FUNGAL INFECTIONS IN THE ICU PATIENTS
– State of the Art –

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Why is this topic important?

- Increasing problem
- Mortality higher than in bacterial infections
- Early diagnosis is a challenging problem
- New strategies for recognition and treatment
- Good example of a multidisciplinary approach
FUNGAL INFECTIONS IN THE ICU PATIENTS

Topics to be addressed

Epidemiology
Physiopathology
Risk factors
Clinical diagnosis
Laboratory diagnosis
Therapeutic approaches
<table>
<thead>
<tr>
<th>Organisms addressed</th>
<th>Organisms not addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Candida</em></td>
<td><em>Cryptococcus</em></td>
</tr>
<tr>
<td><em>Aspergillus</em></td>
<td>other yeasts</td>
</tr>
<tr>
<td><em>Mucorales</em></td>
<td>other mould</td>
</tr>
<tr>
<td></td>
<td>dimorphic fungi</td>
</tr>
</tbody>
</table>
Epidemiology

General trends

Fungal Infections in the ICU Patients

Epidemiology

Invasive candidiasis – Candidemia

0.2 - 3 / 1000 hospital admissions
2 - 12 / 1000 ICU patients

DK 2003-4  0.49 / 1000 discharges  (Arendrup 2005)
SE 1998-9  0.32 / 1000 admissions  (Klingspor 2004)
NO 1993-6  0.29 / 10'000 pt days   (Sandven 1998)
CH 1991-2000  0.49 / 10'000 pt days (Marchetti 2004)
EU 1997-9  0.2-0.38 / 1000 admissions (Tortorano 2004)
FUNGAL INFECTIONS IN THE ICU PATIENTS

**Epidemiology**

1'417 ICUs in 17 European countries (EPIC Study 1992)

<table>
<thead>
<tr>
<th></th>
<th>Total (%)</th>
<th>BSI</th>
<th>wound (%)</th>
<th>UTI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. aureus</em></td>
<td>30.0</td>
<td>21.9</td>
<td>26.5</td>
<td>6.0</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>28.7</td>
<td>9.7</td>
<td>21.2</td>
<td>18.7</td>
</tr>
<tr>
<td>CN Staph.</td>
<td>19.1</td>
<td>44.9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Yeasts</td>
<td>17.1</td>
<td>9.3</td>
<td>8.3</td>
<td>21.2</td>
</tr>
<tr>
<td>Enterococci</td>
<td>11.7</td>
<td>10.9</td>
<td>18.2</td>
<td>14.8</td>
</tr>
</tbody>
</table>

Vincent J.L. et al. (EPIC), *JAMA* 1995; 274: 639-44.
Fungal Infections in the ICU Patients

Epidemiology – Contribution of ICUs

Marchetti O., Bille J. et al., *Clinical Infectious Diseases* 2004; 38: 311.
Physiopathology

Risk factors for invasive candidiasis

OR (multivariable analyses)

- Colonisation
- Antibiotics
- Vascular access
- Bladder catheter
- Neutropenia
- TPN
- Surgery
- AF prophylaxis
- Renal failure
- Disease severity

## Risk factors

<table>
<thead>
<tr>
<th>Colonisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spread from abdominal cavity to other body sites</td>
</tr>
<tr>
<td>Heavy or increased growth from peritoneal cavity</td>
</tr>
<tr>
<td>High amounts in stool</td>
</tr>
<tr>
<td>Multiple site colonization</td>
</tr>
<tr>
<td>Patient specific strain carriage</td>
</tr>
</tbody>
</table>

Colonisation rate at entry 5-15%  
During prolonged ICU stay 50-85%
**Risk factors**  
*Candida* colonisation

Colonisation index: ratio of the nb of body sites colonised to the total nb of body sites cultured

Clinical Diagnosis

Problematic

Clinical presentation variable and non specific
fever 80%
leukocytosis 50%
chorioretinitis 25%
endophtalmitis 10-20%
skin lesions
muscle abscesses
septic arthritis
high grade candiduria in non catheterized patients
signs of multi-organ failure
Fungal Infections In The ICU Patients

Skin – Candidemia
FUNGAL INFECTIONS IN THE ICU PATIENTS

Candida – Retinitis

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Laboratory diagnosis

 Cannabis – Conventional methods

• Culture blood
  other sterile body sites
  urines
  other sites (dd colonisation-infection)

⁻ insensitive slow

⊕ identification to species level
  antifungal susceptibility testing

• Histology biopsies (liver, skin)
FUNGAL INFECTIONS IN THE ICU PATIENTS
Fungal Infections in the ICU Patients

Laboratory diagnosis

*Candida* – indirect tests

- antigen-antibodies
- fungal DNA detection

Mostly evaluated in onco-hematology patients

Very few studies in ICU patients

Very few commercially available tests
FUNGAL INFECTIONS IN THE ICU PATIENTS

Diagnosis of invasive Candida infections

Antigen based tests

Detection limit

Mannan 0.1 \( \mu \text{g/mL} \) specific to *Candida* spp

\( \beta \)-1-3 D glucan 0.1 pg/mL non specific to *Candida* spp
FUNGAL INFECTIONS IN THE ICU PATIENTS

Diagnosis of invasive Candida infections
Mannan (+ antimannan)

Frequency of testing 2-3 times/week
Ag peak very short


FIG. 4. Examples of kinetic evolution of antigenemia (○) and antimannan antibody response (●) detected by EIA. Patients 39 (a) and 43 (b) had systemic candidiasis. The arrow marks the date of mycological isolation of *C. albicans* from blood and a drain. The curves are drawn by using the interpolate regression.
FUNGAL INFECTIONS IN THE ICU PATIENTS

Diagnosis of invasive Candida infections

Mannan (+ antimannan)

Sensitivity factors

main variables:

- type of disease candidemia in:
  - oncohematology
  - ICU patients
  hepatosplenic candidiasis

- species of Candida
- stage of the disease (antibodies)
- frequency of testing (per test or per episode evaluation)
**Fungal Infections in the ICU Patients**

Mannan – antimannan
Kinetics according to the type of patients

<table>
<thead>
<tr>
<th></th>
<th>n=</th>
<th>+ test before BC</th>
<th>ag</th>
<th>ab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemato-oncol.</td>
<td>11</td>
<td>100%</td>
<td>82%</td>
<td>36%</td>
</tr>
<tr>
<td>ICU pts</td>
<td>15</td>
<td></td>
<td>40%</td>
<td>33%</td>
</tr>
<tr>
<td>Surgical pts</td>
<td>17</td>
<td></td>
<td>47%</td>
<td>65%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>73%</td>
<td></td>
</tr>
</tbody>
</table>

FUNGAL INFECTIONS IN THE ICU PATIENTS

Mannan – antimannan Kinetics

45 patients with positive blood culture

Mannan – antimannan
Sensitivity according to species

<table>
<thead>
<tr>
<th>Species</th>
<th>n</th>
<th>+ test before</th>
<th>+BC</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>23</td>
<td>74%</td>
<td>17/23</td>
<td></td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>9</td>
<td>100%</td>
<td>9/9</td>
<td></td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>5</td>
<td>60%</td>
<td>3/5</td>
<td></td>
</tr>
<tr>
<td>C. glabrata</td>
<td>4</td>
<td>50%</td>
<td>2/4</td>
<td></td>
</tr>
<tr>
<td>C. krusei</td>
<td>4</td>
<td>50%</td>
<td>2/4</td>
<td></td>
</tr>
</tbody>
</table>

Mannan screening in ICU patients

Prospective study of 105 ICU patients (>7 days in ICU)
Screening 1x/week

IC  n=10  (2 proven, 3 probable)
Colonization rate :  70%
Mannan positive in 60% pt with IC
  43% pt colonized
  25% pt without colonization

20% of false positive results!

**Laboratory diagnosis** – Candida
Detection of mannan and antimannan in hepatosplenic candidiasis

UPDATE ON DIAGNOSIS OF INVASIVE CANDIDA INFECTIONS

Multicenter Clinical Evaluation of $\beta$-D-glucan Assay

163 patients with IFI, 170 without - 1 sample taken within 72 hours after diagnosis

107 patients with proven candidiasis

- sensitivity: 81.3%

All patients

- sensitivity: 70%
- specificity: 87%
- PPV: 83.8%
- NPV: 75.1%

Ostrosky-Zeichner et al., Clinical Infectious Diseases 2005; 41: 654.
**β-D-glucan for diagnosis of IFI in patients with acute infections**

<table>
<thead>
<tr>
<th>BG assay positive</th>
<th>(Digby 2003)</th>
<th>(Pickering 2005)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFI confirmed</td>
<td>96% (25/26)</td>
<td>87% (13/15)</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>73% (8/11)</td>
<td>56% (14/25)</td>
</tr>
<tr>
<td>No infection</td>
<td>22% (2/9)</td>
<td></td>
</tr>
</tbody>
</table>

Low positive predictive value
High negative predictive value ($\geq 95\%$)

Molecular based tests

**DNA detection (PCR)**

- Single species/genus versus panfungal
- High sensitivity (1-10 fg of DNA)
- Applied to various body fluids: blood, serum, CSF, BAL

Quantification possible (response to antifungal therapy, differentiation colonization-infection)

No standardized (commercial) assay
→ no prospective multicenter large studies
### UPDATE ON DIAGNOSIS OF INVASIVE CANDIDA INFECTIONS

#### Nucleic acid detection in patients with Candida fungemia and/or invasive candidiasis (IC)

<table>
<thead>
<tr>
<th>Patients (%) with positive NA test</th>
<th>Controls (%) with positive NA test</th>
<th>Sample</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/14 (79%) 0/29 (0%) serum</td>
<td>Kan JID <strong>168</strong>: 779, 1993</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15/16 (93%) 0/34 (0%) blood</td>
<td>Jordan JCM <strong>32</strong>: 2962, 1994</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16/18 (89%) 0/6 (0%) serum</td>
<td>Chryssanthou Scand JID <strong>26</strong>: 479, 1994</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28/28 (100%) 3/31 (10%) serum</td>
<td>Burnie EJCMID <strong>16</strong>: 346, 1997</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8/8 (100%) 3/100 (3%) blood</td>
<td>Einsele JCM <strong>35</strong>: 1353, 1997</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13/14 (93%) 18/58 (31%) blood</td>
<td>Morace JCM <strong>37</strong>: 1871, 1999</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28/30 (95%) (3%) blood</td>
<td>White JCM <strong>43</strong>: 2181, 2005</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>