Preventing Invasive Candida Infections – Where Could We Do Better?
Dr. Philippe Eggimann, Centre Hospitalier Universitaire Vaudois, Switzerland
A Webber Training Teleclass

Preventing invasive candida infections - Where could we do better?

Dr Philippe Eggimann, PD&MER
Service de Médecine Intensive Adulte
www.soins-intensifs.chuv.ch

April 7, 2016
Hosted by Paul Webber
paul@webbertraining.com

Anything I say can be highly biased

DISCLOSURE

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

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

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ICU: the world of infection

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

17% (11%-18.5%)

EPIC II study

Epidemiology of severe Candida infections

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

EPIC II study

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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)

population 0.1
hospitalized 1
ICU 10
BMT 20

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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

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Outcome of candidemia

Crude mortality
30% to 60%

Attributable mortality
25% to 40%


Epidemiology of severe Candida infections

Incidence (/1000)

population 0.1
hospitalized 1
ICU 10
BMT 20

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

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Epidemiology of severe *Candida* infections

Incidence (/1000)
- Population: 0.1
- Hospitalized: 1
- ICU: 10
- BMT: 20

Non candidemtic invasive candidiasis

Recognized patients

Colonization

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colonization

Exogenous

immunosuppression

Endogenous

immunosuppression

colonization

Prematurity / bruns
Neutropenia / ileus

Exogenous

Endogenous

1699 ICU patients (70 spanish ICU) staying > 7 days

Progressive colonization over 9 weeks

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Risk factors | Odds Ratio
---|---
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

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Pathophysiology of invasive candidiasis


Pathophysiology of invasive candidiasis


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Treatment:
770 clinical studies
20 editorials
9 meta-analyses

Guidelines?

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Treatment:
770 clinical studies
20 editorials
9 meta-analyses
Which drug?
What delay?
Catheter removal?

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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

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

(Azoles)
- inhibition (Cy P450) of ergosterol synthesis

Treatment of documented candidiasis

Failure rates in randomized adult studies 1994 to 2007

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Rex NEJM 1994; Phillips CFI 1997; Mora-Duarte NEJM 02; Rex CJD 03;
Kullberg Lancet 05; Pappas CID 07; Kuse Lancet 07; Reboli NEJM 07

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Treatment of documented candidiasis

**IDSA Guidelines**

Treatment of documented candidiasis
Pooled data from 7 randomized adult studies 1994 to 2007

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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

<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>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 (71.9)</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

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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
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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 !!!

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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.

Candidemia: catheter 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>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVC removal within 24 h after treatment initiation</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>NT</td>
<td>1.15 (0.79–1.67)</td>
<td>0.45</td>
<td>1.19 (0.84–1.67)</td>
<td>.33</td>
</tr>
<tr>
<td>Persistent neutropenia</td>
<td>NT</td>
<td>0.36 (0.15–0.88)</td>
<td>0.03</td>
<td>.03</td>
</tr>
<tr>
<td>Higher APACHE II score</td>
<td>NT</td>
<td>0.90* (0.88–0.93)</td>
<td>&lt;.001</td>
<td>0.91* (0.89–0.93)</td>
</tr>
<tr>
<td>Liver failure</td>
<td>NT</td>
<td>0.23 (0.07–0.72)</td>
<td>0.01</td>
<td>NT</td>
</tr>
<tr>
<td>Surgery</td>
<td>NT</td>
<td>1.46 (0.87–2.47)</td>
<td>0.16</td>
<td>1.97 (1.23–3.18)</td>
</tr>
<tr>
<td>Older age</td>
<td>NT</td>
<td>0.98 (0.97–0.99)</td>
<td>0.02</td>
<td>0.98 (0.97–0.99)</td>
</tr>
</tbody>
</table>


Candidemia: catheter removal?

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

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

Erard V, et al. 50th ICAAC 2010

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Candidemia: catheter removal?

7 pooled studies: 1915 candidemia


---

Candidemia: catheter removal?

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>IL</td>
<td>Andes CID 2012</td>
</tr>
</tbody>
</table>

Interventions are intended to clear candidaemia and to improve survival.

ESCMI Guidelines

---

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Candidemia: catheter removal?

Please, remove this catheter!

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

Which drug? What delay? Catheter removal?

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Impact of Therapeutic Strategies on the Prognosis of Candidemia in the ICU

Mireia Puig-Asensio, MD; Javier Pemán, MD; Rafael Zarragoza, MD; José Garnacho-Montero, PhD; Estrella Martín-Mañuelos, MD, Manuel Cuénca-Estrella, MD and Benito Almirante, MD;
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


Antifungals in critically ill patients

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Invasive candidiasis in critically ill patients

| Pelz et al. | Surg Infect. 2000 |
| Nola et al. | ICAAC 2000 |
| Eggimann et al. | Crit Care Med. 1999 |

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

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![Diagram showing percentages of colonization and infection, and questions about prophylaxis and empirical treatment.]

Invasive candidiasis: the real challenge

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Preemptive</th>
<th>Empirical</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSAC CID 1994</td>
<td>yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edwards CID 1997</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vincent ICM 1998</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rex CID 2000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buchner EJCMID 2002</td>
<td>yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denning Lancet ID 2003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pappas CID 2004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFAR/SPILF/SRLF 2004</td>
<td>yes, but</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESCMID 2014</td>
<td>yes, but</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDSA CID 2009/2015</td>
<td>yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Antifungal prophylaxis in critically ill patients?

Meta-analysis of randomized studies
Fungal infections

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Antifungal prophylaxis in critically ill patients?

Empirical Fluconazole versus Placebo for Intensive Care Unit Patients
A Randomized Trial

Table 4: Reasons for Failure at the End of the Primary Observation Period*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fluconazole Recipients</th>
<th>Placebo Recipients</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>

Positive studies

% invasive candidiasis in placebo recipients

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Prophylaxis in critically ill patients?
Fluconazole prophylaxis prevents intra-abdominal candidiasis in high-risk surgical patients

- Philippe Eggimann, MD; Patrick Franciolli, MD; Jacques Bille, MD; Remy Schneider, MD;
- Mei-Miau Wu, DPH; Germain Chapuis, MD; Rene Chiolero, MD; Andre Pannatier, PharmD;
- Julian Schilling, MD; Stefanos Geroulanos, MD, FCCM; Michel P. Glausser, MD; Thierry Calandra, MD, PhD

Recent abdominal surgery
AND recurrent
gastrointestinal
perforations or
anastomotic leakages

Days
Patients Without Fungal Infection (%)

(Fluconazole)

(Placebo)

p = .04

(critic Med 1999; 27:1066–1072)

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

- Laurence Senn
- Philippe Eggimann
- Rhiadh Kouitini
- Andres Pascual
- Nicolas Demartines
- Jacques Bille
- Thierry Calandra
- Oscar Marchetti

Expected candidiasis: 6
Observed candidiasis: 0

Colonization Index

P = 0.03

Baseline
End of CSP Therapy


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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 gastrosopic leakages</td>
<td>To prevent intraabdominal candida 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 patients with an expected length of ICU stay ≤ 3d</td>
<td>To delay the time to fungal infection</td>
<td>Caspofungin 70/30mg/d</td>
<td>C</td>
<td>II</td>
<td>Sinn ICM 2009</td>
<td>Single arm, N=19</td>
</tr>
<tr>
<td>Ventilated for 48th and expected to be ventilated for another 372h</td>
<td>To prevent invasive candida / candidaemia</td>
<td>Fluconazole 400mg/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, or immunosuppression</td>
<td>To prevent invasive candida / candidaemia</td>
<td>Caspofungin 70/30mg/d</td>
<td>C</td>
<td>I</td>
<td>Ostrosky SHEA 2011</td>
<td>Should be restricted to selected groups of patients</td>
</tr>
<tr>
<td>Surgical ICU patients with risk factors for invasive candidaemia / candidaemia</td>
<td>To prevent invasive candidaemia / candidaemia</td>
<td>Amphotericin B 4MioIU/d</td>
<td>D</td>
<td>I</td>
<td>Hovlicek Int Surg 2008</td>
<td>Open, N=147</td>
</tr>
<tr>
<td>Surgical ICU with catabolism and meningitis</td>
<td>To prevent invasive candidaemia / candidaemia</td>
<td>Caspofungin 70/30mg/d</td>
<td>C</td>
<td>I</td>
<td>Cerra Arch Surg 1992</td>
<td>Placebo, N=46</td>
</tr>
</tbody>
</table>

Note: The table displays the published strengths of recommendation (SoR) and quality of evidence; ICU, intensive care unit; CVC, central venous catheter; IU, international units.

Prophylaxis: very high risk surgical patients

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

B. J. Holsthuis,1, J. Thorp,2, M. C. Arendrup,1, S. E. Andersen,1, M. Steensøe,1, P. Hesselfeldt,1, J. M. Nielsen2 and J. D. Knudsen1

Pre-intervention | Post-intervention

*perforation
*leakage

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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>∅</td>
</tr>
<tr>
<td>Vincent ICM 1998</td>
<td>∅</td>
</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
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<td>yes, but...</td>
</tr>
</tbody>
</table>

Empirical antifungal tx in critically ill patients?

![Graph showing the progression from colonized patient to infected patient over 3 to 5 days.](image)


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![Graph showing failure of empirical systemic antifungal therapy in mechanically ventilated critically ill patients.]

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


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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:
- Septis + 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 candidia infection (n=11)

Threshold reached 5-6 days before infection

Just colonized (n=18)


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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 ~ 1985 patients
- the value of candiduria: 5 studies
- the efficacy of antifungal prophylaxis:

To guide empirical antifungal treatment:
7 studies \( \geq 714 \) patients

To compare the accuracy of CR:
- Candida score
- Mannans/antimannans
- CAGTA
- Beta

\[ \begin{align*}
& \text{4 studies} \\
& \text{2 studies} \\
& \text{1 study} \\
& \text{2 studies}
\end{align*} \]
\[1582 \text{ patients} \]

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

Anna F. Lau,⁎ Mridula Kabir,⁎ Sharon C.-A. Chen,⁎⁎ E. Geoffrey Playford,⁎ Deborah J. Marriott,⁎⁎⁎ Penelope Southey Lipman,⁎ Emma McBride,⁎ Thomas Gottlieb,⁎ Winston Cheung,⁎ Ian Seppelt,⁎ Jonathan Iredell,⁎⁎⁎ Tar exhibition

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>(n = 4,095)</th>
<th>(n = 4,095)</th>
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<th>(n = 4,095)</th>
<th>(n = 4,095)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(95% confidence interval (low)</td>
<td>95% confidence interval (high)</td>
<td>Sensitivity (%)</td>
<td>Specificity (%)</td>
<td>PPV (%)</td>
<td>NPV (%)</td>
</tr>
<tr>
<td>At least 2 sites in 48 h</td>
<td>1.671</td>
<td>2.251</td>
<td>0.0005</td>
<td>1.4</td>
<td>3.5</td>
<td>48</td>
</tr>
<tr>
<td>All 3 sites in 48 h</td>
<td>3.421</td>
<td>2.251</td>
<td>0.016</td>
<td>1.16</td>
<td>4.34</td>
<td>14</td>
</tr>
<tr>
<td>At least 1 heavy density (COX ≥ 0.3)</td>
<td>1.549</td>
<td>2.739</td>
<td>0.00001</td>
<td>2.26</td>
<td>5.93</td>
<td>58</td>
</tr>
<tr>
<td>At least 1 least dense heavy density</td>
<td>0.005</td>
<td>1.77</td>
<td>0.00001</td>
<td>2.06</td>
<td>1.44</td>
<td>18</td>
</tr>
<tr>
<td>At least 1 least gas heavy density</td>
<td>0.005</td>
<td>1.77</td>
<td>0.00001</td>
<td>2.06</td>
<td>1.44</td>
<td>18</td>
</tr>
<tr>
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<td>0.005</td>
<td>1.77</td>
<td>0.00001</td>
<td>2.06</td>
<td>1.44</td>
<td>18</td>
</tr>
</tbody>
</table>

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Empiric antifungal tx in critically ill patients?

**Colonization index**

- $N-$sites /$N-$sites screened
- 2x weekly
- $>0.5$ or $\geq 0.4$ corrected

**Candida score**

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

**Predictive rules**

- 4th day of ICU stay:
  - Septis + CVC + Mec Vent.
  - 1 one of:
    - TPN (day 1-3)
    - Dialysis (day 1-3)
    - Major surgery (within 7 days)
    - Pancreatitis (within 7 days)
    - Immunosupp. (within 7 days)
    - Steroids (within 7 days)

**NPV $>$ PPV**

Start empiric antifungal treatment

<table>
<thead>
<tr>
<th>Patients treated</th>
<th>10-15%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidiasis captured</td>
<td>85-90%</td>
</tr>
</tbody>
</table>

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**Candida score**

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 Alvarez-Lemar, MD, PhD; José Garachico-Montero, MD; Maria Angeles León, MD, PhD; EP CN 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>Candidate score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery on ICU admission</td>
<td>6.9</td>
<td>&lt;.001</td>
<td>2.71 (1.45-5.06)</td>
<td>+1</td>
</tr>
<tr>
<td>No</td>
<td>16.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.8</td>
<td></td>
<td></td>
<td>+1</td>
</tr>
<tr>
<td>Total parenteral nutrition</td>
<td>2.8</td>
<td></td>
<td>2.48 (1.16-5.31)</td>
<td>+1</td>
</tr>
<tr>
<td>No</td>
<td>15.5</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>4.5</td>
<td>&lt;.001</td>
<td>7.68 (4.14-14.22)</td>
<td>+1</td>
</tr>
<tr>
<td>No</td>
<td>28.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12.3</td>
<td>&lt;.001</td>
<td>3.04 (1.45-6.39)</td>
<td></td>
</tr>
</tbody>
</table>

$>2.5 \rightarrow 7.75$ (CI 4.7-12.7) time to develop candidiasis

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Dr. Philippe Eggimann, Centre Hospitalier Universitaire Vaudois, Switzerland
A Webber Training Teleclass

**Candida score**

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

<table>
<thead>
<tr>
<th>Cut-off Value</th>
<th>Incidence Rate (%)</th>
<th>Relative Risk</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
- N\(^n\) sites / N\(^n\) 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

NPV>PPV

Start empiric antifungal treatment

Predictive rules
- ≥4th day of ICU stay:
  - Sepsis + CVC + Mec.Vent.
  - 1 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)

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

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

Patients treated:
- 30-15%
- Candidiasis captured: 60-75%

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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:
    - Septis + 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)
      - 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%


---

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 Timis

- 175 patients with ≥ 7 days of IVAT
  - 185 patients without parenteral FFP
  - 154 ICU non-ventilated, non-transplant patient
  - 16 patients with antifungal therapy

Failure of IVAT in ventilated patients

- With IVAT
  - Alive at 30 days: 65 (53-76)
  - IVAT = 4
- Without IVAT
  - Alive at 30 days: 65 (53-76)
  - IVAT = 4

Am J Respir Crit Care Med. First published online 13 Mar 2015 as DOI: 10.1164/rccm.201409-

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Table 2: Effect of SAT on 30-day mortality or invasive candidiasis on different subgroups (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=3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicine</td>
<td>1251 (84)</td>
<td>84 (84)</td>
<td>300 (30)</td>
<td>0.21</td>
</tr>
<tr>
<td>Surgery</td>
<td>240 (16)</td>
<td>24 (16)</td>
<td>117 (16)</td>
<td>0.88</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>No</td>
<td>177 (49)</td>
<td>4 (15)</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>45 (45)</td>
<td>1 (3)</td>
<td>0.88</td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>No</td>
<td>186 (51)</td>
<td>11 (50)</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>58 (58)</td>
<td>2 (2)</td>
<td>0.15</td>
</tr>
<tr>
<td>Other</td>
<td>No</td>
<td>198 (55)</td>
<td>5 (23)</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>52 (52)</td>
<td>2 (2)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

M. citri colonization at inclusion: Yes 261 (17) 24 (14) 52 (23) 5 (23) 0.56

Am J Respir Crit Care Med. First published online 17 Mar 2015 as DOI: 10.1164/rcrm.2014409

Empiric antifungal tx in critically ill patients?

Empiric antifungal tx in critically ill patients?

Biomarkers of candidiasis in critically ill patients

Patients treated: 10-15%
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Biomarkers of candidiasis in critically ill patients


Biomarkers of candidiasis in critically ill patients

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


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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

Median ΔT vs. Microbiological Diagnosis of IAC (Days)

BG ≥ 80 pg/ml (16/16)  
CS ≥ 3 (16/16)  
CI ≥ 0.5 (14/16)  
CCI ≥ 0.4 (11/16)  
AF (14/16)

Days  
(0 = Microbiological Diagnosis of IAC)

Tissot F, et al.  
Am J Respir Crit Care Med.  
2013;188:1100-1109.

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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=44).

Patients responding to antifungal therapy (n=22).

D0: Start Antifungal Therapy

Median BG (pp/ml)


The near future

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A simplified approach

40%–80% colonized

1%–20% infected

1) Clinical scores  
→ Exclude low risk patients

2) Biomarkers (beta-glucan)  
→ Start antifungals empirically

? Prophylaxis?  
? Empirical treatment?


Pratically

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    - Dialysis (day 1-3)
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    - Pancreatitis (within 7 days)
    - Immunosup. (within 7 days)
    - or Steroids (within 7 days)

**Empiric antifungal tx**
- Low
- Low

Do not start empirical antifungal treatment

**Empiric antifungal tx**
- High
- High

**CONSIDER empirical antifungal treatment**

---

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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 Revelli, MD, Tok-Ai Qu, MD, PhD, and Philippe Eggimann, MD

Critically ill surgical patients at risk of invasive candidiasis
- Acute surgical gastrointestinal disease
- Major infection
- ICU stay > 3 days after abdominal surgery
- At least one site colonized by Candida spp.

Clinician decision to start empirical treatment

- B-1-glucan Day 1,2
- SOFA score ≥ 8
- SOFA score ≥ 8 and sepsis shock

Empirical treatment

- No treatment
- Empirical treatment
- Clinical assessment

Sofa score ≥ 8
- Septic shock
- Foscarnet
- Echinocandins

Continuation of treatment

Stop treatment

(painful)
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 Revell, MD, Yok-At Qu, MD, PhD,
and Philippe Eggimann, MD

Critically ill surgical patients at risk of invasive candidiasis

- Acute respiratory distress syndrome (ARDS) (3)
- ICU stay >5 days after abdominal surgery with at least one site colonized by Candida spp.
- Candida score 16 h

High risk (≥3) – Low risk (<3)

- B-D-glucan 16 h

- >60 pg/mL → 2x >40 pg/mL

- No treatment
- Empyema treatment
- No treatment

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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 Reveilly, MD, Yoko-I Qua, MD, PhD, and Philippe Eggimann, MD

Critically ill surgical patients at risk of invasive candidiasis

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

B-D-glucan 10,000 ng/mL

- High risk (b)

- Candida score 100 ng/mL

- Low risk (c)

- No treatment

- Empirical treatment

- No treatment

Clinical assessment

- SOFA score 8

- SOFA score ≥ 10

- Septic shock

- Echinocandins

- Emicilin

Treatment decision

- Continue treatment

- Stop treatment

(Clin Pathol 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

Candida score

Predictive rules

High

Low

CONSIDER empiric antifungal treatment

Empiric antifungal tx in critically ill patients?

Colonization index

Candida score

Predictive rules

High

Low

Do not start empirical antifungal treatment

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and for the invitation

April 13  (South Pacific Teleclass)
UTILIZATION OF METHYLGLOXAL IN MANUKA HONEY TO REDUCE S. AUREUS NASAL COLONIZATION
Dr. Julian Ketel, Waiaariki 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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