Empiric Therapy for Suspected Fungal Sepsis

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Objectives

- Describe the importance of fungal sepsis in the ICU.
- Discuss prediction rules for the diagnosis of suspected fungal sepsis in the ICU.
- Outline treatment strategies for fungal sepsis in the ICU.
Epidemiology: Fungal Sepsis in the ICU
Distribution of Fungal Pathogens in 2 Canadian Centres
(PATH Alliance Data N=347)

- Candida: 85.0%
- Aspergillus: 14.4%
- Cryptococcus: 3.0%
- Mucorales: 6.0%
- Other fungi: 9.0%
- Other mold: 5.2%

Haider S, et al. CJIDMM 2014;25:17-23
### Point Prevalence Nosocomial Infections USA 2015

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Bloodstream Infection (N = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>12 (23)</td>
</tr>
<tr>
<td>Candida species</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Enterococcus species</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Coagulase-negative staphylococcus</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Streptococcus species</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>4 (8)</td>
</tr>
</tbody>
</table>

- 12,299 pt. in 199 hospitals surveyed for nosocomial infections; 16.8% ICU pt.
- Survey date selected between May 1 to Sept. 30, 2015.

Magill SS, et al. NEJM 2018;379:1732-1744
ICU Infections: SOAP study in Europe 5/1-15/2002

198 ICUs, 3,147 patients, 37% infected

Point Prevalence Study in ICUs in Canada (N=357 pt.)

- 10/6/2004 in ICUs across Canada point prevalence study done - 357 pt. assessed.
- 2 pt. positive blood cultures for Candida (2/357, 0.56%).
- No data to assess invasive candidiasis.
Economic Impact of *Candida* Colonization & *Candida* Infection in ICU Patients (Europe)


- *Candida* infected patients had prolonged LOS in ICU of 12.7 d (p<.0001).

- *Candida* colonization produced increased costs of 8,126€ & *Candida* infection 15,803€.

Risk Factors for Candidiasis

- BS Antibiotics
- Neutropenia
- TPN
- CV Lines
- Steroids
- High Apache Score
- Multiple Sites Colonized
- LOS in ICU
- Invasive Candidiasis

References:
Pathogenesis of Invasive Candidiasis

A. IV Catheter Related

- Skin
- Bloodstream

B. GI Tract Related

- GI tract
- Insult
- Antibiotics
- Normal commensal flora
- Candida species
- Selection
- Infection
- Translocation
- Disease

Skin

Bloodstream

GI tract

Insult

Antibiotics

Normal commensal flora

Candida species

Selection

Infection

Translocation

Disease
Fungal Sepsis in the ICU
How do we diagnose it?

- **Candidemia** - blood cultures.

- **Invasive candidiasis** - culture from sterile site.

- **Surrogate markers** (β-D-glucan) suboptimal predictive value (lack sensitivity & specificity).

- Rely on constellation of risk factors, signs and cultures.
Prediction Rule for Identifying Surgical ICU Patients at Risk for IC

- 221 Surgical ICU pt. with peritonitis
- Independent risk factors were:
  - Female gender
  - Upper GI origin of peritonitis
  - Intra-operative cardiovascular failure
  - Antimicrobial therapy for ≥ 48 hours before onset of peritonitis
- Presence of ≥ 3 factors associated with high rate of detecting yeasts in peritoneal fluid (sensitivity 84%, specificity 50%).

Dupont H et al. Crit Care Med 2003;31:752-757
Prediction Rule for Identifying ICU Patients at Risk for IC

- ICU LOS > 4 d
  - And
- Any systemic antibiotic (days 1-3)
  - Or
- CVC (days 1-3)
  - And
- At least 2 of:
  - TPN (days 1-3)
  - Any dialysis (days 1-3)
  - Major surgery (days -7-0)
  - Pancreatitis (days -7-0)
  - Any use of steroids (days -7-3)
  - Immunosuppressive agents (days -7-0)

- Incidence of IC 3% in 2,890 Med-Surg ICU patients.
- Captured 34% of IC cases.

Multivariate analysis showed that the following factors significant for proven IC (p<.001):
- Surgery on ICU admission
- Total parenteral nutrition
- Severe sepsis
- Candida spp. colonization

Clinical Score for Diagnosing IC (cont’d)

- Candida score derived:
  
<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>severe sepsis</td>
<td>2.038</td>
</tr>
<tr>
<td>multifocal Candida colonization</td>
<td>1.112</td>
</tr>
<tr>
<td>surgery on ICU admission</td>
<td>.997</td>
</tr>
<tr>
<td>TPN</td>
<td>.908</td>
</tr>
</tbody>
</table>

- Cut off value of 2.5; sensitivity 81%, specificity 74%.

- Scores >2.5, 7.75X more likely to have proven infection.

Candida Score to Discriminate Between Candida Colonization & IC

- 1107 non-neutropenic adult pt. in 36 ICUs for >7 days in Spain, Argentina & France.
- Beta glucan [Fungitell] (≥75 pg/mL) done once weekly.
- Candida score calculated:
  - Surgery 1
  - Multifocal colonization 1
  - TPN 1
  - Severe sepsis 2
- 5.2% (58/1107) developed IC.
- Of colonized pt. or those with IC: 13.8% developed IC if CS ≥3 vs. 2.3% if CS <3.
- Beta glucan sensitivity 77.8% & specificity 53% for IC.

Empiric Antifungal Therapy for Suspected Fungal Sepsis
Empiric Fluconazole vs. Placebo for ICU Patients

- 1-2% of all ICU pt. develop IC during their ICU stay.
- RCT double blind placebo controlled vs. Fluconazole 800 mg IV daily for 2 weeks.
- Entry criteria: ICU stay ≥96 hr., APACHE II score>16, 4 days of fever (≥38.3C), BSA for 4 of 6 days prior to entry and presence of CVC.
- Success (composite 1st endpoint) = no fever (>38C) for 72 hours, no emergent IFI (blood or sterile site for Candida), no discontinuation of study drug due to toxicity and no use of alternative antifungal agent.
- Secondary endpoints: 30 d mortality & time to ICU discharge.

Outcomes During the Primary Observation Period

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Fluconazole Recipients (n = 122), n (%)</th>
<th>Placebo Recipients (n = 127), n (%)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Success</td>
<td>44 (36)</td>
<td>48 (38)</td>
<td>0.95 (0.69 – 1.32)</td>
<td>0.78</td>
</tr>
<tr>
<td>Failure</td>
<td>78 (64)</td>
<td>79 (62)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Reasons for Failure at the End of the Primary Observation Period

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fluconazole Recipients (n = 122), n (%)</th>
<th>Placebo Recipients (n = 127), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Failures</td>
<td>67 (55)</td>
<td>73 (57)</td>
</tr>
<tr>
<td>No resolution of fever</td>
<td>62 (51)</td>
<td>68 (54)</td>
</tr>
<tr>
<td>Documented invasive fungal infection</td>
<td>6 (5)</td>
<td>11 (9)</td>
</tr>
<tr>
<td>Need for alternative antifungal agent</td>
<td>12 (10)</td>
<td>20 (16)</td>
</tr>
</tbody>
</table>

Prevention of Fungal Sepsis in ICU
Caspofungin Prophylaxis in ICU

- RCT, double blind & placebo controlled: caspofungin 50 mg IV daily (up to 28 d) vs. placebo as prophylaxis for pt. in ICU ≥72 hr.
- Pt. in ICU satisfying Ostrosky-Zeichner prediction rule.
- Endpoint – proven or probable IC.

Table 1. Definitions of Proven and Probable Invasive Candidiasis

<table>
<thead>
<tr>
<th>Definition</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven invasive candidiasis</td>
<td>Blood culture that yields Candida spp OR histopathologic or cytopathologic examination of a needle aspiration or biopsy specimen from a normally sterile site excluding mucous membranes showing yeast cells OR recovery of a yeast by culture from a sample obtained by a sterile procedure (including a freshly [&lt;24 h] placed drain) from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process.</td>
</tr>
</tbody>
</table>
| Probable invasive candidiasis    | Serum BG levels >80 pg/mL in 2 consecutive samples AND 1 of the following:  
  1. Temperature >38°C or <36°C.  
  2. Hypotension defined as systolic BP <90 mm Hg or a significant drop (40 mm Hg) in BP from baseline.  
  3. WBC count >12 000 cells/μL. |

Ostrosky-Zeichner L, et al. CID 2014;58:1219-1226
### Caspofungin Prophylaxis in ICU: Study Endpoints and Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Caspofungin (n = 102)</th>
<th>Placebo (n = 84)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of proven or probable IC by DRC, %</td>
<td>9.8</td>
<td>16.7</td>
<td>0.14</td>
</tr>
<tr>
<td>Incidence of proven IC by DRC, %</td>
<td>1.0</td>
<td>4.8</td>
<td>0.11</td>
</tr>
<tr>
<td>Use of antifungals within 7 d EOT, %</td>
<td>13.7</td>
<td>17.9</td>
<td>0.35</td>
</tr>
<tr>
<td>All-cause mortality within 7 d EOT, %</td>
<td>16.7</td>
<td>14.3</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Preemptive Antifungal Therapy for Intraabdominal (AI) Sepsis in ICU

- RCT (double blind) – 241 pt. with AI requiring surgery and ICU stay (both CA & HA).
- Excluded pt. with antifungal therapy within 14 d of study.
- Treatment: placebo or micafungin 100 mg IV for 6 weeks.
- Biomarkers performed: β-D-glucan, Candida antibody & mannan antigen

Biomarkers: only β-D-glucan was related to a response to therapy.

Preemptive Antifungal Therapy for Intraabdominal (AI) Sepsis in ICU


<table>
<thead>
<tr>
<th>No. Infections/No. Patients</th>
<th>Difference (Micafungin–Placebo), % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Incidence, %)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>Micafungin (100 mg/d)</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
</tr>
<tr>
<td>20/120 (16.7)</td>
<td>17/115 (14.8)</td>
</tr>
<tr>
<td>NAI patients</td>
<td></td>
</tr>
<tr>
<td>18/77 (23.4)</td>
<td>14/74 (18.9)</td>
</tr>
<tr>
<td>Patients aged &gt;65 years</td>
<td></td>
</tr>
<tr>
<td>10/60 (16.7)</td>
<td>8/51 (15.7)</td>
</tr>
<tr>
<td>NAI patients aged &gt;65 years</td>
<td></td>
</tr>
<tr>
<td>9/39 (23.1)</td>
<td>6/31 (19.4)</td>
</tr>
<tr>
<td>NAI patients with infection day 8–21</td>
<td></td>
</tr>
<tr>
<td>6/77 (7.8)</td>
<td>1/74 (1.4)</td>
</tr>
<tr>
<td>NAI patients aged &gt;65 years with infection day 8–21</td>
<td></td>
</tr>
<tr>
<td>4/39 (10.3)</td>
<td>0/31 (0)</td>
</tr>
</tbody>
</table>
Treatment:
Empiric, Prophylaxis, Preemptive
<table>
<thead>
<tr>
<th>Therapeutic strategy</th>
<th>Antifungal therapeutic options</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preferred</td>
</tr>
<tr>
<td></td>
<td>Alternative</td>
</tr>
<tr>
<td><strong>Prophylaxis in ICU:</strong></td>
<td></td>
</tr>
<tr>
<td>Non-neutropenic</td>
<td>IV fluconazole 800 mg → 400 mg IV (Weak – moderate)</td>
</tr>
<tr>
<td></td>
<td>IV ECH (anidulafungin, caspofungin or micafungin) (Weak – low)</td>
</tr>
<tr>
<td><strong>Empirical therapy in ICU patients based on fever, risk factors &amp; markers:</strong></td>
<td></td>
</tr>
<tr>
<td>Non-neutropenic</td>
<td>IV ECH (IV anidulafungin 200 mg → 100 mg daily; or IV caspofungin 70 mg → 50 mg daily; or IV micafungin 100 mg daily) (Strong – moderate) Duration: 2 weeks (Weak- low)</td>
</tr>
<tr>
<td></td>
<td>IV fluconazole 800 mg → 400 mg IV; no recent azole exposure &amp; no azole resistant colonization (Strong – moderate)</td>
</tr>
</tbody>
</table>

Summary of Key Points for Treatment of C/IC

- Prediction rules helpful in diagnosis of IC in the ICU.
- Surrogate markers not overly helpful.
- Echinocandins preferred for initial therapy of C/IC in ICU non-neutropenic pt.
- Fluconazole alternative (beware of prior azole exposure past 30 d & azole resistant Candida colonization).
- Empiric therapy is recommended.
- Prophylaxis received weaker recommendation but is reasonable in certain circumstances (SOT - Liver).
- Preemptive therapy not recommended.