21 (23%)
<b>Candida colonization : inclusion / during study</b>	
Colonization index $\geq 0.5$	75 (84%) / 87 (98%)
Corrected colonization index $\geq 0.4$	51 (57%) / 71 (80%)
Candida score $\geq 3$	45 (49%) / 78 (88%)
<b>Intra-abdominal candidiasis (peritonitis)</b>	
With candidemia	29 (33%) 2 (7%)



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## Beta-Glucan in NON-Fungemic Intra-Abdominal Candidiasis

- Differentiates EARLY infection from colonization
- Performs better than (corrected) *Candida* colonization index & *Candida* score
- Values > 400 pg / ml reflect severity of infection and may predict clinical outcome
- In follow-up it remains positive at low levels despite response to antifungal therapy ....

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Funginos

Université de Bourgogne

CHU

## Clinical Case

- 45-year old male patient, pancytopenia : diagnosis of acute myeloblastic leukemia, AML
- Day 1, induction chemotherapy
- Day 5, febrile neutropenia + diarrhea + abdominal pain : piperacillin/tazobactam
- Day 6, call from microbiol. lab: *E. coli* bacteremia, pt. afebrile
- Day 15 (on pip/tazo): relapsing fever + abdominal pain + painful nodular red skin lesions + white retinal lesions + hypotension not responding to volume repletion .... ICU admission during the night ...

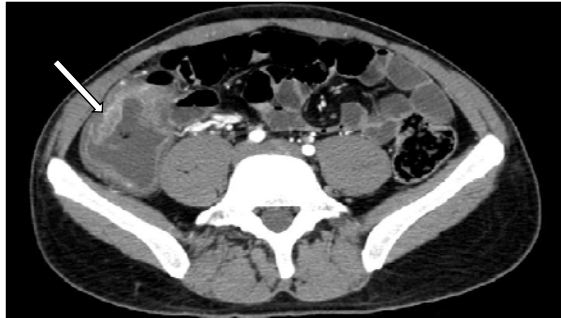
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Funginos

Université de Bourgogne

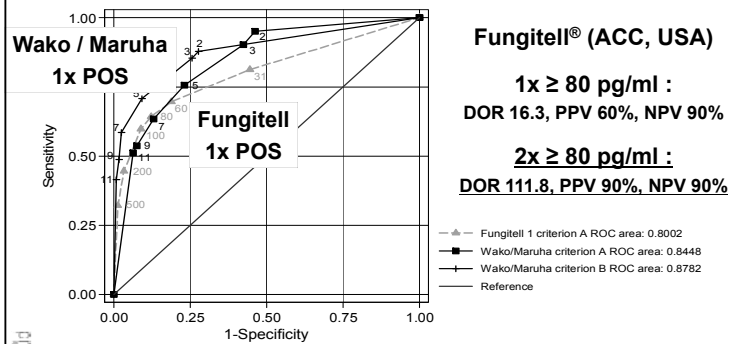
CHU

### NEUTROPENIC ENTEROCOLITIS : ARE FUNGI INVOLVED ?



Courtesy S. Giulieri

### ECIL Meta-Analysis of Beta-Glucan Antigenemia for Diagnosis of IFI in High-Quality Hemato-Oncological Cohort Studies *Lamoth, Cruciani, Mengoli, et al. for ECIL, Clin Infect Dis, 2012 ; 54 (5) : 633 - 43*



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### ECIL Meta-Analysis of Beta-Glucan Antigenemia for Diagnosis of IFI in High-Quality Hemato-Oncological Cohort Studies

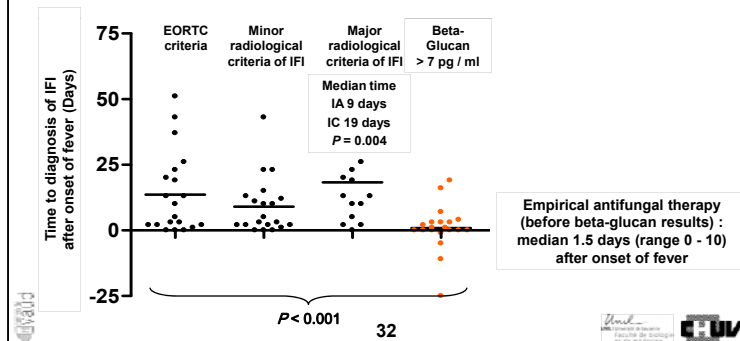
*Lamoth, Cruciani, Mengoli, et al. for ECIL, Clin Infect Dis, 2012 ; 54 (5) : 633 - 43*

Proven + probable invasive candidiasis (IC) /  
Proven + probable invasive aspergillosis (IA)

BG Assay	Cut-off	Sensitivity	Specificity	PPV	NPV	Efficiency
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 - 98 89 - 99
Fungitec - G	20 - 40 pg/ml (1 value)	50 63 - 100	83 76 - 83	21 16 - 19	95 96 - 100	81 75 - 84
Wako / Maruha	7 - 11 pg/ml (2 values)	59 45 - 60	96 96 - 99	67 64 - 83	94 95	91 91 - 95

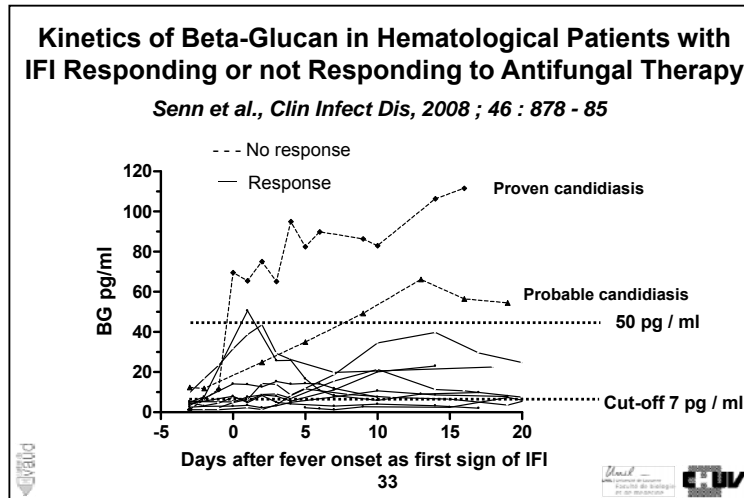
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### Hematological Patients : Time Interval Between Onset of Neutropenic Fever as First Sign of IFI and Diagnosis *Senn et al., Clin Infect Dis, 2008 ; 46 : 878 - 85*



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## Beta-Glucan in Hematological Patients

- Meta-analysis of high-quality cohorts of HEM pts from ECIL-3
  - 2 positive values : higher diagnostic accuracy / PPV / NPV ... BUT, SENSITIVITY 50-80% : needs to be combined with clinical, radiological, and microbiological assessment
- Early diagnosis
- Kinetics reflects severity of infection and response to therapy
- Similar performance of North-American and Japanese beta-D-glucan assays

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## Beta-Glucan in 2013 - I

- ICU PATIENTS : *Candida* >> *Aspergillus*
  - IDSA *Candida* (*CID*, 2009 ; 48 : 503 – 535)  
Empirical antifungal therapy in critically ill pts. at high risk for invasive candidiasis : clinical + cultures + serologic markers, incl. BGL
  - ESCMID *Candida* (*CMI*, 2012 ; 18 (S7) : 9-18 and 19-37)  
Diagnosis of candidemia : II  
Diagnosis of invasive candidiasis : II  
Early fever- or diagnosis-driven treatment of candidemia / invasive candidiasis : CII
  - Recurrent GI perforation / leakage : early detection of non-fungemic intra-abdominal candidiasis (NNT 3)

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## Beta-Glucan in 2013 - II

- HEMATOLOGICAL PATIENTS : *Aspergillus* + *Candida*
  - EORTC – MSG Diagnosis (*CID*, 2008 ; 46 : 1813 - 21) Microbiological criterion for probable diagnosis
  - IDSA Febrile Neutropenia (*CID*, 2011 ; 52 : 56 - 93)  
NOT mentioned in pre-emptive approach
  - ECIL Diagnosis (*BMT*, 2012 ; 47 : 846 - 54)  
Monitoring in acute leukemia / allo-HSCT : BII
  - ESCMID *Candida* (*CMI*, 2012 ; 18 (S7) : 9 - 18 and 53 - 67) Diagnosis of chronic disseminated candidiasis : II  
NO recommendation for therapy of invasive candidiasis
  - Ready for prime-time in pre-emptive antifungal therapy ?

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