Fungal Biomarkers

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« Meet-The-Expert Session 10 »
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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 ?

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

Possible Invasive Aspergillosis:
WHAT ELSE?

Candida
Aspergillus

Courtesy S. Giulieri
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?

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

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
10/18/2013

**ROC CURVES**

- **BGL ≥ 80 pg / ml**
  - AUC 0.98 (95%CI 0.92 - 1.00)
  - Sens. 92.9% / Spec. 93.7%
  - PPV 72.2% / NPV 98.7%

- **Candida Score ≥ 3**
  - AUC 0.80 (95%CI 0.69 - 0.92)

- **Colonization Index ≥ 0.5**
  - AUC 0.63 (95%CI 0.57 - 0.79)

Positive BGL results
1 - 3 days before positive blood cultures

**Beta-Glucan in Candidemia**

- Single BGL ≥ 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)

**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: 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

<table>
<thead>
<tr>
<th>Surgical condition</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent GI perforation/anastomotic leakage</td>
<td>68</td>
<td>77%</td>
</tr>
<tr>
<td>Acute necrotizing pancreatitis</td>
<td>21</td>
<td>23%</td>
</tr>
</tbody>
</table>

| Candida colonization : inclusion / during study    |     |     |
| Colonization index ≥ 0.5                          | 75  | 84% |
| Corrected colonization index ≥ 0.4                | 51  | 57% |
| Candida score ≥ 3                                 | 34  | 38% |

| Intra-abdominal candidiasis (peritonitis)         |     |     |
| With candidemia                                   | 29  | 33% |

CLINICAL CHARACTERISTICS (n = 89)  
Tissot, Lamoth et al. for FUNGINOS, Am J Respir Crit Care Med, 2013, in press

**Beta-D-Glucan at Time of Infection**  
Tissot, Lamoth et al. for FUNGINOS, Am J Respir Crit Care Med, 2013, in press

Receiver Operating Characteristics Curve for Diagnosis of Intra-Abdominal Candidiasis (NOT Candidemic)  
Tissot, Lamoth et al. for FUNGINOS, Am J Respir Crit Care Med, 2013, in press

### Receiver Operating Characteristics Curve

**Legend**
- **Sensitivity**  
- **Specificity**  
- **PPV** (Positive Predictive Value)  
- **NPV** (Negative Predictive Value)

**Figure Notes:**
- *14 patients from a different cohort of ICU patients with primary bacterial peritonitis + 2 patients from the present cohort.*
- *Candida colonized treated patients were excluded for this analysis (patients analyzed=71).*
- *Candida infected pts: BDG at diagnosis of infection. Candida colonized but treated pts: BDG on day 7 after ICU admission.*
**Timing of Diagnosis of Abdominal Candidiasis in SICU Patients (n = 16 / 29 after Inclusion)**

- BDG ≥ 80 pg/ml: - 5 Days
- Antifungal therapy: + 1 Day

**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....

**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....
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

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 90 – 100 96 – 99 89 – 98 89 – 99
Fungitell - G 20 - 40 pg/ml (1 value) 50 63 – 100 16 – 19 95 81 75 – 84
Wako / Maruha 7 - 11 pg/ml (2 values) 59 45 – 60 96 94 91 91 – 95

Fungitell® (ACC, USA)
1x ≥ 80 pg/ml :
DOR 16.3, PPV 60%, NPV 90%
2x ≥ 80 pg/ml :
DOR 111.8, PPV 90%, NPV 90%

Wako / Maruha
1x POS
Fungitell
1x POS

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

Empirical antifungal therapy (before beta-glucan results) : median 1.5 days (range 0 - 10) after onset of fever
**Kinetics of Beta-Glucan in Hematological Patients with IFI Responding or not Responding to Antifungal Therapy**

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

![Graph showing kinetics of beta-glucan](image1)

**Beta-Glucan in 2013 - I**

- **ICU PATIENTS**: *Candida >> Aspergillus*
    - 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: CI
  - Recurrent GI perforation / leakage: early detection of non-fungemic intra-abdominal candidiasis (NNT 3)

**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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