Treatment of invasive candidiasis in non-haematological patients

AML Oude Lashof, MD PhD
Internist-infectiologist
History of antifungal treatment

1958: 1st use of amphotericin B
1963: 5-FC synthesized
1967: 1st use of azole as antifungal
1972: 1st echinocandin discovered
1990: Fluconazole FDA-approved
1997: CSLI Breakpoint fluconazole is established
2002: Caspofungin FDA-approved
2012: The search for antifungals continues

Butts, Plos Pathog 2012
Risk factors for candidemia

Presence of intravascular catheters*
Neutropenia
Cancer chemotherapy
Prior colonization with *Candida* spp
Broad spectrum antibiotics*
Renal failure
Hemodialysis
Pathophysiology of invasive candidiasis

Owergrowth ← Modified microbiota

Mucosal colonization
- Oro-pharyngeal
- Upper + lower digestive tract
- Genital tract
- Urinary tract

Micro-invasion
- Multiple antibiotics
- Vascular accesses
- Parenteral nutrition
- ICU stay > 7 days
- Candida colonization
- Renal failure
- Major abdominal surgery

Candidemia
- Endophthalmitis
- Endocarditis
- Catheter-related Abscess
- CNS
- Hepato-splenic

Candidemia ← Disseminated disease

Figure 1: Pathophysiology of invasive candidiasis.

Eggimann et al. Ann of Intensive Care 2011, 1:37
Epidemiology

Mainly data from the USA or from individual European countries
Candidemia incidence in Leuven

Lagrou, EJCMID 2007
Survival in candidemia, species related

- Parapsilosis
- Other species
- Albicans
- Glabrata
- Tropicalis
- Krusei

Horn Clin Infect Dis 2009
Question 1: Which Candida species is most frequently cultured from blood next to C. albicans (in Belgium)?

1 - C. glabrata
2 - C. krusei
3 - C. parapsilosis
4 - C. tropicalis
**Question 1:** Which Candida species is most frequently cultured from blood next to C. albicans (in Belgium)?

1. C. glabrata | 0%
2. C. krusei | 0%
3. C. parapsilosis | 0%
4. C. tropicalis | 0%
Candida blood stream infections

Mean 22% C. glabrata candidaemia

What would you start as primary therapy?
Incidence and mortality of *Candida* Species in Europe

![Bar chart showing the percentage of patients and hospital mortality for different Candida species in Europe.](chart)

- **C. albicans**: 56% (37% mortality)
- **C. glabrata**: 14% (50% mortality)
- **C. parapsilosis**: 13% (28% mortality)
- **C. tropicalis**: 7% (43% mortality)
- **C. krusei**: 2% (59% mortality)
- **C. lusitaniae**: 1% (25% mortality)

*Tortorano, EJCMID 2004;23:317-22*  
*Wispinghoff, CID 2004;39:309-17*
Crude mortality rate is high, the attributable mortality rate varies between 5-71%!

*Falagas EJCMID 2006*

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**Morrell M, et al. AAC 2005**

157 patients – 2001-2004

Independent determinants of mortality:
- APACHE II score (one-point increments) ($p < 0.001$)
- Administration of antifungal therapy >12 hours after the first positive blood culture (AOR, 2.09; $p = 0.018$)

---

**Garey KW et al, CID 2006**

230 patients

Independent determinants of mortality:
- APACHE II score ($\Delta 1$-pt.; $p < 0.05$)
- Time to fluconazole (AOR, 1.42; $p = 0.0009$)
HOW TO IDENTIFY PATIENTS AT RISK FOR CANDIDEMIA?
Question 2: Which factor has the greatest independent association with development of invasive candidiasis?

1 - Abdominal surgery at baseline
2 - Multifocal colonization
3 - Severe sepsis at baseline
4 - Total parenteral nutrition
**Question 2: Which factor has the greatest independent association with development of invasive candidiasis?**

<table>
<thead>
<tr>
<th>Factor</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal surgery at baseline</td>
<td>0%</td>
</tr>
<tr>
<td>Multifocal colonization</td>
<td>0%</td>
</tr>
<tr>
<td>Severe sepsis at baseline</td>
<td>0%</td>
</tr>
<tr>
<td>Total parenteral nutrition</td>
<td>0%</td>
</tr>
</tbody>
</table>

Prediction rules

- **Paphitou**: TPN, hemodialysis, diabetes, broad spectrum antibiotics

- **Ostrosky-Zeichner**:
  - CVC +/- broad spectrum antibiotics
    - *and* at least 2 of:
      - TPN, hemodialysis, major surgery, pancreatitis, corticosteroids, immunosuppression

- **Candida score**: Multivariate analysis of risk factors that predispose for invasive candidiasis
Identification of patients

“Ostrosky rules”

≥ 4 days on ICU

AND

-Antibiotics (d 1-3)

OR

-CVC (d 1-3)

And at least 2 of these

TPN (d 1-3)

Dialysis (d 1-3)

Major surgery (d -7-0)

Use steroids (d -7-3)

Immunosupp. (d -7-0)

Ostrosky-Zeichner, 2007;26:271
Identify patients for empirical/pre-emptive therapy

Development of “Candida score”

1699 patients, ≥ 7 days on IC

Multivariate analysis of risk factors for candidemia

- Colonization on multiple locations: weight 1.112, points 1
- TPN: weight 0.908, points 1
- Surgery at admission: weight 0.997, points 1
- Severe sepsis: weight 2.038, points 2
Question 3: What’s the problem with the prediction rules to start empirical treatment?

1 - High sensitivity, low specificity

2 - Low sensitivity, high specificity

3 - Only useful in high incidence areas

4 - 1+3

5 - 2+3
**Question 3:** What’s the problem with the prediction rules to start empirical treatment?

1. High sensitivity, low specificity  |  0%
2. Low sensitivity, high specificity  |  0%
3. Only useful in high incidence areas  |  0%
4. 1+3  |  0%
5. 2+3  |  0%
Identification of patients

“Ostrosky rules”

≥ 4 days on ICU

AND

-Antibiotics (d 1-3)

OR

-CVC (d 1-3)

And at least 2 of these

TPN (d 1-3)

Dialysis (d 1-3)

Major surgery (d -7-0)

Use steroids (d -7-3)

Immunosupp. (d -7-0)

Sensitivity 34%, specificity 90%, PPV 1%, NPV 97%

Prevalence 7% invasive candidiasis

Ostrosky-Zeichner, 2007;26:271
Identify patients for empirical/pre-emptive therapy

Development of “Candida score”
1699 patients, ≥ 7 days on IC
Multivariate analysis of risk factors for candidemia

- Colonization on multiple locations 1 point
- TPN 1 point
- Surgery at admission 1 point
- Severe sepsis 2 points

≥3: sensitivity 81%, specificity 74%
PPV 16%, NPV 98%
Prevalence 5.8%

León, CCM 2006;34:730
Are the risk predictive models generalizable?

Geographical variability in epidemiology of IC, case-mix & medical practices

Validation in Australia:

<table>
<thead>
<tr>
<th></th>
<th>Candida score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>As reported In Spain (prev = 5.8%)</td>
</tr>
<tr>
<td></td>
<td>Applied to Australian data (prev = 0.2% 2.0%)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>81%</td>
</tr>
<tr>
<td></td>
<td>15-26%</td>
</tr>
<tr>
<td>Specificity</td>
<td>74%</td>
</tr>
<tr>
<td></td>
<td>98%</td>
</tr>
<tr>
<td>PPV</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>NPV</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td>98%</td>
</tr>
<tr>
<td>Comments</td>
<td>Application to patients with ICU LOS ≥7d excludes ½-½ cases</td>
</tr>
</tbody>
</table>
Question 4: Empirical treatment is most often inappropriate in septic ICU patients infected with...

1 - Staphylococcus aureus

2 - Pseudomonas aeruginosa

3 - Klebsiella species

4 - Candida albicans
**Question 4:** Empirical treatment is most often inappropriate in septic ICU patients infected with...

<table>
<thead>
<tr>
<th>Option</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - Staphylococcus aureus</td>
<td>0%</td>
</tr>
<tr>
<td>2 - Pseudomonas aeruginosa</td>
<td>0%</td>
</tr>
<tr>
<td>3 - Klebsiella species</td>
<td>0%</td>
</tr>
<tr>
<td>4 - Candida albicans</td>
<td>0%</td>
</tr>
</tbody>
</table>
Appropriate empirical treatment in ICU

Kumar Chest 2009
HOW TO PREVENT INVASIVE CANDIDIASIS IN THE ICU?
Antifungal prophylaxis in the ICU?

Pro:
- Reduces the incidence of invasive candidiasis!
  - with app. 50%
- Again: identification of target patients difficult
- High risk patients
  - In high incidence area
  - Necrotizing pancreatitis
  - Recurrent GI leakage

Con:
- Unselected ICUs: 1-2% invasive candidiasis
- In most hospitals; Ineffective strategy
Empirical antifungal therapy in ICU

RCT Prospective study in ICU patients

Inclusion:
• Unexplained fever > 4 d
• Broadspectrum antibiotics ≥ 4 d
• APACHE-II score ≥ 16
• CVC ≥ 1 d

(no colonization criteria!)

⇒ 14d Fluconazole (800mg/d) or placebo

# Outcome empirical therapy in ICU

## Outcome:
- resolution of fever (<38.3, >72h)
- no invasive mycosis
- no discontinuation for toxicity
- no other antifungal drugs

<table>
<thead>
<tr>
<th></th>
<th>Fluconazole (122)</th>
<th>Placebo (127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>34%</td>
<td>38% (0.69-1.32)</td>
</tr>
<tr>
<td>Inv. Mycoses</td>
<td>5%</td>
<td>9% (0.22-1.49)</td>
</tr>
<tr>
<td>Mortality</td>
<td>24%</td>
<td>17% (0.23-1.67)</td>
</tr>
</tbody>
</table>

No effect of empirical fluconazole! Why?

Total failures: 55% vs 57%
No resolution of fever 51% vs 54%
TREATMENT OF INVASIVE CANDIDIASIS
Crude mortality rate is high, the attributable mortality rate varies between 5-71%!

Falagas EJCMID 2006

Morrell M, et al. AAC 2005
157 patients – 2001-2004
Independent determinants of mortality:
- APACHE II score (one-point increments) (p <0.001)
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Garey KW et al, CID 2006
230 patients
Independent determinants of mortality:
- APACHE II score (Δ1-pt.; p <0.05)
- Time to fluconazole (AOR, 1.42; p = 0.0009)
Why do we choose which antifungal drug?

- Broad spectrum of antifungal activity
- Efficacy
- Patient characteristics
- Safety / interactions
Antifungal agents

**Amphotericin B**
- deoxycholate AmB
- lipid formulations

**Azols**
- Fluconazole
- voriconazole

**Echinocandins**
- Caspofungin
- Anidulafungin
- Micafungin
Randomized Non-Inferior Trials

AmB vs fluconazole: equally effective (3 trials)
AmB/fluc vs Fluc: equally effective Rex, 2003
AmB -> fluc vs Vori: equally effective Kullberg, 2005

Caspofungin vs AmB: equally effective Mora-Duarte, 2002
Micafungin vs L-AmB: equally effective Kuse, 2007
Mica vs Caspo: equally effective Pappas, 2007
Anidulafungin vs fluc: favours Anidula Reboli, 2007
# Susceptibility

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>Albicans</th>
<th>Glabrata</th>
<th>Parapsilosis</th>
<th>Tropicalis</th>
<th>Krusei</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmB-d</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>L-AmB</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>S (SDD)-R</td>
<td></td>
<td>S</td>
<td>S</td>
<td>R</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>S</td>
<td>SDD-R</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>S</td>
<td>S</td>
<td>S/?</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>S</td>
<td>S</td>
<td>S/?</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Micafungin</td>
<td>S</td>
<td>S</td>
<td>S/?</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>
Caspofungin vs. Amphotericin B trial

Time to First Negative Blood Culture

Caspofungin 70/50 mg
Amphotericin B 0.6-1.0 mg/kg

Success (MITT)
n=224
73% 62% P=0.09

Crude Mortality
34% 30% P=0.53

Toxicity Discontinuations
3% 23% P=0.03

Mora-Duarte NEJM2002
Caspofungin vs. AmB in ICU Patients (n=97)

Favourable Response:
- Caspofungin: 68%
- AmB: 56%

All cause mortality:
- Caspofungin: 45%
- AmB: 40%

Attributable mortality:
- Caspofungin: 5%
- AmB: 11%
Micafungin vs. L-AmB in ICU Patients (n=230)

Survival Estimate (P)

Weeks

Micafungin versus liposomal amphotericin B: log rank test P=0.6840
ICU versus non-ICU: log rank test P<0.0001

Dupont Crit Care 2009
Micafungin vs. L-AmB in ICU Patients (n=230)

- Overall treatment success: 63% (Micafungin) vs. 66% (Liposomal AmB)
- All-cause mortality D30: 38% (Micafungin) vs. 34% (Liposomal AmB)

p=n.s.
Anidulafungin vs. fluconazole study

<table>
<thead>
<tr>
<th>MITT population</th>
<th>Anidulafungin</th>
<th>Fluconazole</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=127 (%)</td>
<td>N=118 (%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Success EIV</td>
<td>96 (75.6)</td>
<td>71 (60.2)</td>
<td>15.4 (3.9-27.0) (p&lt;0.02)</td>
</tr>
<tr>
<td>EOT (all)</td>
<td>94 (74.0)</td>
<td>67 (56.8)</td>
<td>17.2 (5.5-29) (p&lt;0.02)</td>
</tr>
<tr>
<td>2 wk follow-up</td>
<td>82 (64.4)</td>
<td>58 (49.2)</td>
<td>15.4 (3.1-27.7) (p&lt;0.02)</td>
</tr>
<tr>
<td>Crude Mortality Rate (8wks)</td>
<td>23%</td>
<td>31%</td>
<td>P=0.15</td>
</tr>
</tbody>
</table>

Reboli NEJM 2007
Survival in ICU patients: 
*anidulafugin vs fluconazole*

![Graph showing survival rates for ICU patients comparing anidulafugin vs fluconazole. The graph includes a log-rank test with a p-value of 0.0717.](Kett, Int J Antimicr Ag 2008)
Success rates different echinocandins

- Anidulafungin vs. fluconazole
- Caspofungin vs. amphotericin B*
- Micafungin 150 mg vs. caspofungin
- Micafungin 100 mg vs. caspofungin
- Micafungin vs. liposomal amphotericin B

Source for Tables (modified) and Figure: Glöckner A and Cornely OA; Echinocandine bei Candida - Infectionen [Treatment of Invasive Candidiasis with Echinocandins] Med Klin 2008; 103:397–405; (Copyright Yrban & Vogel. Reproduced with permission.)
## Indications per echinocandin

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>Indications</th>
<th>Required daily dose (ld/md (minimum treatment duration in days))</th>
<th>Date of approval by US FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspofungin</td>
<td>Empirical therapy for presumed fungal infections in febrile, neutropenic patients</td>
<td>70/50 (7)</td>
<td>February 2005</td>
</tr>
<tr>
<td></td>
<td>Candidemia, intra-abdominal abscess, peritonitis, pleural space infections</td>
<td>70/50 (14)</td>
<td>July 2003</td>
</tr>
<tr>
<td></td>
<td>Esophageal candidiasis</td>
<td>50 (n.s.)</td>
<td>September 2002</td>
</tr>
<tr>
<td></td>
<td>Invasive aspergillosis if refractory or intolerant to other therapies</td>
<td>70/50 (n.s.)</td>
<td>January 2001</td>
</tr>
<tr>
<td>Micafungin</td>
<td>Prophylaxis for <em>Candida</em> infections in hematological stem cell transplantation</td>
<td>50 (n.s.)</td>
<td>March 2005</td>
</tr>
<tr>
<td></td>
<td>Esophageal candidiasis</td>
<td>150 (n.s.)</td>
<td>March 2005</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>Candidemia and intra-abdominal abscess, peritonitis</td>
<td>200/100 (14)</td>
<td>February 2006</td>
</tr>
<tr>
<td></td>
<td>Esophageal candidiasis</td>
<td>100/50 (14)</td>
<td>February 2006</td>
</tr>
</tbody>
</table>

ld/md = Loading dose/daily maintenance dose in milligrams; n.s. = not specified.
Question 5: Should the intravascular catheters be removed < 24h?

1 - Yes, when > 24h mortality is higher

2 - No, but < 48h; > 48h mortality is higher

3 - No, but it should be removed

4 - Removal of the catheter has no effect on mortality
Question 5: Should the intravascular catheters be removed < 24h?

1 - Yes, when > 24h mortality is higher

2 - No, but < 48h; > 48h mortality is higher

3 - No, but it should be removed

4 - Removal of the catheter has no effect on mortality
Antifungal agents and survival

Candidemia and invasive candidiasis

• 7 randomized controlled trials
• 7 antifungal agents (flu, vori, amB, L-amB, caspo, anidula, mica)
• New analysis of all individual patients
• Primary endpoint: 30 day survival
• Excluding: combination therapy, unknown candida species, multiple species infection
• 1915 patients!
Andes pooled data analysis

1915 patients, two polyenes, two triazoles, three candins
Logistic regression using 30-day mortality as primary outcome

**Increased mortality**
- Age
- APACHE II
- Immunosuppressive therapy
- *C. tropicalis*

**Decreased mortality**
- CVC removal during therapy
- Echinocandin antifungal

"These results support first-line treatment with an echinocandin to the majority of patients”

Andes et al., Clin Infect Dis 2012
In conclusion

- Invasive candidiasis still has a high mortality rate
- Antifungal prophylaxis in ICU is effective but inappropriate
- Empirical antifungal therapy in ICU is not proven effective
- Prediction rules to start pre-emptive therapy have a high NPV, and a reasonable specificity. Especially useful in high incidence areas/patients
- Intravascular catheters should be removed/replaced whenever feasible
- Treatment with an echinocandin is preferred, for the higher response rate
Treatment of invasive candidiasis in non-haematological patients

AML Oude Lashof, MD PhD
Internist-infectiologist
Treatment of candidemia

- Candida species and susceptibility
- Localization of infection
  - Candidemia only
  - Disseminated disease
- Mode of administration
- Duration of candidemia
- …
Empirical treatment is most often inappropriate in septic ICU patients infected with...

1. *Staphylococcus aureus*
2. *Pseudomonas aeruginosa*
3. *Klebsiella species*
4. *Candida albicans*
Success at EIV treatment by pathogen

*Patients with a single baseline pathogen

**Difference driven by C. albicans infections!**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Anidulafungin Success</th>
<th>Fluconazole Success</th>
<th>Δ% Difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>75.6%</td>
<td>60.2%</td>
<td>15.4%</td>
<td>0.009</td>
</tr>
<tr>
<td>C. albicans</td>
<td>81.1%</td>
<td>62.3%</td>
<td>18.8%</td>
<td>0.015</td>
</tr>
<tr>
<td>Non-albicans</td>
<td>71.1%</td>
<td>60.0%</td>
<td>11.1%</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Reboli NEJM 2007
Question 6: Should the intravascular catheters be removed < 24h?

1 - Yes, when > 24h mortality is higher

2 - No, but < 48h; > 48h mortality is higher

3 - No, but it should be removed

4 - Removal of the catheter has no effect on mortality
Question 6: Should the intravascular catheters be removed < 24h?

1 - Yes, when > 24h mortality is higher 0%

2 - No, but < 48h; > 48h mortality is higher 0%

3 - No, but it should be removed 0%

4 - Removal of the catheter has no effect on mortality 0%
Mortality

Crude mortality rate is high, the attributable mortality rate varies between 5-71% depending on the study.

Moraell AAC 2005, Kumar Chest 2009
Candida Score

*in practice*

Prospective observational multicenter study

- $\geq 7$ days IC with multifocal colonization (1)
- TPN(1)
- Surgery (1)
- Sepsis(2)

**Goal:** <5% invasive candidiasis in colonized patients

Treatment of a *Candida* infection was initiated by the local team only!
Results Candida Score

in practice

1107 patients

892: colonized / infected

- 565: CS <3 -> 13 (2.3%) invasive Candida infection
- 327: CS ≥3 -> 45 (13.8%) invasive Candida infection

Table 4. Rates of invasive candidiasis according to the Candida score

<table>
<thead>
<tr>
<th>Cutoff 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>