Preventing invasive candida infections - Where could we do better?

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Hosted by
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www.webbertraining.com

April 7, 2016
Anything I say can be highly biased

Dr Eggimann collaborated in several industry-sponsored clinical trials since 1990.

Dr Eggimann served on advisory board for and/or presented sponsored lectures for Pfizer, MSD, Astellas, Roche, Weyth-Lederle, Lilly, Medex Kenta-Biotech
ICU-acquired sepsis

79 year old
BMI 41
Transferred for septic shock

D-9: cholecystectomy
D-2: septic shock
→ duodenal perforations
→ laparostoma

Norepinephrine
Mechanical ventilation
HCVV
Parenteral nutrition
Broad spectrum AB
No antifungals

→ fever /chills
→ worsening hypotension

Could it be a candidiasis?
ICU: the world of infection

1,265 worldwide ICU
14,414 patients
51% with infection
(08.05.2007)

17% (11%-18.5%)

Gram positives
S. aureus
Gram negatives
Pseudomonas spp
Candida spp

Asia
Africa
Oceania
North America
South America
Eastern Europe
Western Europe

EPIC II study

Epidemiology of severe Candida infections

843 Candida infections

1,265 worldwide ICU
14,414 patients
51% with infection
(08.05.2007)

Western Europe 18.5%
Eastern Europe 18.5%
South America 12.8%
North America 18.2%
Oceania 12.7%
Africa 11.1%
Asia 15.7%

EPIC II study
Epidemiology of severe *Candida* infections

843 *Candida* infections

1,265 worldwide ICU
14,414 patients
51% with infection
(08.05.2007)

**Candidemia:** 61

EPIC II study
Kett D et al.
CCM 2011; 39:665-70
Epidemiology of severe *Candida* infections

Incidence (/1000)

- Candidemia

Population
- Hospitalized 0.1
- ICU 1
- BMT 10

Deaths/100 cases

*Bitar D, et al. Em Infect Dis 2014; 20:1149-55*
Outcome of candidemia

Crude mortality
30% to 60%

2507 candidemia in Paris area (2002-2010)

The French Mycosis Study Group
Outcome of candidemia

Crude mortality
30% to 60%

1206 candidemia in ICU patients (2002-2010)

The French Mycosis Study Group
Outcome of candidemia

**Crude mortality**
30% to 60%

**Attributable mortality**
25% to 40%

Epidemiology of severe *Candida* infections

Incidence (/1000)

- Candidemia
  - population 0.1
  - hospitalized 1
  - ICU 10
  - BMT 20

PCR Diagnosis of Invasive Candidiasis: Systematic Review and Meta-Analysis

Tomer Avni, Leonard Leibovici, and Mical Paul

![Graphs showing sensitivity and specificity](image-url)

Epidemiology of severe *Candida* infections

Incidence (/1000)

- Candidemia
- Non-candidemic invasive candidiasis

Finding the “Missing 50%” of Invasive Candidiasis: How Nonculture Diagnostics Will Improve Understanding of Disease Spectrum and Transform Patient Care

Epidemiology of severe *Candida* infections

Incidence (/1000)

- population: 0.1
- hospitalized: 1
- ICU: 10
- BMT: 20
- Non candidemic invasive candidiatis: ??
- Colonization: ???

Recognized patients

- wounds
- UTI
- pneumonia
- ??
1699 ICU patients (70 Spanish ICU) staying > 7 days

Progressive colonization over 9 weeks

Candidemia 5-10/10,000 admissions

Risk factors

- Colonization by *Candida*: 5.0-27.0
- Antibiotics: 1.7-30.0
- Central venous catheter: 3.8-26.4
- ICU stay: 1.5-12.2
- Neutropenia: 3.0-45.0
- Previous surgery: 2.1-20.0
- Renal failure: 3.8-22.1

Pathophysiology of invasive candidiasis

Progressive colonization

Pathophysiology of invasive candidiasis

Treatment:
770 clinical studies
20 editorials
9 meta-analyses
Treatment:
770 clinical studies
20 editorials
9 meta-analyses

Guidelines?
Candida-university
Treatment:
770 clinical studies
20 editorials
9 meta-analyses

Which drug?
What delay?
Catheter removal?
Treatment of documented candidiasis

Amphotericin B
- Binding to ergosterol of outmembrane
- Loss of permeability
- Very broad spectrum
- 50-90% side effects
- 20-40% for L-forms

Echinocandins
- Inhibition of cell wall synthesis (fungicidal)
- Very broad spectrum
- 10-15% side effects
- Parenteral use only

5-flucytosine
- Inhibition of nucleic acid synthesis
- (Very) broad spectrum
- 30-50% side effects
- Potential myelotoxicity

Azoles
- Inhibition (Cy P450) of ergosterol synthesis
- 10-20% side effects
- Many interactions
- Available for oral use
Treatment of documented candidiasis

Failure rates in randomized adult studies 1994 to 2007

- amphotericin B
- L-amphotericin B
- amphotericin B + flucytosine
- fluconazole
- voriconazole
- caspofungin
- micafungin
- anidulafungin

Rex NEJM 1994; Phillips CIF 1997; Mora-Duarte NEJM 02; Rex CID 03; Kullberg Lancet 05; Pappas CID 07; Kuse Lancet 07; Reboli NEJM 07
Treatment of documented candidiasis

Step 1

- Previousazole exposure?
  - No: High risk for C. glabrata or C. krusei?
    - No: fluconazole
    - Yes: echinocandin
  - Yes: echinocandin

Step 2

- Patient clinically stable?
  - Yes: Candida sensitive to fluconazole
    - Yes: fluconazole
    - No: L-ampho, echinocandin
  - No: fluconazole, L-ampho, echinocandin

IDSA Guidelines
### Treatment of documented candidiasis

Pooled data from 7 randomized adult studies 1994 to 2007

<table>
<thead>
<tr>
<th>Organisms(^a)</th>
<th>Factor</th>
<th>Mortality</th>
<th></th>
<th></th>
<th>Factor</th>
<th>Mortality</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All organisms</td>
<td></td>
<td></td>
<td>(P)</td>
<td>(OR)</td>
<td>(95% CI)</td>
<td></td>
<td>(P)</td>
<td>(OR)</td>
</tr>
<tr>
<td>(n = 978)</td>
<td>Age</td>
<td>.02</td>
<td>1.01</td>
<td>1.00–1.02</td>
<td>APACHE II</td>
<td>.0001</td>
<td>0.94</td>
<td>.93–.96</td>
</tr>
<tr>
<td></td>
<td>APACHE II score</td>
<td>.0001</td>
<td>1.11</td>
<td>1.08–1.14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immunosuppressive therapy</td>
<td>.001</td>
<td>1.69</td>
<td>1.18–2.44</td>
<td>CVC removed</td>
<td>.001</td>
<td>1.69</td>
<td>1.23–2.33</td>
</tr>
<tr>
<td></td>
<td>Candida tropicalis</td>
<td>.01</td>
<td>1.64</td>
<td>1.11–2.39</td>
<td>Study</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Echinocandin</td>
<td>.02</td>
<td>0.65</td>
<td>.45–.94</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CVC removed</td>
<td>.0001</td>
<td>0.50</td>
<td>.35–.72</td>
<td>Study</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organisms(^a)</th>
<th>Factor</th>
<th>Mortality</th>
<th></th>
<th></th>
<th>Factor</th>
<th>Mortality</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida albicans</td>
<td></td>
<td></td>
<td>(P)</td>
<td>(OR)</td>
<td>(95% CI)</td>
<td></td>
<td>(P)</td>
<td>(OR)</td>
</tr>
<tr>
<td>(n = 408)</td>
<td>APACHE II score</td>
<td>.0001</td>
<td>1.09</td>
<td>1.05–1.13</td>
<td>APACHE II</td>
<td>.005</td>
<td>0.92</td>
<td>.92–.99</td>
</tr>
<tr>
<td></td>
<td>Immunosuppressive therapy</td>
<td>.002</td>
<td>2.22</td>
<td>1.30–3.70</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>.05</td>
<td>0.58</td>
<td>.34–.98</td>
<td>Study</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Malignancy</td>
<td>.08</td>
<td>1.89</td>
<td>1.05–3.45</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Echinocandin</td>
<td>.03</td>
<td>0.55</td>
<td>.32–.95</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CVC removed</td>
<td>.01</td>
<td>0.52</td>
<td>.31–.90</td>
<td>Study</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Organisms

Treatment of documented candidiasis

Anidulafungin compared with fluconazole for treatment of candidemia and other forms of invasive candidiasis caused by Candida albicans: a multivariate analysis of factors associated with improved outcome

Annette C Reboli, Andrew F Shorr, Coleman Rotstein, Peter G Pappas, Daniel H Kett, Haran T Schlamm, Arlene L Reisman, Pinaki Biswas and Thomas J Walsh

<table>
<thead>
<tr>
<th>End point</th>
<th>Global response</th>
<th>Absolute percent difference between treatments (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fluconazole</td>
<td>Anidulafungin</td>
</tr>
<tr>
<td></td>
<td>(n = 61)</td>
<td>(n = 74)</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>End of IV therapy</td>
<td>38 (62.3)</td>
<td>60 (81.1)</td>
</tr>
<tr>
<td>End of all therapy</td>
<td>34 (55.7)</td>
<td>59 (79.7)</td>
</tr>
<tr>
<td>2-Week follow-up</td>
<td>30 (49.2)</td>
<td>53 (71.6)</td>
</tr>
<tr>
<td>6-Week follow-up</td>
<td>29 (47.5)</td>
<td>44 (59.5)</td>
</tr>
</tbody>
</table>

BMC Infectious Diseases 2011, 11:261
Treatment of documented candidiasis

Anidulafungin compared with fluconazole for treatment of candidemia and other forms of invasive candidiasis caused by Candida albicans: a multivariate analysis of factors associated with improved outcome

Annette C Reboli, Andrew F Shorr, Coleman Rotstein, Peter G Pappas, Daniel H Kett, Haran T Schlamm, Arlene L Reisman, Pinaki Biswas and Thomas J Walsh

Median time to negative blood cultures:
Anidulafungin: 2 days (95% CI, 2.0–4.0)
Fluconazole: 5 days (95% CI, 2.0–7.0)

BMC Infectious Diseases 2011, 11:261
# Treatment of documented candidiasis

## Candidiasis in Adult Patients

<table>
<thead>
<tr>
<th>Intervention</th>
<th>E/E</th>
<th>V/E</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anidulafungin 200/168 mg</td>
<td>A</td>
<td>I</td>
<td>Rubai Ri-MH 2007</td>
<td>Consider local epidemiology (C: parapsilosis; E: anidulafungin, less drug-drug interactions than caspofungin)</td>
</tr>
<tr>
<td>Caspofungin 70/60 mg</td>
<td>A</td>
<td>I</td>
<td>Stirling CD 2009</td>
<td>Consider local epidemiology (C: parapsilosis, E: caspofungin)</td>
</tr>
<tr>
<td>Micafungin 100 mg</td>
<td>A</td>
<td>I</td>
<td>Kassa Leonet 2007</td>
<td>Consider local epidemiology (C: parapsilosis), less drug-drug interactions than caspofungin, consult EMA warning label</td>
</tr>
<tr>
<td>Amphotericin B liposomal 3 mg/kg</td>
<td>B</td>
<td>I</td>
<td>Kassa Leonet 2007</td>
<td>Similar efficacy as micafungin, higher renal toxicity than micafungin</td>
</tr>
<tr>
<td>Voriconazole 6/5 mg/kg/d</td>
<td>B</td>
<td>I</td>
<td>Kolberg Leonet 2005</td>
<td>Limited spectrum compared to echinocandins, drug-drug interactions, limitation of IV formulation in renal impairment, consider therapeutic drug monitoring</td>
</tr>
<tr>
<td>Fluconazole 400-800 mg</td>
<td>C</td>
<td>I</td>
<td>Amorsolo CID 1996</td>
<td>Limited spectrum; inferiority to anidulafungin (especially in the subgroup with high APACHE scores), may be better than echinocandins against C. parapsilosis</td>
</tr>
<tr>
<td>Amphotericin B lipid complex 6 mg/kg</td>
<td>C</td>
<td>I</td>
<td>Amorsolo ICAAC 1995; CID 2005</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B deoxycholate 5.7–1.3 mg/kg</td>
<td>D</td>
<td>I</td>
<td>Ulbrich CID 2000</td>
<td>Substantial renal and infusion-related toxicity</td>
</tr>
<tr>
<td>Amphotericin B deoxycholate plus fluconazole</td>
<td>D</td>
<td>I</td>
<td>Rubai Ri-MH 2007</td>
<td>Efficacy, but increased risk of toxicity in ICU patients No survival benefit</td>
</tr>
<tr>
<td>Amphotericin B deoxycholate plus 5-fluorocytosine</td>
<td>D</td>
<td>B</td>
<td>Adam-Ham Intest 1995</td>
<td></td>
</tr>
<tr>
<td>Efungumab plus lipid-associated amphotericin B</td>
<td>D</td>
<td>B</td>
<td>Pacific CID 2006</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B colloidal dispersion</td>
<td>D</td>
<td>I</td>
<td>Rubai Ri-MH 2007</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>D</td>
<td>B</td>
<td>Rubai Ri-MH 2007</td>
<td></td>
</tr>
<tr>
<td>Posaconazole</td>
<td>D</td>
<td>B</td>
<td>Rubai Ri-MH 2007</td>
<td></td>
</tr>
</tbody>
</table>

**ESCMID Guidelines**

Treatment of documented candidiasis

- The Panel favors an echinocandin for patients with moderately severe to severe illness, or patients who have had recent azole exposure.

- Fluconazole is recommended for patients who are less critically ill and who have no recent azole exposure.

ESCMIID Guidelines
Treatment:
770 clinical studies
20 editorials
9 meta-analyses

Which drug?
What delay?
Catheter removal?
Treatment of documented candidiasis
Impact of delayed antifungal treatment

Early treatment should be empirical!!!

Treatment:
770 clinical studies
20 editorials
9 meta-analyses

Which drug?
What delay?
Catheter removal?
Candidemia: catheter removal?

2 pooled studies: 1109 candidemia

Both survival and treatment success were significantly less likely for the non-removal of catheter versus removal.

2 pooled studies: 842 candidemia

Table 5. Multivariate Analysis of the Effect of Early Removal of the Central Venous Catheter (CVC) on Treatment Success and Survival at 28 and 42 Days after Treatment Initiation in 842 Patients with Candidemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment success</th>
<th>Survival at 28 days</th>
<th>Survival at 42 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>CVC removal within 24 h after treatment initiation</td>
<td>NT</td>
<td>NT</td>
<td>1.15 (0.79–1.67)</td>
</tr>
<tr>
<td>CVC removal</td>
<td>NT</td>
<td>NT</td>
<td>1.19 (0.84–1.67)</td>
</tr>
<tr>
<td>Persistent neutropenia</td>
<td>NT</td>
<td>NT</td>
<td>0.36 (0.15–0.88)</td>
</tr>
<tr>
<td>Higher APACHE II score</td>
<td>NT</td>
<td>NT</td>
<td>0.90(^a) (0.88–0.93)</td>
</tr>
<tr>
<td>Liver failure</td>
<td>NT</td>
<td>NT</td>
<td>0.23 (0.07–0.72)</td>
</tr>
<tr>
<td>Surgery</td>
<td>NT</td>
<td>NT</td>
<td>1.46 (0.87–2.47)</td>
</tr>
<tr>
<td>Older age</td>
<td>NT</td>
<td>NT</td>
<td>0.98(^a) (0.97–0.99)</td>
</tr>
</tbody>
</table>

\(^a\) Denotes that this analysis accounted for a likelihood ratio of 0.0001.

Early Removal of Central Venous Catheter in Patients with Candidemia Does Not Improve Outcome: Analysis of 842 Patients from 2 Randomized Clinical Trials

Candidemia: catheter removal?

Swiss fungal network 2004-2006: 566 candidemia
hospital mortality 232 (41%)
attributable mortality 45 (8%)

OR for death CVC retained : 4.07 (1.5–10.6)
antifungals> 72 h : 1.41 (0.9-4.52)

Erard V, et al. 50th ICAAC 2010
Candidemia: catheter removal?

7 pooled studies: 1915 candidemia

Table 7. Recommendations on Catheter Management in Candidaemia

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central venous catheter can be removed</td>
<td>Remove indwelling lines (not over a guidewire)</td>
<td>A</td>
<td>IIR</td>
<td>Andes CID 2012</td>
</tr>
</tbody>
</table>

Interventions are intended to clear candidaemia and to improve survival.

ESCMID Guidelines
Candidemia: catheter removal?

Please, remove this catheter!
Treatment:
770 clinical studies
20 editorials
9 meta-analyses

Which drug?
What delay?
Catheter removal?
Impact of Therapeutic Strategies on the Prognosis of Candidemia in the ICU

Mireia Puig-Asensio, MD1; Javier Pemán, MD2; Rafael Zaragoza, MD3; José Garnacho-Montero, PhD4; Estrella Martín-Mazuelos, MD5; Manuel Cuenca-Estrella, MD6 and Benito Almirante, MD1; on behalf of the Prospective Population Study on Candidemia in Spain (CANDIPOP) Project, Hospital Infection Study Group (GEIH) and Medical Mycology Study Group (GEMICOMED) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), and Spanish Network for Research in Infectious Diseases

![Graph showing impact of therapeutic strategies on the prognosis of candidemia in the ICU. The graph illustrates the cumulative survival rate over days from onset of candidemia, distinguishing between appropriate combined therapy and delayed or inappropriate therapy. Key points such as central venous catheter removal and adequate antifungal treatment are highlighted. Log-rank = 0.024.]

Antifungals in critically ill patients

Eggimann, Bille, Marchetti, Annals of Intensive Care 2011, 1:37
Invasive candidiasis in critically ill patients

Colonized patients

- Pelz et al. 78%
- Petri et al. 64%
- Garbino et al. 48%
- Nola et al. 46%
- Eggimann et al. 45%

Infected patients

- Surg Infect. 2000
- Intensive Care Med. 1997
- Intensive Care Med. 2002
- ICAAC 2000
- Crit Care Med. 1999

9% 2% 8% 8%
40%-80% colonized

1%-10% infected
40%-80% colonized

1%-10% infected

? Prophylaxis?

? Empirical treatment?
## Invasive candidiasis: the real challenge

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Preemptive Empirical</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSAC CID 1994</td>
<td>yes</td>
<td>Ø</td>
</tr>
<tr>
<td>Edwards CID 1997</td>
<td>Ø</td>
<td>Ø data</td>
</tr>
<tr>
<td>Vincent ICM 1998</td>
<td>Ø</td>
<td>SDD ?</td>
</tr>
<tr>
<td>Rex CID 2000</td>
<td>Ø</td>
<td>yes, but at risk patients</td>
</tr>
<tr>
<td>Buchner EJCMID 2002</td>
<td>yes</td>
<td>Ø</td>
</tr>
<tr>
<td>Denning Lancet ID 2003</td>
<td>Ø</td>
<td>carfully selected pts</td>
</tr>
<tr>
<td>Pappas CID 2004</td>
<td>Ø</td>
<td>Ø indication</td>
</tr>
<tr>
<td>SFAR/SPILF/SRLF 2004</td>
<td>yes, but</td>
<td>carfully selected pts</td>
</tr>
<tr>
<td>ESCMID 2014</td>
<td>yes, but</td>
<td>carfully selected pts</td>
</tr>
<tr>
<td>IDSA CID 2009/2015</td>
<td>yes</td>
<td>carfully selected pts</td>
</tr>
</tbody>
</table>
Antifungal prophylaxis in critically ill patients?

Flucanazole prophylaxis in critically ill surgical patients: analysis

Andrew F. Short, MD, MPH, Kevin Chang, MD, Martin H. Kollef, MD

Overall mortality

Intensive C
DOI 10.100

Prophylaxis review and trial

Candida colonization

Review Articles

Antifungal prophylaxis unit patients: placebo-controlled

Constantinos Z. Vardakas, MD
Epidiotoros S. Stetades, MD

Van Till et al. J Crit Care 07
Antifungal prophylaxis in critically ill patients?

Meta-analysis of randomized studies

Fungal infections

- **RR 37 (27-44)**
- **RR 34 (28-40)**
- **RR 12 (2-25)**

Risk factors and Odds Ratio:
- Colonization: 5.0-27.6
- Antifungals: 1.7-10.0
- Central venous catheter: 3.9-20.4
- ICU stay: 1.5-12.2
- Neutropenia: 3.0-45.0
- Previous surgery: 2.1-20.0
- Renal failure: 3.8-72.1

Candidemia: 5-10/1000 admissions

**Placebo**

**Prophylaxis**

- *p<0.01
- **p<0.001

Cruciani M, et al. ICM; 31: 1356-61
Antifungal prophylaxis in critically ill patients?

### Table 4. 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><strong>Documented invasive fungal infection</strong></td>
<td><strong>6 (5)†</strong></td>
<td><strong>11 (9)‡</strong></td>
</tr>
<tr>
<td>Need for alternative antifungal agent</td>
<td>12 (10)</td>
<td>20 (16)</td>
</tr>
</tbody>
</table>

*Fungal infection, no discontinuation because of toxicity, and no need for a nonstudy, systemic antifungal medication (as assessed by the investigators) resulted in failure of study medication.*

Antifungal prophylaxis in critically ill patients?

% invasive candidiasis in placebo recipients

Positive studies

Negative studies

Desai
Slotman
He
Eggimann
Michalopoulos
Todd
Pelz
Thresehold
Savino
Ables
Sandven
Garbino
Schuster
Prophylaxis in critically ill patients?

Fluconazole prophylaxis prevents intra-abdominal candidiasis in high-risk surgical patients

Philippe Eggimann, MD; Patrick Francioli, MD; Jacques Bille, MD; Rémy Schneider, MD; Mei-Miau Wu, DPH; Germain Chapuis, MD; René Chiolero, MD; André Pannatier, PharmD; Julian Schilling, MD; Stefanos Geroulanos, MD, FCCM; Michel P. Glauser, MD; Thierry Calandra, MD, PhD

Recent abdominal surgery AND recurrent gastrointestinal perforations or anastomotic leakages

(Crit Care Med 1999; 27:1066–1072)
Prophylaxis: very high risk surgical patients

Caspofungin for prevention of intra-abdominal candidiasis in high-risk surgical patients

Critical Care (2009) 35:903–908

Expected candidiasis: 6
Observed candidiasis: 0
# Table 3. Recommendations on Antifungal Prophylaxis in ICU Patients

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent abdominal surgery AND recurrent gastrointestinal perforations or anastomotic leakages</td>
<td>To prevent intraabdominal <em>Candida</em> infection</td>
<td>Fluconazole 400mg/d</td>
<td>B</td>
<td>I</td>
<td>Eggimann CCM 1999</td>
<td>Placebo N=43</td>
</tr>
<tr>
<td>Critically ill surgical patients with an expected length of ICU stay ≥ 3d</td>
<td>To delay the time to fungal infection</td>
<td>Fluconazole 400mg/d</td>
<td>C</td>
<td>I</td>
<td>Senn ICM 2009</td>
<td>Single arm N=19</td>
</tr>
<tr>
<td>Ventilated for 48h and expected to be ventilated for another ≥ 72h</td>
<td>To prevent invasive candidiasis / candidaemia</td>
<td>Fluconazole 100mg/d</td>
<td>C</td>
<td>I</td>
<td>Pelz Ann Surg 2001</td>
<td>Placebo N=260</td>
</tr>
<tr>
<td>Ventilated, hospitalized for ≥ 3d, received antibiotics, CVC, and ≥ 1 of: parenteral nutrition, dialysis, major surgery, pancreatitis, systemic steroids, immunosuppression</td>
<td>To prevent invasive candidiasis / candidaemia</td>
<td>Caspofungin 70/50mg/d</td>
<td>C</td>
<td>I</td>
<td>Garbino ICM 2002</td>
<td>Placebo N=204 SDD used</td>
</tr>
</tbody>
</table>

The table displays the published before other available antifungal agents are not mentioned here. SoR, Strength of recommendation; QoE, Quality of evidence; ICU, intensive care unit; CVC, central venous catheter; IU, international units.

---

*Should be restricted to selected groups of patients*
Prophylaxis: very high risk surgical patients

Decreasing candidaemia rate in abdominal surgery patients after introduction of fluconazole prophylaxis*

B. J. Holzknecht¹, J. Thorup², M. C. Arendrup³, S. E. Andersen⁴, M. Steensen⁵, P. Hesselfeldt⁶, J. M. Nielsen⁷ and J. D. Knudsen¹

*perforation
*leakage

Clin Microbial Infect 2011; 17: 1372–1380
**Empirical antifungal tx in critically ill patients?**

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Preemptive treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSAC CID 1994</td>
<td>yes</td>
</tr>
<tr>
<td>Edwards CID 1997</td>
<td>Ø</td>
</tr>
<tr>
<td>Vincent ICM 1998</td>
<td>Ø</td>
</tr>
<tr>
<td>Rex CID 2000</td>
<td>Ø</td>
</tr>
<tr>
<td>Buchner EJCMID 2002</td>
<td>yes</td>
</tr>
<tr>
<td>Denning Lancet ID 2003</td>
<td>Ø</td>
</tr>
<tr>
<td>Pappas CID 2004</td>
<td>Ø</td>
</tr>
<tr>
<td>SFAR/SPILF/SRLF 2004</td>
<td>yes, but...</td>
</tr>
<tr>
<td>ESCMID 2004</td>
<td>yes, but...</td>
</tr>
<tr>
<td>IDSA CID 2009/2015</td>
<td>yes, but...</td>
</tr>
</tbody>
</table>
Empirical antifungal tx in critically ill patients?

3 to 5 days

colonized patient ≠ infected patient

Failure of Empirical Systemic Antifungal Therapy in Mechanically Ventilated Critically Ill Patients

Sébastien Bailly\textsuperscript{1,2}, Lila Bouadma\textsuperscript{3}, Elie Azoulay\textsuperscript{4}, Maité Garrouste Orgeas\textsuperscript{5}, Christophe Adrie\textsuperscript{6,7}, Bertrand Souweine\textsuperscript{8}, Carole Schwebel\textsuperscript{9}, Danièle Maubon\textsuperscript{10,11}, Rebecca Hamidfar-Roy\textsuperscript{9}, Michael Darmon\textsuperscript{12}, Michel Wolff\textsuperscript{3}, Muriel Cornet\textsuperscript{10,11}, and Jean-François Timsit\textsuperscript{2,3}

1735 patients with at least 5 days of IMV

1687 patients without proven IFI

1541 non neutropenic, non-transplanted patients

1491 included patients

With SAT
\(N = 100\) (6.7%)

Without SAT
\(N = 1391\) (93.2%)

Died at 30 days
\(N = 30\) (30%)
IC = 0

Alive at 30 days
\(N = 70\) (70%)
IC = 4

Died at 30 days
\(N = 342\) (24.5%)
IC = 9

Alive at 30 days
\(N = 1049\) (65.5%)
IC = 9
### Table 2. Effect of SAT on 30-Day Mortality or Invasive Candidiasis on Different Subgroups (Sensitivity Analyses)

<table>
<thead>
<tr>
<th>Type of admission</th>
<th>Total (n = 1,491)</th>
<th>SAT (n = 100)</th>
<th>Death (n = 363)</th>
<th>IC (n = 22)</th>
<th>SAT Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Type of admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicine</td>
<td>1,251 (84)</td>
<td>84 (84)</td>
<td>314 (86)</td>
<td>16 (73)</td>
<td>0.89 (0.44-1.4)</td>
</tr>
<tr>
<td>Surgery</td>
<td>240 (16)</td>
<td>16 (16)</td>
<td>49 (13)</td>
<td>6 (27)</td>
<td>1.00 (0.53-1.8)</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1,370 (92)</td>
<td>86 (86)</td>
<td>326 (90)</td>
<td>6 (27)</td>
<td>0.89 (0.44-1.4)</td>
</tr>
<tr>
<td>Yes</td>
<td>121 (8)</td>
<td>14 (14)</td>
<td>6 (13)</td>
<td>1 (4)</td>
<td>1.00 (0.53-1.8)</td>
</tr>
<tr>
<td>Abdominal surgery or pancreatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1,413 (95)</td>
<td>91 (91)</td>
<td>326 (90)</td>
<td>9 (41)</td>
<td>1.00 (0.53-1.8)</td>
</tr>
<tr>
<td>Yes</td>
<td>78 (5)</td>
<td>7 (7)</td>
<td>6 (17)</td>
<td>2 (9)</td>
<td>1.00 (0.53-1.8)</td>
</tr>
<tr>
<td>SOFA at inclusion*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-6</td>
<td>994 (67)</td>
<td>55 (55)</td>
<td>154 (45)</td>
<td>2 (9)</td>
<td>1.49 (0.69-3.25)</td>
</tr>
<tr>
<td>7-23</td>
<td>497 (33)</td>
<td>45 (45)</td>
<td>83 (24)</td>
<td>4 (18)</td>
<td>1.49 (0.69-3.25)</td>
</tr>
<tr>
<td>Candida score at inclusion*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>781 (52)</td>
<td>38 (38)</td>
<td>153 (45)</td>
<td>5 (23)</td>
<td>1.48 (0.67-3.26)</td>
</tr>
<tr>
<td>3-5</td>
<td>710 (48)</td>
<td>62 (62)</td>
<td>155 (45)</td>
<td>17 (77)</td>
<td>0.78 (0.28-2.18)</td>
</tr>
<tr>
<td>Multifocal Candida colonization at inclusion*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1,230 (83)</td>
<td>66 (66)</td>
<td>281 (77)</td>
<td>17 (77)</td>
<td>1.08 (0.32-3.61)</td>
</tr>
<tr>
<td>Yes</td>
<td>261 (17)</td>
<td>34 (34)</td>
<td>82 (23)</td>
<td>5 (23)</td>
<td>1.24 (0.60-2.55)</td>
</tr>
</tbody>
</table>

In conclusion, this study fails to show that systematic early antifungal treatment based on risk factors of IC influence the 30-day survival without proved IC in nonneutropenic, nontransplanted patients.
Empirical antifungal tx in critically ill patients?

Invasive candidiasis: it takes 7 to 14 days
Continuous exposure to risk factors

Progressive colonization

Empirical antifungal tx in critically ill patients?

Invasive candidiasis: it takes 7 to 14 days
Continuous exposure to risk factors

Progressive colonization

Empiric antifungal tx in critically ill patients?

Colonization index
Nºsites / Nºsites screened 2x weekly >0.5 or ≥0.4 corrected

Candida score
- Surgery on ICU admission
- Total parenteral nutrition
- Severe sepsis
- Candida colonization >2.5 points

Predictive rules
≥ 4th day of ICU stay:
Sepsis + CVC + Mec.Vent. + 1 one of:
- TPN (day 1-3)
- Dialysis (day 1-3)
- Major surgery (within 7 days)
- Pancreatitis (within 7 days)
- Immunosup. (within 7 days) or steroids (within 7 days)

Start empiric antifungal treatment

Patients treated: 10-15%
Candidiasis captured: 85-90%

Patients treated: 15-20%
Candidiasis captured: 75-85%

Patients treated: 10-15%
Candidiasis captured: 60-75%

Candida colonization index

650 surgical ICU patients followed over 6 months
29 colonized by Candida spp (≥3 sites nonvascular)

Documented candidemia infection (n=11)
Threshold reached 5-6 days before infection
Just colonized (n=18)

Candida colonization index

Candida colonization index and subsequent infection in critically ill surgical patients: 20 years later
--Manuscript Draft--

Assessment of
- the risk of invasive candidiasis: 7 studies
- the value of candiduria: 5 studies
- the efficacy of antifungal prophylaxis: 6 studies

To guide empirical antifungal treatment:
714 patients

To compare the accuracy of on-th-shirt tests:
- Candida score
- Mannans/antimannan
- CAGTA
- Beta-D

4 studies
2 studies
1 study
2 studies

1582 patients

Despite its limited bedside practicality and before confirmation of potentially more accurate predictors, such as specific biomarkers, the CI remains an important way to characterize the dynamics of colonization, which increases early in patients who develop invasive candidiasis.

**Candida colonization index**

*Candida* Colonization as a Risk Marker for Invasive Candidiasis in Mixed Medical-Surgical Intensive Care Units: Development and Evaluation of a Simple, Standard Protocol


73/6015 (1%) IC (43 candidemia; 15 probable IC; 15 probable IC)

<table>
<thead>
<tr>
<th>Variablea</th>
<th>Time point 1 (~studied = 6,015) days 3 to 4 post-ICU admisb</th>
<th>95% confidence interval (low)</th>
<th>95% confidence interval (high)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 2 sites</td>
<td>1,671 2.25</td>
<td>0.0005</td>
<td>1.4</td>
<td>3.5</td>
<td>48</td>
<td>71</td>
<td>2</td>
</tr>
<tr>
<td>All 3 sites</td>
<td>342 2.25</td>
<td>0.016</td>
<td>1.16</td>
<td>4.34</td>
<td>14</td>
<td>94</td>
<td>3</td>
</tr>
<tr>
<td>At least 2 sites heavy density (CCI ≥ 0.3)</td>
<td>1,549 3.7</td>
<td>&lt;0.0001</td>
<td>2.36</td>
<td>5.93</td>
<td>58</td>
<td>74</td>
<td>3</td>
</tr>
<tr>
<td>At least 2 sites heavy density</td>
<td>448 3.1</td>
<td>0.001</td>
<td>1.77</td>
<td>5.4</td>
<td>21</td>
<td>92</td>
<td>3</td>
</tr>
<tr>
<td>At least throat heavy density</td>
<td>1,025 3.77</td>
<td>&lt;0.0001</td>
<td>2.39</td>
<td>5.94</td>
<td>45</td>
<td>82</td>
<td>3</td>
</tr>
<tr>
<td>At least perineum heavy density</td>
<td>703 2</td>
<td>0.01</td>
<td>1.15</td>
<td>3.46</td>
<td>22</td>
<td>88</td>
<td>2</td>
</tr>
<tr>
<td>At least urine heavy density</td>
<td>327 NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: PPV: Positive Predictive Value; NPV: Negative Predictive Value.

---

Negative predictive value >> positive predictive value
Empiric antifungal tx in critically ill patients?

Colonization index

- Number of sites / Number of sites screened
- 2x weekly
- > 0.5 or ≥0.4 corrected

Candida score

- Surgery on ICU admission
- Total parenteral nutrition
- Severe sepsis
- Candida colonization > 2.5 points

Predictive rules

- ≥ 4th day of ICU stay
- Sepsis + CVC + MeC Vent.
- + 1 one of:
  - TPN (day 1-3)
  - Dialysis (day 1-3)
  - Major surgery (within 7 days)
  - Pancreatitis (within 7 days)
  - Immunosup, (within 7 days)
  - or steroids (within 7 days)

NPV > PPV

Start empiric antifungal treatment

Patients treated: 10-15%
Candidiasis captured: 85-90%

Patients treated: 15-20%
Candidiasis captured: 75-85%

Patients treated: 10-15%
Candidiasis captured: 60-75%

A bedside scoring system ("Candida score") for early antifungal treatment in nonneutropenic critically ill patients with *Candida* colonization

Cristóbal León, MD; Sergio Ruiz-Santana, MD, PhD; Pedro Saavedra, PhD; Benito Almirante, MD, PhD; Juan Nolla-Salas, MD, PhD; Francisco Álvarez-Lerma, MD, PhD; José Garnacho-Montero, MD; María Ángeles León, MD, PhD; EPCAN Study Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Proven Candidal Infection</th>
<th>p Value</th>
<th>Adjusted Odds Ratio (95% Confidence Interval)</th>
<th>Candida score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery on ICU admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6.9</td>
<td>&lt;.001</td>
<td>2.71 (1.45–5.06)</td>
<td>+1</td>
</tr>
<tr>
<td>Yes</td>
<td>16.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total parenteral nutrition</td>
<td></td>
<td></td>
<td></td>
<td>+1</td>
</tr>
<tr>
<td>No</td>
<td>2.8</td>
<td>&lt;.001</td>
<td>2.48 (1.16–5.31)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe sepsis</td>
<td></td>
<td></td>
<td></td>
<td>+2</td>
</tr>
<tr>
<td>No</td>
<td>4.5</td>
<td>&lt;.001</td>
<td>7.68 (4.14–14.22)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>28.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida species colonization</td>
<td></td>
<td></td>
<td></td>
<td>+1</td>
</tr>
<tr>
<td>No</td>
<td>4.2</td>
<td>&lt;.001</td>
<td>3.04 (1.45–6.39)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

> 2.5 → 7.75 (CI 4.7–12.7) time to develop candidiasis

Candida score

1007 ICU patients (36 units) staying >7 days
58 candidiasis (5.8%)

<table>
<thead>
<tr>
<th>Value</th>
<th>Incidence Rate (%) (95% CI)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>2.3 (1.1–3.5)</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>8.5 (4.2–12.7)</td>
<td>3.7 (1.8–7.7)</td>
</tr>
<tr>
<td>4</td>
<td>16.8 (9.7–23.9)</td>
<td>7.3 (3.7–14.5)</td>
</tr>
<tr>
<td>5</td>
<td>23.6 (12.4–34.9)</td>
<td>10.3 (5.0–21.0)</td>
</tr>
</tbody>
</table>

High negative predictive value

Empiric antifungal tx in critically ill patients?

- **Colonization index**
  - Number of sites/number of sites screened
  - 2x weekly
  - >0.5 or ≥0.4 corrected

- **Candida score**
  - Surgery on ICU admission
  - Total parenteral nutrition
  - Severe sepsis
  - Candida colonization ≥2.5 points

- **Predictive rules**
  - ≥4th day of ICU stay:
    - Sepsis + CVC + Mec.Vent.
  - + 1 one of:
    - TPN (day 1-3)
    - Dialysis (day 1-3)
    - Major surgery (within 7 days)
    - Pancreatitis (within 7 days)
    - Immunosup. (within 7 days)
    - or steroids (within 7 days)

NPV > PPV

Start empiric antifungal treatment:

- Patients treated: 10-15%
- Candidiasis captured: 85-90%

NPV > PPV

- Patients treated: 15-20%
- Candidiasis captured: 75-85%

Candida predictive rules

40%-80% colonized

Impossible to im at the bed

MSG-04 (MK 0991 Protocol 067) caspofungin in high-risk patients

INTENSE study micafungin in surgical patients

? Prophylaxis?

? Empirical treatment?
**Candida** predictive rules

40%-80% colonized

Impossible to im at the bed

MSG-04 (MK 0991 Protocol 067) caspofungin in high-risk patients

INTENSE study micafungin in surgical patients

? Prophylaxis ?

? Empirical treatment ?
Empiric antifungal tx in critically ill patients?

**Colonization index**
- N°sites / N°sites screened
- 2x weekly
- > 0.5 or ≥0.4 corrected

**Candida score**
- Surgery on ICU admission
- Total parenteral nutrition
- Severe sepsis
- Candida colonization
- > 2.5 points

**Predictive rules**
- ≥ 4th day of ICU stay:
  - Sepsis + CVC + Mec.Vent.
  + 1 one of:
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    - Dialysis (day 1-3)
    - Major surgery (within 7 days)
    - Pancreatitis (within 7 days)
    - Immunosup. (within 7 days)
    or steroids (within 7 days)

**NPV > PPV**

Start empiric antifungal treatment

Patients treated:
- Colonization index: 10-15%
- Candidiasis captured: 85-90%
- Candida score: 15-20%
- Candidiasis captured: 75-85%
- Predictive rules: 10-15%
- Candidiasis captured: 60-75%
Failure of Empirical Systemic Antifungal Therapy in Mechanically-ventilated Critically Ill Patients

Sebastien Bailly, Lila Bouadma, Elie Azoulay, Maité Garrouste Orgeas, Bertrand Souweine, Carole Schwebel, Danièle Maubon, Rebecca Hamidfar-Roy, Michael Darmon, Michel Wolff, Muriel Cornet, and Jean-François Timsit

1735 patients: with at least 5 days of D/B

1687 patients: without proven IFI

1541 non-neutropenic, non-transplanted patients

50 patients with SAT administration started before inclusion

1491 included patients:

With SAT
N=100 (6.7%)

Without SAT
N=1391 (93.3%)

Died at 30 days
N=30 (20%)
IC = 0

Alive at 30 days
N=70 (70%)
IC = 4

Died at 30 days
N=542 (24.5%)
IC = 9

Alive at 30 days
N=1049 (65.5%)
IC = 9

Variables at ICU Admission

<table>
<thead>
<tr>
<th></th>
<th>All (N=1491)</th>
<th>Untreated (N=1391)</th>
<th>Treated (N=100)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65 (53 - 76)</td>
<td>65 (53 - 76)</td>
<td>63 (54 - 75)</td>
<td>0.85</td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>950 (64)</td>
<td>898 (65)</td>
<td>52 (52)</td>
<td>0.01</td>
</tr>
<tr>
<td>Center</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>A</td>
<td>745 (50)</td>
<td>679 (49)</td>
<td>66 (66)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>486 (33)</td>
<td>465 (33)</td>
<td>21 (21)</td>
<td></td>
</tr>
<tr>
<td>C, D, E</td>
<td>260 (17)</td>
<td>247 (18)</td>
<td>13 (13)</td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicine</td>
<td>1251 (84)</td>
<td>1167 (84)</td>
<td>84 (84)</td>
<td>0.04</td>
</tr>
<tr>
<td>Elective surgery</td>
<td>85 (6)</td>
<td>84 (6)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>155 (10)</td>
<td>140 (10)</td>
<td>15 (15)</td>
<td></td>
</tr>
</tbody>
</table>

Am J Respir Crit Care Med. First published online 17 Mar 2015 as DOI: 10.1164/rccm.201409
Failure of Empirical Systemic Antifungal Therapy in Mechanically-ventilated Critically Ill Patients

Sebastien Bailly, Lila Bouadma, Elie Azoulay, Maité Garrouste Orgeas, Bertrand Souweine, Carole Schwebel, Danièle Maubon, Rebecca Hamidfar-Roy, Michael Darmon, Michel Wolff, Muriel Cornet, and Jean-Francois Timsit

Table 2: Effect of SAT on 30-day mortality or invasive candidiasis on different sub-groups (sensitivity analysis)

<table>
<thead>
<tr>
<th>Type of admission</th>
<th>Total N=1491</th>
<th>SAT N=100</th>
<th>Death N=363</th>
<th>IC N=...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicine</td>
<td>1251 (84)</td>
<td>84 (84)</td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>Surgery</td>
<td>240 (16)</td>
<td></td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>No</td>
<td></td>
<td></td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td></td>
<td></td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td></td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>781 (52)</td>
<td>38 (38)</td>
<td>186 (51)</td>
<td>1.49 [0.69: 3.25]</td>
</tr>
<tr>
<td></td>
<td>45 (45)</td>
<td></td>
<td>177 (49)</td>
<td>0.44 [0.15: 1.34]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>11 (50)</td>
<td>1.05 [0.57: 1.95]</td>
</tr>
<tr>
<td></td>
<td>198 (55)</td>
<td>5 (23)</td>
<td>17 (77)</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>165 (45)</td>
<td></td>
<td></td>
<td>1.48 [0.67: 3.26]</td>
</tr>
<tr>
<td></td>
<td>710 (48)</td>
<td>62 (62)</td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.78 [0.28: 2.18]</td>
</tr>
<tr>
<td>M.colonization at inclusion*</td>
<td>1230 (83)</td>
<td>66 (66)</td>
<td>281 (77)</td>
<td>1.08 [0.32: 3.61]</td>
</tr>
<tr>
<td></td>
<td>261 (17)</td>
<td>34 (34)</td>
<td>82 (23)</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.24 [0.60: 2.55]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.56</td>
</tr>
</tbody>
</table>

Experienced clinicians failed to identify ICU patients susceptible to benefit from empirical antifungal treatment.
Empiric antifungal tx in critically ill patients?

Biomarkers of candidiasis in critically ill patients

- Mannoproteins
  - \(\beta(1,6)-\text{glucan}\)
  - \(\beta(1,3)-\text{glucan}\)
- Chitin
- Phospholipid bilayer of cell membrane

Patients treated: 10-15%
Candidiasis captured: 85-90%

Patients treated: 15-20%
Candidiasis captured: 75-85%

Patients treated: 10-15%
Candidiasis captured: 60-75%

Biomarkers of candidiasis in critically ill patients

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 Posteraro1, Gennaro De Pascale2, Mario Tumbarello3, Riccardo Torelli1, Mariano Alberto Pennisi2, Giuseppe Bello2, Riccardo Maviglia2, Giovanni Fadda1, Maurizio Sanguinetti1 and Massimo Antonelli2

β-Glucan Antigenemia Anticipates Diagnosis of Blood Culture-Negative Intraabdominal Candidiasis

Frederic Tissot1, Frederic Lamoth1, Philippe M. Hauser2, Christina Orasch1,3, Ursula Flückiger3, Martin Siegemund4, Stefan Zimmerli1, Thierry Calandra1, Jacques Bille2, Philippe Eggimann6, Oscar Marchetti1, and the Fungal Infection Network of Switzerland (FUNGINOS)

1Infectious Diseases Service, Department of Medicine, 2Institute of Microbiology, and 6Adult Intensive Care Service, Lausanne University Hospital, Lausanne, Switzerland; 3Division of Infectious Diseases and Hospital Epidemiology and 4Intensive Care Service, Basel University Hospital, Basel, Switzerland; and 5Institute for Infectious Diseases, University of Bern, Bern, Switzerland


Biomarkers of candidiasis in critically ill patients

95 roman ICU patients developing sepsis >5th day of stay
(diag: medical 61; surgical: 12 trauma: 22)

→ 16 fungal infections
→ 14 invasive candidiasis
→: 13 candidemia

Biomarkers of candidiasis in critically ill patients

89 Swiss ICU patients at very high risk of candidiasis (recurrent GI tract perforation / necrotizing pancreatitis)

29 invasive candidiasis

Biomarkers of candidiasis in critically ill patients

89 Swiss ICU patients at very high risk of candidiasis (recurrent GI tract perforation / necrotizing pancreatitis)

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Number of Patients</th>
<th>Median ΔT vs. Microbiological Diagnosis of IAC (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BG ≥ 80 pg/ml (16/16)</td>
<td></td>
<td>-5</td>
</tr>
<tr>
<td>CS ≥ 3 (16/16)</td>
<td></td>
<td>-4.5</td>
</tr>
<tr>
<td>CI ≥ 0.5 (14/16)</td>
<td></td>
<td>-3.5</td>
</tr>
<tr>
<td>CCI ≥ 0.4 (11/16)</td>
<td></td>
<td>-1</td>
</tr>
<tr>
<td>AF (14/16)</td>
<td></td>
<td>+1</td>
</tr>
</tbody>
</table>

Days (0 = Microbiological Diagnosis of IAC)

Beta-glucan in critically ill patients

89 Swiss ICU patients at very high risk of candidiasis (recurrent GI tract perforation / necrotizing pancreatitis)

Patients not responding to antifungal therapy (n=4).

Patients responding to antifungal therapy (n=22).

---

The near future
A simplified approach

40%-80% colonized

1) Clinical scores
→ Exclude low risk patients

2) Biomarkers (betaglucan)
→ Start antifungals empirically

? Prophylaxis?

? Empirical treatment?

Pratically
Empiric antifungal tx in critically ill patients?

Colonization index

- N° sites / N° sites screened
- 2x weekly
- > 0.5 or ≥ 0.4 corrected

Candida score

- Surgery on ICU admission
- Total parenteral nutrition
- Severe sepsis
- Candida colonization
  > 2.5 points

Predictive rules

- ≥ 4th day of ICU stay:
  - Sepsis + CVC + Mec Vent.
  + 1 one of:
    - TPN (day 1–3)
    - Dialysis (day 1–3)
    - Major surgery (within 7 days)
    - Pancreatitis (within 7 days)
    - Immunosup (within 7 days)
    - or steroids (within 7 days)

Low

Low

Do not start empirical antifungal treatment

Patients treated:
- 10–15%
  Candidiasis captured: ≥ 90%

Patients treated:
- 15–20%
  Candidiasis captured: ≥ 85%

Patients treated:
- 10–15%
  Candidiasis captured: ≥ 75–75%

Empiric antifungal tx in critically ill patients?

Colonization index
N°sites /N°sites screened
2x weekly
>0.5 or ≥0.4 corrected

Candida score
- Surgery on ICU admission
- Total parenteral nutrition
- Severe sepsis
- Candida colonization
>2.5 points

Predictive rules
≥ 4th day of ICU stay:
Sepsis + CVC + Mec Vent. 
+ 1 one of:
- TPN (day 1-3)
- Dialysis (day 1-3)
- Major surgery (within 7 days)
- Pancytopenia (within 7 days)
- Immunosup. (within 7 days)

High

High

CONSIDER empiric antifungal treatment

Patients treated:
10-15%
Candidiasis captured: 85-90%

Patients treated:
15-20%
Candidiasis captured: 75-85%

Patients treated:
10-15%
Candidiasis captured: 60-75%

Empiric antifungal tx in critically ill patients?

The Role of Biomarkers for Starting Antifungals in the Intensive Care Unit

Jean-Luc Pagani, MD, Jean-Pierre Reveley, MD, Yok-Ai Que, MD, PhD, and Philippe Eggimann, MD

Critically ill surgical patients at risk of invasive candidiasis
- Recurrent gastrointestinal tract perforation
- Acute necrotizing pancreatitis (Balthazar grade D or E)
- ICU stay > 3 days after abdominal surgery with at least one site colonized by Candida spp.

Clinician decision to start empirical treatment

β-D-glucan Day 1,2

- >80 pg/ml
- <80 pg/ml

Candida score 1x/48 h

High risk (≥3) → Low risk (<3)

β-D-glucan 1x/48 h

<80 pg/ml

2x >80 pg/ml

No treatment

Empirical treatment

Clinical assessment

- SOFA score < 8
- SOFA score ≥ 8

septic shock

fluconazole

echinocandin

(Treatment choice)

(Clin Pulm Med 2015;00:000–000)
Empiric antifungal tx in critically ill patients?

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- ICU stay >3 days after abdominal surgery with at least one site colonized by Candida spp.

Candida score 1x/48 h

High risk (≥3)  Low risk (<3)

Step 1

Treatment choice

Step 2

(Clin Pulm Med 2015;00:000–000)
Empiric antifungal tx in critically ill patients?

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- Recurrent gastrointestinal tract perforation
- Acute necrotizing pancreatitis (Balthazar grade D or E)
- ICU stay > 3 days after abdominal surgery with at least one site colonized by *Candida* spp.

1. **Candida score 1x/48 h**
   - High risk (≥3) → Low risk (<3)

2. **β-D-glucan 1x/48 h**
   - <80 pg/mL
     - No treatment
   - ≥80 pg/mL
     - 2x >80 pg/mL
       - Empirical treatment
     - No treatment

Treatment choice

(Clin Pulm Med 2015;00:000–000)
Empiric antifungal tx in critically ill patients?

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- Recurrent gastrointestinal tract perforation
- Acute necrotizing pancreatitis (Balthazar grade D or E)
- ICU stay > 3 days after abdominal surgery with at least one site colonized by Candida spp.

- Candida score 1x/48 h

  - High risk (≥3)
  - Low risk (<3)

- β-D-glucan 1x/48 h

  - <80 pg/mL
  - 2x >80 pg/mL

  - No treatment
  - Empirical treatment

- Clinical assessment

  - SOFA score < 8
  - SOFA score ≥ 8

    - Septic shock
    - Echinocandin

    - Fluconazole

(Clin Pulm Med 2015;00:000–000)
Empiric antifungal tx in critically ill patients?

The Role of Biomarkers for Starting Antifungals in the Intensive Care Unit

Jean-Luc Pagani, MD, Jean-Pierre Revelly, MD, Yok-Ai Que, MD, PhD, and Philippe Eggimann, MD

Critically ill surgical patients at risk of invasive candidiasis
- Recurrent gastrointestinal tract perforation
- Acute necrotizing pancreatitis (Balthazar grade D or E)
- ICU stay > 3 days after abdominal surgery with at least one site colonized by Candida spp.

1. Clinician decision to start empirical treatment
   - **β-D-glucan Day 1,2**
     - >80 pg/mL
     - ≤80 pg/mL
     - Continue treatment
     - Stop treatment

2. Candida score 1x/48 h
   - High risk (≥3)
   - Low risk (<3)

3. **β-D-glucan 1x/48 h**
   - <80 pg/mL
   - 2x >80 pg/mL
   - No treatment
   - Empirical treatment

4. Clinical assessment
   - SOFA score < 8
     - Fluconazole
   - SOFA score ≥ 8
     - Septic shock
     - Echinocandin

(Clin Pulm Med 2015;00:000–000)
To summarize
Invasive candidiasis in ICU patients

Etiology of infections in the ICU

Do not wait until candidemia

Empiric antifungal tx in critically ill patients?

Colonization index
- N\textsuperscript{*}sites / N\textsuperscript{*}sites screened
  2x weekly
- >0.5 or ≥0.4 corrected

Candida score
- Surgery on ICU admission
- Total parenteral nutrition
- Severe sepsis
- Candida colonization >2.5 points

Predictive rules
- 80% of ICU patients with candidemia have a colonization index >0.5
- Colonization index ≥0.5 is predictive of candidemia

? Empirical treatment?

Thank you for your attention

and for the invitation
April 13  (South Pacific Teleclass)
UTILIZATION OF METHYLGLYOXAL IN MANUKA HONEY TO REDUCE S. AUREUS NASAL COLONIZATION
Dr. Julian Ketel, Waiariki Institute of Technology, New Zealand

April 20  (Free WHO Teleclass ... Europe)
THE CORE DOMPONENTS FOR INFECTION PREVENTION AND CONTROL PROGRAMS AND ACTION PLAN
Julie Storr, World Health Organization, Geneva
Sponsored by the World Health Organization

April 26  (Free British Teleclass .... Denver Russell Memorial Teleclass Lecture)
INFECTION PREVENTION – IT’S NOT JUST WASHING HANDS
Dr. Peter Hoffman, Public Health England

April 28  (Free Teleclass)
INFECTION PREVENTION AND CONTROL WITH ACCREDITATION CANADA QMENTUM PROGRAM

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