Practical Management of Invasive Fungal Infections in Critically Ill Patients

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Faculty disclosure (2012-14)

- Pfizer Asian Pacific, USA, Australia
- Astellas UK, Asia
- Bayer Europe
- MERCK USA,
- MSD Europe
- Baxter France
- Clinigen UK
- EU-FP7 Project
- Cardeas USA
Invasive Fungal Infections

- *Candida* spp: 70% to 90% of all invasive mycoses
- In patients with BSIs, *Candida* spp are
  - the 4th commonly isolated pathogen in USA
  - the 7th in Europe
- In ICU patients *Candida* spp
  - is the 3rd cause of nosocomial BSIs
- Candidemia is associated with
  - high crude and attributable mortality rates
  - increased costs
  - prolonged hospitalization

Factors leading to *Candida spp* infections in ICU patients

- Prolonged ICU stay
- Treatment with corticosteroids
- Diabetes mellitus
- Advanced age
- Central venous catheter (CVC)
- Gastrointestinal surgery
- Total parenteral nutrition (TPN)
- Prolonged antimicrobial use
- Pancreatitis
- Immunosuppressive agents
- Chemotherapy
- APACHE II >20
- Neutropenia
- Renal replacement therapy
- Malnutrition
- Multiple site colonisation
- Burns over 50% of body sites
- Major trauma

APACHE II, Acute Physiology and Chronic Health Evaluation II

Adhesion

Colonization

Immunosuppression
Prematurity/bruns
Neutropenia/ileus

Invasion

Eggimann & Pittet Lancet Infectious Diseases 2003

Candidemia
5-10/10'000 admissions (10% of + blood cultures)

Dissemination (eye, kidney, liver, CNS,...)

Mechanisms of Candida infections development
1. **C. albicans**
   - polymorphic fungus
   - yeast, hyphae, pseudohyphae
   - critical for virulence and response to environmental changes

2. **This switch depends on**
   - temperature and pH alterations
   - CO₂ concentration
   - mammalian serum

3. **Densities <10⁶ cells/mm³**
   - *C. albicans* cells develop into filamentous forms

4. **Higher densities**
   - grow as budding yeasts

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Epifluorescence photocomposition stained with calcofluor white

Candidaemia
Underlying pathology / medical care

Patients with candidaemia (n=2089)

Pathology / medical care

Surgery: 48.2%
Intensive care: 40.2%
Solid tumour: 22.5%
Steroids: 17.4%
Haematological malignancy: 12.3%

APACHE II score and risk of death in candidaemia

Mortality at 3 months (%)

- C. tropicalis (n=159)
- C. albicans (n=551)
- C. glabrata (n=268)
- C. parapsilosis (n=147)

APACHE II score

## Candida non-albicans

### The different face

| **C. glabrata** | Elderly pts, malignancies, geographical variation  
Specific antibiotics (piperacillin / tazobactam, vancomycin)  
TPN, CVC, isolation system, solid organ transplantation  
Fluconazole exposure |
|-----------------|------------------------------------------------------|
| **C. parapsilosis** | Nosocomial outbreaks - formation of biofilms on CVC  
Implanted devices - TPN  
Second most commonly isolated strain in children  
Less susceptible to echinocandins *in vitro* |
| **C. tropicalis** | Haematological malignancies  
Neutropenia |
| **C. krusei** | Specific antibiotics (piperacillin / tazobactam, vancomycin)  
Haematological malignancies - neutropenia  
Recent gastrointestinal surgery  
Fluconazole exposure  
Innate resistance to fluconazole |
| **C. guilliermondii** | Intravascular catheters  
Less susceptible to echinocandins *in vitro*  
Less susceptible to fluconazole *in vitro* |
Candida albicans vs non-albicans

4 geographically diverse intensive care units

% albicans and non-albicans candidemia over study period

% albicans and non-albicans candidemia by country

Mortality associated with *Candida spp* infections by species

<table>
<thead>
<tr>
<th></th>
<th>CAC (n=36)</th>
<th>NAC (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment response rate</td>
<td>80.6%</td>
<td>45%</td>
<td>0.006</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>52.8%</td>
<td>90%</td>
<td>0.005</td>
</tr>
</tbody>
</table>

- **CAC**: *Candida albicans* candidaemia, **NAC**: non-*albicans* candidaemia

Importance of early treatment

157 patients (2001–2004)
Antifungal therapy <12 to >48 h after culture sample
Independent determinants of hospital mortality:
- APACHE II score (Δ one point) (p<0.001)
- Antifungal therapy >12 h after 1st positive blood culture (AOR, 2.09; p=0.018)

Initiation of fluconazole 0 to >3 days
Independent determinants of mortality:

- APACHE II score (Δ one point; p<0.001)
- Time to fluconazole (AOR, 1.50; p=0.0138)

Effective antimicrobial therapy after onset of septic shock
Hospital mortality:

- Delay (per hour) OR 1.119 (1.103–1.136) (p=0.0001)
Kumar A et al, Crit Care Med 2006;34:1589–96
Importance of early treatment

224 consecutive patients with septic shock and a positive blood culture for *Candida* species were identified

Importance of adequate treatment

Appropriately treated *C. albicans* candidaemia
Inappropriately treated *C. albicans* candidaemia
Overall (shock population)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Appropriate</th>
<th>Inappropriate</th>
<th>Survival (%)</th>
<th>n</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td></td>
<td></td>
<td></td>
<td>597</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>20</td>
<td>284</td>
<td></td>
<td></td>
<td>0.0101</td>
</tr>
<tr>
<td><em>Enterococcus</em> spp</td>
<td>10</td>
<td>181</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other <em>Streptococcus</em> spp</td>
<td>100</td>
<td>268</td>
<td></td>
<td></td>
<td>0.0005</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>100</td>
<td>869</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><em>Klebsiella</em> spp</td>
<td>100</td>
<td>312</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><em>Enterobacter</em> spp</td>
<td>100</td>
<td>148</td>
<td></td>
<td></td>
<td>0.0002</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>100</td>
<td>295</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><em>C. albicans</em></td>
<td>100</td>
<td>290</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-albicans yeast</td>
<td>100</td>
<td>153</td>
<td></td>
<td></td>
<td>0.0002</td>
</tr>
</tbody>
</table>
Importance of early treatment & source control

224 consecutive patients with septic shock and a positive blood culture for *Candida* species were identified.

## Importance of adequate treatment & source control

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Chi-square</th>
<th>OR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II score (1-point increments)</td>
<td>12.79</td>
<td>0.93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adequate antifungal therapy</td>
<td>3.9</td>
<td>5.99</td>
<td>0.048</td>
</tr>
<tr>
<td>Source control</td>
<td>10.38</td>
<td>2.99</td>
<td>0.001</td>
</tr>
</tbody>
</table>

1st message
Invasive fungal infections in the ICU
Early adequate and appropriate treatment
Risk factors (+)  
Biomarkers (−)  
Clinical signs (−)  
Mycology (−)

Risk factors (+)  
Biomarkers (+)  
Clinical signs (−)  
Mycology (−)

Risk factors (+)  
Biomarkers (−)  
Clinical signs (±)  
Mycology (−)

Prophylaxis*  
Fluconazole

Pre-emptive treatment

Empirical treatment

*In specific ICU populations
Fluconazole prophylaxis in the ICU

• Does it work?
  – Yes, absolutely!

• Does it work well enough?
  – Hmm… less than optimal results
  • 9.9% (placebo) vs 3.9% (fluconazole)\(^1\)
  • 15.4% (placebo) vs 8.5% (fluconazole)\(^2\)
  • 7% (no prophylaxis) vs 3.8% (fluconazole prophylaxis)\(^3\)

• Has it been investigated in the ICU?
  – No, in highly selected subgroups of patients only
  – No study ever done in general ICU population

• How can we select the specific patients who would benefit from prophylaxis?

Antifungal prophylaxis

- Surgical ICU
- 260 patients
- Expected ICU stay >3 days

260 patients included (130 received prophylaxis) of 1228 admissions in 1 year

A high-risk subset

Two cases of candidaemia prevented among 1228 patients (0.16%)

<table>
<thead>
<tr>
<th>Infections</th>
<th>Fluconazole</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from all causes</td>
<td>14 (10.8%)</td>
<td>16 (12.3%)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Antifungal prophylaxis in the ICU

• **Meta-analysis**
  - 9 RCTs (1226 adult patients following trauma or surgery)
  - Ketoconazole (3 studies), fluconazole (6 studies) vs placebo (8 studies)
  - Azole prophylaxis (with both azoles) associated with
    -↓ candidaemia (RR 0.30, 95% CI 0.10–0.82)
    -↓ crude mortality (RR 0.60, 95% CI 0.45–0.81)

• **Prophylaxis with nystatin**
  - Prospective, randomised, open-label study
  - 98 patients under MV (51 prophylaxis, 47 controls)
  - Oral nystatin 3x10^6 U per day
  - *Candida* colonisation (25% controls vs 0% with nystatin prophylaxis)
    - Multivariate analysis
    - Independent factors for colonisation: ICU LOS, no nystatin prophylaxis
    - Absence of prophylaxis was a risk factor

CI, confidence interval; LOS, length of stay
MV, mechanical ventilation
RCT, randomised controlled trial; RR, risk ratio

<table>
<thead>
<tr>
<th>Author</th>
<th>Criteria</th>
<th>Factors and prediction rule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leon</td>
<td>Non-neutropenic critically ill patients in medical/surgical ICUs</td>
<td>“Candida score” ≥3  early antifungal treatment Multifocal colonisation, surgery on ICU admission, severe sepsis, TPN</td>
</tr>
<tr>
<td>Agvald-Öhman</td>
<td>Patients at risk of IC among those with a length of ICU stay of at least 7 days</td>
<td>Candida Colonisation Index (CCI) ≥0.8 and recent extensive gastroabdominal surgery</td>
</tr>
<tr>
<td>Pittet</td>
<td>Patients in surgical and neonatal ICUs at increased risk</td>
<td>Patients with CCI ≥0.4 at high risk</td>
</tr>
<tr>
<td>Dupont</td>
<td>Patients with severe peritonitis</td>
<td>At least three of the following factors predicted yeast isolation in the peritoneal fluid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Female sex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cardiovascular failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Upper gastrointestinal tract origin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Recent antimicrobial therapy</td>
</tr>
</tbody>
</table>

IC, invasive candidiasis
## Empirical antifungal treatment (II)

<table>
<thead>
<tr>
<th>Author</th>
<th>Criteria</th>
<th>Factors and prediction rule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ostrosky-Zeichner</strong></td>
<td>Medical–surgical ICUs</td>
<td>Any systemic antibiotic (Days 1–3) OR CVC (Days 1–3) AND at least TWO of: • TPN (Days 1–3) • Dialysis (Days 1–3) • Surgery (Days -7–0) • Pancreatitis (Days -7–0) • Steroid use (Days -7–3) • Immunosuppressive drugs (Days -7–0)</td>
</tr>
<tr>
<td><strong>Hermsen</strong></td>
<td>↑ NPV applies best to identify patients who are LEAST likely to benefit from antifungal therapy</td>
<td>• Current systemic broad-spectrum antibiotic use • CVC, TPN (Days 1–3) • Abdominal surgery (Days -7–3) • Imunosuppressant use (Days -7–0) • Pre-ICU hospital LOS</td>
</tr>
<tr>
<td><strong>Paphitou</strong></td>
<td>Surgical ICUs</td>
<td>• New-onset haemodialysis • TPN • Diabetes mellitus • Broad-spectrum antibiotics</td>
</tr>
<tr>
<td><strong>Ostrosky-Zeichner</strong></td>
<td>ICU</td>
<td>Mechanical ventilation (≥48 h) AND antibacterial use (Days 1–3) AND CVC (Days 1–3) AND at least ONE of: • TPN (Days 1–3) • Dialysis (Days 1–3) • Surgery (Days -7–0) • Pancreatitis (Days -7–0) • Steroid use (Days -7–0) • Immunosuppressive drugs (Days -7–0)</td>
</tr>
</tbody>
</table>

NPV, negative predictive value
"Candida Score" in critically ill patients staying $\geq 7$ days in ICU

- Severe sepsis: 0 or 2
- Multifocal *Candida* colonisation: 0 or 1
- Surgery: 0 or 1
- Total parenteral nutrition: 0 or 1

How to use “Candida Score”

Variables are coded (0) when absent and (1) when present (severe sepsis coded “2” when present).

A “Candida Score” $\geq 3$ selected patients at high risk for invasive candidiasis (IC)

- A linear association between increasing the value of CS and IC rate was observed ($P \leq 0.001$)

2nd message
Prophylaxis in selected populations
Empirical treatment according to risk factors and clinical condition
Pre-emptive: there is a role in the ICU?
How to select the right antifungal agent in the ICU?
1st Question: Should all patients with candidaemia be treated?

- We are unable to identify those patients who may have a transient candidaemia.
- Every positive blood culture with *Candida* species may lead to disseminated disease and requires antifungal therapy.
Clinical studies
Invasive candidiasis / candidaemia

Direct comparisons of efficacy between publications are not possible, due to differences in study design and patient populations.
### 2nd question: What problems we have with azoles?

**Candida spp. resistance to fluconazole**

<table>
<thead>
<tr>
<th>Species</th>
<th>Fluconazole MIC (µg/ml)</th>
<th>Percentage of isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50%</td>
<td>90%</td>
</tr>
<tr>
<td>Candida spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>16</td>
</tr>
<tr>
<td>C. albicans</td>
<td>≤0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>8</td>
<td>64</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>C. krusei</td>
<td>64</td>
<td>128</td>
</tr>
</tbody>
</table>

**Azoles cross-resistance**

**In vitro activity of triazole antifungals against isolates of Candida spp. resistant to fluconazole**

<table>
<thead>
<tr>
<th>Triazole antifungals</th>
<th>N of isolates</th>
<th>Percent by category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>SDD</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>272</td>
<td>46.7</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>396</td>
<td>48.5</td>
</tr>
</tbody>
</table>

S = Susceptible [MIC (Minimum Inhibitory Concentration) ≤1µg/mL], SDD = Susceptible Dose-Dependent [MIC >1 but <2 µg/mL], R = Resistant [MIC ≥2 µg/mL].

Fluconazole PK/PDs
We don’t use the right dose !!!!!!!

24 Hour AUC/MIC

AUC/MIC 25–50

24 Hour AUC/MIC

ED 50
Fluconazole MIC - Dose/MIC

24- hour MICs

48- hour MICs

Dose /MIC > 50  ☝ > 70% efficacy

- DALI study: multicenter point prevalence PK study
- 68 ICUs across Europe
- To describe PK/PDs in critically ill fluconazole (n=15), anidulafungin (n=9) caspofungin (n=7)
- Fluconazole, caspofungin, and anidulafungin showed large interindividual variability

- In patients receiving fluconazole
  - 33% did not attain the PK/PD target, ratio of free drug area under the concentration-time curve from 0 to 24 hours to minimum inhibitory concentration (fAUC0–24/MIC) ≥100.

- The fluconazole doses (mg/kg) were significantly associated with achievement of fAUC0–24/MIC ≥100 (p = 0.0003).
Should we monitor therapeutic drug serum concentration and response?

<table>
<thead>
<tr>
<th>Medication</th>
<th>Serum concentration monitoring recommended</th>
<th>Peak</th>
<th>Trough</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>No</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Flucytosine</td>
<td>Yes</td>
<td>2 h post-dose: 30-80 mg/L for cryptococcal infections; 40-60 mg/L for candidal meningitis</td>
<td>N/A</td>
<td>Toxicity seen with 2 h post-dose concentrations &gt; 100 mg/L</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>No</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Yes</td>
<td>N/A</td>
<td>&gt; 0.5 to 1 mg/L</td>
<td>To ensure adequate absorption</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Yes</td>
<td>&lt; 6 mg/L</td>
<td>&gt; 2 mg/L</td>
<td>To ensure efficacy, limit toxicity</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Yes</td>
<td>&gt; 1.48 mg/L</td>
<td>N/A</td>
<td>Limited data, average concentration of 1.25 mg/L associated with 75% response</td>
</tr>
<tr>
<td>Caspofungin, micafungin and anidulafungin</td>
<td>No</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

Empirical use of fluconazole for suspected candidiasis in the ICU

- Double-blind, placebo-controlled trial
- Fluconazole 800 mg /d (x14 days) - 270 adult ICU patients with:
  - 4 days of fever (>38.3°C)
  - ICU stay >96 hours
  - APACHE II score ≥16
  - Broad-spectrum antibiotics
  - CVC ≥24 hours

<table>
<thead>
<tr>
<th></th>
<th>Fluconazole</th>
<th>Placebo</th>
<th>RR (95% CI); p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (ITT/evaluated)</td>
<td>133/122</td>
<td>137/127</td>
<td></td>
</tr>
<tr>
<td>Success</td>
<td>44 (36%)</td>
<td>48 (38%)</td>
<td>0.95 (0.69–1.32); p=0.78</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>29 (24%)</td>
<td>22 (17%)</td>
<td>1.36 (0.82–2.24); p=0.23</td>
</tr>
</tbody>
</table>

ITT, intention to treat

Empirical use of fluconazole for suspected candidiasis in the ICU

- Endpoint at 4 days after EOT (Day 18) assessed by blinded data review committee:
  - Absence of invasive fungal infection
  - Resolution of fever (<38°C for 72 hours)
  - No other antifungals given
  - No discontinuation due to toxicity

<table>
<thead>
<tr>
<th></th>
<th>Fluconazole</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>122</td>
<td>127</td>
</tr>
<tr>
<td>Total failures</td>
<td>67 (55%)</td>
<td>73 (57%)</td>
</tr>
<tr>
<td>Invasive fungal infection</td>
<td>6 (5%)</td>
<td>11 (9%)</td>
</tr>
<tr>
<td>No resolution of fever</td>
<td>62 (51%)</td>
<td>68 (54%)</td>
</tr>
<tr>
<td>Alternative antifungals</td>
<td>12 (10%)</td>
<td>20 (16%)</td>
</tr>
</tbody>
</table>

EOT, end of treatment

3rd Question: what problems we have with AmB?

- ? Agent of choice for C/IC in ICU patients
- Toxicity – nephrotoxicity
  - infusion-related toxicity
  - hypokalemia
  - hypomagnesemia
  - LFT abnormalities
- Toxicity limits efficacy
- At times lack of efficacy = mortality rates of 40%
- Lipid formulations too costly

CAB = Conventional amphotericin B
* P ≤ 0.001 (liposomal ampho B vs. CAB)

Lipo Amphi-B Vs CAB (toxicity)

2 × baseline serum creatinine

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>With concomitant nephrotoxic drugs</th>
<th>Without concomitant nephrotoxic drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAB 1 mg/kg/day</td>
<td>24</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>AmBisome 1 mg/kg/day</td>
<td>26</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>AmBisome 3 mg/kg/day</td>
<td>23</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

n = 81, n = 224, n = 305

*P < 0.01 (CAB versus AmBisome combined doses)
CAB = Conventional amphotericin B

# Amphotericin B - PKs

<table>
<thead>
<tr>
<th></th>
<th>L-AmB</th>
<th>ABLC</th>
<th>CAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mol% AmB</td>
<td>10%</td>
<td>50%</td>
<td>34%</td>
</tr>
<tr>
<td>Lipid Configuration</td>
<td>Liposomes (SUV)</td>
<td>Ribbon-like lipids</td>
<td>-</td>
</tr>
<tr>
<td>Diameter (µm)</td>
<td>0.08</td>
<td>1.6-11.0</td>
<td>&lt;0.4</td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>58</td>
<td>1.7</td>
<td>2.9</td>
</tr>
<tr>
<td>AUC (µg/mL.h)</td>
<td>713</td>
<td>14</td>
<td>36</td>
</tr>
<tr>
<td>Vd (L/kg)</td>
<td>0.22</td>
<td>131</td>
<td>1.1</td>
</tr>
<tr>
<td>Cl (L/h/kg)</td>
<td>0.017</td>
<td>0.476</td>
<td>0.028</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Infusion toxicity</td>
<td>Mild</td>
<td>Moderate</td>
<td>High</td>
</tr>
</tbody>
</table>

L-AmB distribution in the lung
Treatment of *Candida* in non-neutropenic patients according to EFISG guidelines 2012

- **Blood culture positive for yeast (or empiric therapy [CII])**
  - **Start antifungal therapy (AII)**
    - **Strongly recommended:** Echinocandin (AI)
    - **Moderately recommended:** L-AMB or Voriconazole (BI)
    - **Marginally recommended:** Fluconazole (CI) or ABLC (CII)
    - **Not recommended (D):** Amphotericin B deoxycholate, Itraconazole, Posaconazole, Combination

**ABLC** – amphotericin B lipid complex
**L-AMB** – liposomal amphotericin B
**EFISG** – ESCMID Fungal Infection Study Group

4° question : WHY echinocandins ?

ESCMID 2012: recommendations on initial treatment of candidaemia/invasive candidiasis


ESCMID = European Society of Clinical Microbiology and Infectious Diseases
RCT = Randomised controlled trial
Let’s talk for Echinocandins !!!!

Anidulafungin
- Licensed in Europe in 2007
- Derivative from Aspergillus nidulans

Caspofungin
- Licensed in Europe in 2001
- Derived from Glarea lozoyenisi

Micafungin
- Licensed in Europe in 2008
- Derived from Coleophoma empedri

Depletion of major structural components of the fungal cell wall

Catalytic subunit (Fks) 1,3-β-D-glucan

Soluble regulatory subunit (Rho1) UDP

Action of echinocandns

UDP = uridine diphosphate

# PK properties of the echinocandins

Echinocandins have poor oral bioavailability and are therefore administered IV.

<table>
<thead>
<tr>
<th></th>
<th>Anidulafungin</th>
<th>Caspofungin</th>
<th>Micafungin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td>Linear PK over daily doses of 15–130mg</td>
<td>Moderate non-linear PK, increased accumulation as dose is increased</td>
<td>Linear over daily dose range of 12.5–200mg. No evidence of accumulation</td>
</tr>
<tr>
<td><strong>Plasma protein binding</strong></td>
<td>&gt;99%</td>
<td>92.4–96.5%</td>
<td>99%</td>
</tr>
<tr>
<td><strong>Volume of distribution</strong></td>
<td>30–50 litres</td>
<td>Not obtained*</td>
<td>18–19 litres</td>
</tr>
<tr>
<td><strong>Elimination half-life</strong></td>
<td>~24h</td>
<td>9–11h</td>
<td>10–17h</td>
</tr>
<tr>
<td><strong>Clearance</strong></td>
<td>1 L/h</td>
<td>10–12 ml/min</td>
<td>0.15–0.3 ml/min/kg</td>
</tr>
</tbody>
</table>

Activity of echinocandins against *Candida* species

<table>
<thead>
<tr>
<th>Candida isolates</th>
<th>Candida albicans</th>
<th>Candida krusei</th>
<th>Candida parapsilosis</th>
<th>Candida lusitaniae</th>
<th>Candida glabrata</th>
<th>Candida tropicalis</th>
<th>Candida dubliniensis</th>
<th>Candida guilliermondii</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of isolates</strong></td>
<td>45</td>
<td>19</td>
<td>18</td>
<td>18</td>
<td>10</td>
<td>10</td>
<td>4</td>
<td>3</td>
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<tr>
<td><strong>MIC$_{90}$, AND</strong></td>
<td>0.03 -0.5</td>
<td>0.03-0.5</td>
<td>0.5-4</td>
<td>0.03-0.5</td>
<td>0.03-0.12</td>
<td>0.01-16</td>
<td>0.03</td>
<td>2</td>
</tr>
<tr>
<td><strong>MIC$_{90}$, MICA</strong></td>
<td>0.03 -0.5</td>
<td>0.01-8</td>
<td>0.5-4</td>
<td>0.03-2</td>
<td>0.03-0.12</td>
<td>0.01-16</td>
<td>0.03</td>
<td>0.25-2</td>
</tr>
<tr>
<td><strong>MIC$_{90}$, CAS</strong></td>
<td>0.03 -0.5</td>
<td>0.003-4</td>
<td>0.5-4</td>
<td>0.06-1</td>
<td>0.03-0.12</td>
<td>0.03-0.5</td>
<td>0.03-0.06</td>
<td>0.12 -2</td>
</tr>
<tr>
<td><strong>MIC$_{90}$, FC</strong></td>
<td>0.03-32</td>
<td>0.06-64</td>
<td>0.03-0.5</td>
<td>0.12-64</td>
<td>0.03-0.5</td>
<td>0.06-0.5</td>
<td>0.12-1</td>
<td>0.03-0.25</td>
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<td><strong>MIC$_{50}$, POS</strong></td>
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<td>0.03-5</td>
<td>0.01-0.25</td>
<td>0.01-0.25</td>
<td>0.25-1</td>
<td>0.06-1</td>
<td>0.01-0.06</td>
<td>0.25</td>
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<td><strong>MIC$_{50}$, VO</strong></td>
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<td>0.01-0.5</td>
<td>0.12-0.5</td>
<td>0.01-8</td>
<td>0.01-0.12</td>
<td>0.01-0.25</td>
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<td><strong>MIC$_{50}$, IT</strong></td>
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<td>0.06-0.25</td>
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<td>0.03-16</td>
<td>0.01-0.12</td>
<td>0.25-0.5</td>
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<td><strong>MIC$_{50}$, FL</strong></td>
<td>0.12-32</td>
<td>32-64</td>
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<td>0.12-4</td>
<td>8.0-64</td>
<td>0.5-4</td>
<td>0.12-0.25</td>
<td>0.25-4</td>
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<td>0.012-16</td>
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<td>0.03-1</td>
<td>0.25-2</td>
<td>0.12-0.25</td>
<td>0.12-0.5</td>
</tr>
</tbody>
</table>

Dimopoulos G et al, Antim Agents Chemotherapy 2009
Fungicidal activity of echinocandins

Fungicidal activity
✓ against *Candida* species at varying rates and potencies

Anidulafungin
✓ cell killing rate of *C. albicans* at 0.1–1000 times the MIC and with no re-growth at 24 hours
✓ Fungicidal activity is more rapid and/or more potent than caspofungin and/or micafungin

Post-antifungal effect (PAFE)

The suppression of fungal growth that persists after limited exposure to an antifungal agent.

Clinical relevance to the dose of regimens:

Short PAFEs require more frequent dosing.

<table>
<thead>
<tr>
<th>PAFE</th>
<th>ANID-</th>
<th>CASPO-</th>
<th>MICAF-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop growth of <em>C. albicans</em> for more than 12h after short exposure (1h), even at concentrations below MIC</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Prolonged PAFE (&gt;12h) following exposure for 1h at concentrations ≥ MIC</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Prolonged (5.6h and 5.0h respectively) against <em>C. albicans</em> after 1h exposure at concentrations &gt; MIC</td>
<td>-</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>

Scanning electron micrograph of catheters removed from rabbits

- Control
- Anidulafungin
- Fluconazole
Echinocandins in *Candida* biofilm

<table>
<thead>
<tr>
<th>Antifungal Agent</th>
<th>Amph-B</th>
<th>Voricon-</th>
<th>Caspo-</th>
<th>Anidula-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sessile MIC90 (µg/ml)</td>
<td>2</td>
<td>&gt;256</td>
<td>2</td>
<td>≤0.03</td>
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</tbody>
</table>

*In vitro* sessile antifungal susceptibility of 30 clinical *C. albicans* isolates

### MIC<sub>50</sub> and MIC<sub>90</sub>: planktonic form

<table>
<thead>
<tr>
<th></th>
<th>Anid</th>
<th>Mica</th>
<th>Caspo</th>
<th>Fluc</th>
<th>Itra</th>
<th>Fluco</th>
<th>Posa</th>
<th>Vori</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C. albicans</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>0,2</td>
<td>0,2</td>
<td>4</td>
<td>0,25</td>
<td>4</td>
<td>0,5</td>
<td>0,12</td>
<td>0,06</td>
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<td>16</td>
<td>1</td>
<td>32</td>
<td>4</td>
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<tr>
<td><strong>C. tropicalis</strong></td>
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<td>0,06</td>
<td>0,06</td>
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<td>0,25</td>
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<td>0,12</td>
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<td>0,1</td>
<td>4</td>
<td>0,9</td>
<td>14</td>
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<td>0,12</td>
<td>0,4</td>
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<tr>
<td><strong>C. glabrata</strong></td>
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<td>0,06</td>
<td>4</td>
<td>0,5</td>
<td>1,7</td>
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<tr>
<td><strong>C. parapsilosis</strong></td>
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<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
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<td>0,09</td>
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<td>0,12</td>
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<tr>
<td><strong>C. dubliniensis</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>0,265</td>
<td>0,265</td>
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<td>0,56</td>
<td>0,53</td>
<td>0,185</td>
<td>1,005</td>
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<td>0,28</td>
</tr>
<tr>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
<td>0,453</td>
<td>0,453</td>
<td>1,825</td>
<td>0,912</td>
<td>0,906</td>
<td>0,237</td>
<td>1,801</td>
<td>0,453</td>
<td>0,456</td>
</tr>
<tr>
<td><strong>C. guiliermondii</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>1,25</td>
<td>1,125</td>
<td>8,5</td>
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<td>0,28</td>
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<td>0,265</td>
<td>0,14</td>
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<td>0,462</td>
<td>0,226</td>
<td>0,456</td>
<td>0,475</td>
</tr>
</tbody>
</table>
### MIC$_{50}$ and MIC$_{90}$: sessile form

<table>
<thead>
<tr>
<th></th>
<th>Anid</th>
<th>Mica</th>
<th>Caspo</th>
<th>Fluoc</th>
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<th>Posa</th>
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<tbody>
<tr>
<td><strong>C. albicans</strong></td>
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<td><strong>C. glabrata</strong></td>
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<td><strong>C. guiliermondii</strong></td>
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</tr>
<tr>
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<td>29</td>
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<td>3,8</td>
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<td><strong>C. lusitaniae</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MIC50</td>
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<td>3,7</td>
<td>8</td>
<td>1,9</td>
<td>1</td>
</tr>
</tbody>
</table>

*Velegraki A and Dimopoulos G, AAC (in press)*
Mechanisms of Antifungal Resistance

• Multifactorial
  – Efflux pumps
  – Variation in membrane sterol patterns

• Phase-dependent

Mechanisms of resistance

The fungal enzyme CYP51 converts lanosterol to ergosterol.

Ergosterol is a vital component of the fungal cell membrane.

Mutations in CYP51 can confer resistance to antifungal agents.
Echinocandin-resistant fungal strains

Resistance to the echinocandins is rare
Less commonly reported with anidulafungin

- *C. glabrata* strains resistant to caspofungin and micafungin are sensitive to anidulafungin
- Anidulafungin is fungicidal against 90% of *C. parapsilosis*
- Caspofungin and micafungin against 30% and 70% of isolates

 Clearance of echinocandins well-tolerated drugs…..

**Caspofungin**
- Well-tolerated drug
- Biliary elimination

**Micafungin**
- Slow chemical degradation
- Principal circulating compound unchanged micafungin, with metabolites M-1 and M-2 present in trace amounts and M-5 at 6.5% relative to the parent compound

**Anidulafungin**
- N-acetylation
- COMT

Pfizer Ltd. ECALTA® (anidulafungin) SmPC. August 2012.
Merck Sharp & Dohme Ltd. CANDIDAS® (caspofungin) SmPC. April 2013
Astellas Pharma Europe B.V. MYCAMINE™ (micafungin) SmPC. December 2013
...with few Drug-Drug interactions

<table>
<thead>
<tr>
<th>Anidulafungin</th>
<th>Caspofungin</th>
<th>Micafungin</th>
</tr>
</thead>
</table>
| Low potential for clinically relevant interactions | Interactions with:  
- Cyclosporine  
- Tacrolimus  
- Rifampicin  
- Efavirenz  
- Nevirapine  
- Dexamethasone  
- Phenytoin  
- Carbamazepine | Low potential for interactions with medications metabolised via CYP3A-mediated pathways |
| Not an inhibitor, inducer or substrate of CYP450 | | Slight increase in exposure of itraconazole, sirolimus and nifedipine. Co-administration with amphotericin B desoxycholate (AmB-D) associated with 30% increase in AmB-D exposure |

Pfizer Ltd. ECALTA® (anidulafungin) SmPC. August 2012.  
Merck Sharp & Dohme Ltd. CANCIDAS® (caspofungin) SmPC. April 2013  
Astellas Pharma Europe B.V. MYCAMINE™ (micafungin) SmPC. December 2013
4° question : WHY echinocandins?

ESCMID 2012: recommendations on initial treatment of candidaemia/invasive candidiasis

Because of the......

• Broader spectrum
• Low resistance rate
• Activity against biofilm
• The fungicidal profile
• The safety profile
• The fewer drug–drug interactions

ESCMID = European Society of Clinical Microbiology and Infectious Diseases
RCT = Randomised controlled trial
Anidulafungin vs. Fluconazole Candidemia / IC

Primary Endpoint-End of IV Therapy: 75.6 vs. 60.2* (Anidulafungin vs. Fluconazole)
Secondary Endpoint-End of All Therapy: 74.0 vs. 56.8* (Anidulafungin vs. Fluconazole)
Secondary Endpoint-2 Week F/U: 64.6 vs. 49.2* (Anidulafungin vs. Fluconazole)
Secondary Endpoint-6 Week F/U: 55.9 vs. 44.1 (Anidulafungin vs. Fluconazole)

Difference 15.4% (95% CI: 3.9, 27.0)
* = statistically significant, p<.05

Fungal Persistence at the End of Therapy

Clinical and microbiological success rates in randomised trials with echinocandins for invasive *Candida* infections

Anidulafungin for the treatment of candidaemia/invasive candidiasis in selected critically ill patients

M. Ruhrke¹, J. A. Paiva², W. Meersseman³, J. Pachl⁴, I. Grigoras⁵, G. Sganga⁶, F. Menichetti⁷, P. Montravers⁸, G. Auzinger⁹, G. Dimopoulos¹⁰, M. Borges Sá¹¹, P. J. Miller¹², T. Marček¹³ and M. Kantecki¹³

ICE study
Invasive Candidiasis IntensivE Care Study
Clinical Microbiology and Infection 2012
Global Response at EOT
By Population and species

Proportion of patients (%)

Overall eMITT (n=154)
Abdominal surgery (n=79)
Elderly (n=72)
R. insufficiency (n=58)
Solid tumour (n=41)
H. insufficiency (n=25)
Neutropenia (n=12)
Organ transplant (n=8)

Proportion of patients (%)

Overall eMITT (n=154)
C. albicans (n=86)
C. glabrata (n=22)
C. parapsilosis (n=15)
C. tropicalis (n=11)
Global Response at EOT
By APACHE II

Proportion of patients (%)

Overall eMITT (n=154)  APACHE II score ≤20 (n=116)  APACHE II score >20 (n=38)
Anidulafungin for Candidemia, Invasive Candidiasis in patients with abdominal surgery

Montravers P on behalf of ICE study investigators IDSA Boston October 2011
Efficacy and safety of anidulafungin in elderly, critically ill patients with invasive Candida infections: a post hoc analysis

George Dimopoulos, José-Artur Paiva, Wouter Meersseman, Jan Pachl, Ioana Grigoras, Gabriele Sganga, Philippe Montravers, Georg Auzinger, Marcio Borges Sá, Paul J. Miller, Tomas Marček, Michal Kantecki, Markus Ruhnke
Elderly critically ill patients with IFIs  
A specific population

<table>
<thead>
<tr>
<th>Microorganism, n (%)</th>
<th>Age 18–44 n=905 (18.3%)</th>
<th>Age 45–64 n=1672 (33.8%)</th>
<th>Age 65–74 n=1257 (25.4%)</th>
<th>Age 75–84 n=935 (18.9%)</th>
<th>Age ≥85 n=178 (3.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fungi</strong></td>
<td>146 (17%)</td>
<td>320 (20%)</td>
<td>253 (21%)</td>
<td>179 (20%)</td>
<td>31 (18%)</td>
</tr>
<tr>
<td><strong>Species</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Candida</em> spp</td>
<td>117 (13%)</td>
<td>288 (18%)</td>
<td>236 (19%)</td>
<td>171 (19%)</td>
<td>31 (18%)</td>
</tr>
<tr>
<td><em>Aspergillus</em> spp</td>
<td>17 (2%)</td>
<td>26 (2%)</td>
<td>16 (2%)</td>
<td>10 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Other fungus</td>
<td>13 (2%)</td>
<td>20 (2%)</td>
<td>12 (1%)</td>
<td>5 (1%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

IFI, invasive fungal infection

### Aging and impact on drug metabolism

<table>
<thead>
<tr>
<th>Hepatic function</th>
<th>Renal function</th>
<th>Body composition</th>
<th>Comorbidities</th>
<th>Alterations in receptor activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Liver mass</td>
<td>↓ GFR</td>
<td>↓ Total body water</td>
<td>Heart failure</td>
<td>↓ β-receptor</td>
</tr>
<tr>
<td>↓ Hepatic blood flow</td>
<td></td>
<td>↑ Body fat</td>
<td>Hypertension</td>
<td>↓ CYP450</td>
</tr>
<tr>
<td>↓ Phase I metabolism (oxidation by CYP450 enzymes) further inhibited by fluconazole</td>
<td></td>
<td></td>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>↓ Bile secretion</td>
<td></td>
<td></td>
<td>Cancer</td>
<td></td>
</tr>
<tr>
<td>Unaffected phase II metabolism</td>
<td></td>
<td></td>
<td>Pain due to various diseases</td>
<td></td>
</tr>
</tbody>
</table>

- *Candida* colonisation of dental prostheses
- *Candida* colonisation of the urinary tract especially after broad-spectrum antibiotic use

**Antifungal selection**
- AEs
- Drug–drug interactions
481 patients with intrabdominal candidiasis (IAC)
- 27% hospitalized in ICU, mean age 63 years
  - Secondary peritonitis (41%)
  - Abdominal abscesses (30%)
  - 68 (14%) also candidemic
  - 331 (69%) concomitant bacterial infections.
- \textit{C. albicans} (64%), \textit{C. glabrata} (16%)
  - Echinocandins (64%)
  - Azoles (32%)
  - Amphotericin B (4%)
- Septic shock in 40.5% of patients
- Overall 30-day hospital mortality was 27%
Abdominal Candidiasis - Hospital mortality

### Table

<table>
<thead>
<tr>
<th>Variable</th>
<th>χ²</th>
<th>OR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per unit change)</td>
<td>20.74</td>
<td>1.05 (1.03–1.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APACHE II score at the time of diagnosis (per unit change)</td>
<td>6.22</td>
<td>1.05 (1.01–1.08)</td>
<td>0.013</td>
</tr>
<tr>
<td>Secondary peritonitis</td>
<td>4.17</td>
<td>1.72 (1.02–2.89)</td>
<td>0.04</td>
</tr>
<tr>
<td>Septic shock</td>
<td>16.86</td>
<td>3.29 (1.88–5.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No adequate abdominal source control</td>
<td>21.32</td>
<td>3.35 (2.01–5.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No adequate antifungal therapy</td>
<td>4.41</td>
<td>1.81 (1.04–3.16)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Variables selected by backward stepwise multiple logistic regression analysis

### Chart

30-day hospital mortality in patients with or without septic shock and adequate antifungal therapy and/or source control
Anidulafungin in critically ill patients with deep-tissue infection

Rate of successful global response at EOIVT in a pooled analysis of 129 patients with deep-tissue infection, by site of infection.²

Garbino J et al. 2014
Anidulafungin in critically ill patients with neutropenia

Rate of successful global response by baseline pathogen in a pooled analysis of 46 patients with neutropenia

Optimising antifungal therapy

- Monitor patient response
- **Take daily blood cultures**
  - to guide duration of therapy
- Investigate the source of infection
- Obtain further results from microbiology lab
  - species identification
  - susceptibility testing
De-escalation

• De-escalation from an echinocandin to intravenous or oral fluconazole should be encouraged when the patient is clinically stable and the isolated strain is susceptible to fluconazole.

• However, the exact timing for shifting to fluconazole is basically unknown and may vary from patient to patient, depending on patient- and pathogen-related factors.

Step-down therapy in guidelines

If........................................
- the species is susceptible
- the patient is clinically stable
- the patient is able to take oral drug

- Candidaemia (IDSA 2009): 1 3–5 days
- Candidaemia (ESCMID 2012): 2 10 days
- Intra-abdominal candidiasis (SITI/ISC 2013): 3 5–7 days

How to select antifungals in the ICU

Critically ill patient

Fungal infection

Suspected

Risk factors (+)
Biomarkers (-)
Clinical signs (-)
Mycology (-)

Prophylaxis
Fluconazole

Risk factors (+)
Biomarkers (+)
Clinical signs (-)

Pre-emptive Treatment

Risk factors (+)
Clinical signs (+)

Empirical treatment

Echinocandins

YES

Patient is stabilised?
Consider step-down to voriconazole or fluconazole

Echinocandins

Alternative L-AmB

Proven

Blood cultures (+)
Biopsy (+)

Targeted treatment according to Guidelines
Local epidemiology

How to select the antifungal agent?

Haemodynamically unstable patient

YES

Azole resistance
Recent exposure
Local epidemiology
Colonisation

NO

Fluconazole

Risk factors (+)
Biomarkers (+)
Clinical signs (±)

Pre-emptive Treatment

Risk factors (+)
Clinical signs (+)

Empirical treatment

Echinocandins

YES

Patient is stabilised?
Consider step-down to voriconazole or fluconazole

Echinocandins

Alternative L-AmB

Alternatives
Echinocandins
Voriconazole
L-AmB

Conclusions

• Epidemiology / local epidemiology
• Diagnosis
  • Risk factors, prediction scores, serology (?)
• Treatment
  • Early, appropriate (drug), adequate (dose)
    – General move favouring echinocandins (recent European guidelines)
  • Prophylaxis: selected patients
  • Pre-emptive: there is a role in ICU patients?
  • Empirical: with which drug?
    – Prior exposure to antifungals
    – Local resistance pattern
    – Haemodynamic stability of the patient
    – Step-down after susceptibility test