Fungal Infections: Candida

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National and Kapodistrian University of Athens Greece
ATTIKON hospital
Candidiasis - *Candida* spp.
Invasive Candidiasis

The clinical manifestations may be acute, subacute, or chronic to episodic.

Involvement may be localized to the mouth, throat, skin, scalp, vagina, fingers, nails, bronchi, the gastrointestinal tract, or become systemic as in septicaemia, endocarditis, peritonitis, pyelonephritis, osteomyelitis, and meningitis.
Disseminated Candidiasis

Clinical manifestations

- In the **acute form** it presents with fever, tachycardia, tachypnoea and in some cases with rigor and hypotension.
- The **subacute form** is characterized by intermittent fever without any other symptoms and the patient feels well when is afebrile.
- The **chronic form** is characterized by the progressive deterioration of the general condition of the patient who could be febrile or not.
- In some cases the symptoms from the infected organ are prominent.
Candidemia is a broad topic

Candidemia

Organ Involvement

Some trial data

Catheter-related candidemia

Acute disseminated candidiasis

Chronic disseminated candidiasis

Deep organ candidiasis

Mostly anecdotal
Colonization - Invasion

Colonization - Damage of the integument - Invasion
Pathogenesis of Candidiasis

Formation of pseudohyphae and invasion in the epithelium
Epidemiology of Candida infections in ICU
• Approximately 10.4% of infections in an intensive care unit (ICU) are related to *Candida* species, with the majority being nosocomial.

Increasing rate of candidiasis in the US

Martin et al, NEJM 2003;348:1546
Increases in the prevalence of systemic *Candida* infections

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence of candidaemia (episodes/10,000 patient-days/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>1.0</td>
</tr>
<tr>
<td>2000</td>
<td>2.0</td>
</tr>
<tr>
<td>2001</td>
<td>2.5</td>
</tr>
<tr>
<td>2002</td>
<td>3.0</td>
</tr>
<tr>
<td>2003</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Epidemiology of candidemia in intensive care units
Emilio Bouza*, Patricia Muñoz

Fig. 1. Evolution of the episodes of candidemia at Hospital Gregorio Marañon, Madrid, 1985–2007.
Distribution of candidemia fungemia over different ICUs at Hospital Gregorio Marañón, Madrid, 1985–2005.
### Epidemiology

1'417 ICUs in 17 European countries (EPIC Study 1992)

<table>
<thead>
<tr>
<th></th>
<th>Total (%)</th>
<th>BSI (%)</th>
<th>wound (%)</th>
<th>UTI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. aureus</em></td>
<td>30.0</td>
<td>21.9</td>
<td>26.5</td>
<td>6.0</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>28.7</td>
<td>9.7</td>
<td>21.2</td>
<td>18.7</td>
</tr>
<tr>
<td>CN Staph.</td>
<td>19.1</td>
<td>44.9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Yeasts</td>
<td>17.1</td>
<td>9.3</td>
<td>8.3</td>
<td>21.2</td>
</tr>
<tr>
<td><em>Enterococci</em></td>
<td>11.7</td>
<td>10.9</td>
<td>18.2</td>
<td>14.8</td>
</tr>
</tbody>
</table>

Vincent J.L. et al. (EPIC), *JAMA* 1995; **274**: 639-44.
Spencer et al., *ESCMID* 1996; **15**: 281.
CANDIDAEMIA

- 4th more common nosocomial bacteremia in USA. 25-50% of cases occur in the ICU
- Decreasing incidence the last decade
- Increasing incidence of non albicans strains
- Independently related to increased mortality (>30%), increased ICU and hospital stay and cost


<table>
<thead>
<tr>
<th>Rank</th>
<th>Pathogen</th>
<th>BSI per 10,000 admissions</th>
<th>% BSI ICU (n=10,515)</th>
<th>% Crude Mortality ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>CoNS</td>
<td>15.8</td>
<td>35.9</td>
<td>25.7</td>
</tr>
<tr>
<td>2.</td>
<td>S. aureus</td>
<td>10.3</td>
<td>16.8</td>
<td>34.4</td>
</tr>
<tr>
<td>3.</td>
<td>Enterococcus spp.</td>
<td>4.8</td>
<td>9.8</td>
<td>43.0</td>
</tr>
<tr>
<td>4.</td>
<td>Candida spp.</td>
<td>4.6</td>
<td>10.1</td>
<td><strong>47.1</strong></td>
</tr>
<tr>
<td>5.</td>
<td>E. coli</td>
<td>2.3</td>
<td>3.7</td>
<td>33.9</td>
</tr>
<tr>
<td>6.</td>
<td>Klebsiella spp.</td>
<td>2.4</td>
<td>4.0</td>
<td>37.4</td>
</tr>
<tr>
<td>7.</td>
<td>P. aeruginosa</td>
<td>2.1</td>
<td>4.7</td>
<td>47.9</td>
</tr>
<tr>
<td>8.</td>
<td>Enterobacter spp.</td>
<td>1.9</td>
<td>4.7</td>
<td>32.5</td>
</tr>
<tr>
<td>9.</td>
<td>Serratia spp.</td>
<td>0.9</td>
<td>2.1</td>
<td>33.9</td>
</tr>
<tr>
<td>10.</td>
<td>A. baumannii</td>
<td>0.6</td>
<td>1.6</td>
<td>43.4</td>
</tr>
</tbody>
</table>

Secular Trend of Hospital Acquired Candidemia among Intensive Care Unit patients in the United States during 1989-1999

Trick et al CID 2002; 35:627

![Graph showing the secular trend of hospital acquired candidemia among intensive care unit patients in the United States during 1989-1999. The x-axis represents the years from 1989 to 1999, and the y-axis represents the number of BSI/10,000 CVC days. The graph indicates a decrease in BSI rates over the years, with a particular focus on C. albicans and non-albicans species of Candida.]
What is the connection between intensive care and fungal infection?
Fungal infections in the ICU—epidemiology

- ICU admission itself has become an independent risk factor for the development of a *Candida* species infection [3,4].
- While *Candida* spp. are the most common cause of severe fungal infections in the ICU, mould infections are so far rare, but the problem is rapidly rising due to the increased spectrum of patients at risk for aspergillar infections [5].

Candidemia in the ICU

- 10% of ICU bacteremias and 50% of nosocomial candidemias

- 0.50 – 1.8 /1000 pt/days (2% of ICU patients)(100 times more often than in hospital wards)

- 40-70% crude mortality and 20-50% attributed mortality in retrospective studies, 5-7% in prospective clinical studies. Candida septic shock has 30% higher mortality

- Risk factors of adverse outcome include high APACHE SCORE, inappropriate treatment, biofilm producing strains and advanced age.

Underlying conditions in patients with candidaemia

<table>
<thead>
<tr>
<th>Underlying condition*</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>933 (44.7)</td>
</tr>
<tr>
<td><strong>Intensive care</strong></td>
<td><strong>839 (40.2)</strong></td>
</tr>
<tr>
<td>Solid tumour</td>
<td>471 (22.5)</td>
</tr>
<tr>
<td>Haematological malignancy</td>
<td>257 (12.3)</td>
</tr>
<tr>
<td>Premature birth</td>
<td>125 (6.0)</td>
</tr>
<tr>
<td>Solid organ transplantation</td>
<td>74 (3.5)</td>
</tr>
<tr>
<td>HIV infection</td>
<td>63 (3.0)</td>
</tr>
<tr>
<td>Burns</td>
<td>29 (1.4)</td>
</tr>
</tbody>
</table>

A total of 2,089 cases of candidaemia were documented by 106 institutions in the seven participating countries during the 28-month study period.

*364 (17.4%) were treated with steroids

## Risk factors for invasive candidiasis in the intensive care setting

<table>
<thead>
<tr>
<th>Adult Intensive Care Patients</th>
<th>Neonatal and Pediatric Intensive Care Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged length of stay</td>
<td>In addition to the adult risk factors</td>
</tr>
<tr>
<td>High acuity</td>
<td>Prematurity</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Low APCAR score</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Congenital malformations</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td></td>
</tr>
<tr>
<td>Broad-spectrum antibiotics</td>
<td></td>
</tr>
<tr>
<td>Central venous catheter</td>
<td></td>
</tr>
<tr>
<td>Parenteral nutrition</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressive drugs</td>
<td></td>
</tr>
<tr>
<td>Cancer and chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Severe acute pancreatitis</td>
<td></td>
</tr>
<tr>
<td>Candida colonization at multiple sites</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Transplantation</td>
<td></td>
</tr>
</tbody>
</table>

APCAR: American Pediatric Care Assessment Record. Table is adapted from Refs. 14, 17–25.
Incidence of candidaemia and length of stay in the ICU

Blumberg et al, CID 2001

- Incidence: 10/100,000 population
- Male: 53%
- In ICU: 38%
- CVC at diagnosis: 78%
- Surgery during the last 3 months: 50%
- Deaths (during the 30 days post diagnosis): 36%

C. albicans 45%
C. glabrata 24%
C. parapsilosis 13%
C. tropicalis 12%

Reverse to non-albicans strains
SICU 1 year fungal infections causes 90pts 100strains

What Are ICU Fungal Pathogens?

<table>
<thead>
<tr>
<th>Characteristics of fungal infection</th>
<th>Episodes (n [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogens</td>
<td></td>
</tr>
<tr>
<td>Candida albicans</td>
<td>58 (58.0)</td>
</tr>
<tr>
<td>Candida tropicalis</td>
<td>17 (17.0)</td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>15 (15.0)</td>
</tr>
<tr>
<td>Candida parapsilosis</td>
<td>3 (3.0)</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>3 (3.0)</td>
</tr>
<tr>
<td>Others or unclassified</td>
<td>4 (4.0)</td>
</tr>
<tr>
<td>Site of infection</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>62 (56.4)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>25 (22.7)</td>
</tr>
<tr>
<td>Bloodstream or catheter related</td>
<td>15 (13.6)</td>
</tr>
<tr>
<td>Other sites</td>
<td>8 (7.3)</td>
</tr>
</tbody>
</table>

Laverdiere M et al. J Crit Care 2007; 22;245-251

Epidemiology of Candida spp infection in Europe and USA

**Candida spp. isolated in Europe**
(1992-2001; N = 775)

**Candida spp. isolated in the U.S.**
(1992-2001; N = 3,683)

<table>
<thead>
<tr>
<th></th>
<th>Europe</th>
<th>U.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>58%</td>
<td>54%</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>13%</td>
<td>18%</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>14%</td>
<td>10%</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Other non-albicans spp</td>
<td>5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Epidemiology of *Candida* species is complex and varies among different patient care units

Clinicians must consider their own units’ epidemiologic trends

Candida species from “Laikon” Gen. Hospital, Athens Greece

- C. albicans: 52%
- C. tropicalis: 14%
- C. krusei: 2%
- C. glabrata: 2%
- C. parapsilosis: 2%
- C. kefyr: 1%
- Candida sp.: 16%
- Saccharomyces cerevisiae: 14%
- A. flavus: 3%
- A. fumigatus: 3%
ECMM initiated a prospective survey on deep seated *Candida/yeast* infections in surgical ICU patients

- 15 European countries are participating
- The survey started in most countries in September 2006 and ended December 2008 (Italy started May 2006 and France January 2007, Turkey 2008)
- The aim is to include >1000 patients

Lena Klingspor TIMM-4, 2009
Species distribution of 829 *Candida* isolates in 802 patients

<table>
<thead>
<tr>
<th>Candida species</th>
<th>No of episodes</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. albicans</em></td>
<td>446</td>
<td>53.8</td>
</tr>
<tr>
<td><em>C. parapsilosis</em></td>
<td>146</td>
<td>17.6</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>114</td>
<td>13.8</td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td>55</td>
<td>6.6</td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>21</td>
<td>2.5</td>
</tr>
<tr>
<td><em>C. lusitaniae</em></td>
<td>15</td>
<td>1.8</td>
</tr>
<tr>
<td><em>C. dubliniensis</em></td>
<td>10</td>
<td>1.2</td>
</tr>
<tr>
<td><em>C. guillermondii</em></td>
<td>6</td>
<td>0.7</td>
</tr>
<tr>
<td>Other</td>
<td>16</td>
<td>2.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>829</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

Total mortality 40.4%

Lena Klingspor TIMM-4, 2009
Resistance to fluconazole in *Candida* species

<table>
<thead>
<tr>
<th>Species</th>
<th>Fluconazole MIC (µg/ml)</th>
<th>Percentage of isolates</th>
<th>Susceptible</th>
<th>Susceptible–dose-dependent*</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50% 90% Range</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Candida</em> spp.</td>
<td>0.5 16 ≤ 0.12–256</td>
<td>88.5 7.3 4.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C. albicans</em></td>
<td>≤ 0.25 0.5 ≤ 0.12–128</td>
<td>99.4 0.1 0.4</td>
<td></td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>8 64 1–128</td>
<td>52.1 35.8 12.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C. parapsilosis</em></td>
<td>1 2 0.25–64</td>
<td>98.8 0.8 0.4</td>
<td></td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td>1 2 ≤ 0.12–128</td>
<td>98.0 0.7 1.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>64 128 16–256</td>
<td>0.0 25.9 74.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Messer SA, *et al*.* J Clin Microbiol* 2006; *44*:1782–1787

*Refers to isolates with reduced susceptibility that can be overcome by increasing the dose.*
Conclusions:

- More than two thirds of patients with invasive candidiasis in ICU present with candidemia.
- Non-*albicans* *Candida* species reach almost half of the *Candida* isolates.
- Reduced susceptibility to fluconazole is observed in 17.1% of *Candida* isolates.
- Mortality of invasive candidiasis in ICU remains high.

(Crit Care Med 2009; 37:1612–1618)
Antifungals in the ICU
WHERE? – WHEN? – HOW?
Antifungals in the ICU

In patients with proven or presumed fungal infection

Fungal infection in the ICU = invasive Candidiasis (IC)

- Candidaemia
- Acute disseminated candidiasis
- Deep organ involvement
Antifungals in the ICU

When?

- Invasive candidiasis commonly with occult symptoms
- Diagnosis requires histology or positive blood culture (se=50%)
- Increased mortality requires early diagnosis and treatment

Treatment of proven infection

Preemptive or empiric treatment?

Prophylaxis?

SURROGATE MARKERS (PCR, B-GLUCAN)

Risk prediction models

RISK FACTORS
Assessing risk

• The early identification of risk factors for the development of candidemia – such as peritonitis, abdominal surgery, previous administration of broad-spectrum antibiotics, parenteral nutrition, multiple lumen catheters, prior Candida species colonization, renal replacement therapy, and mechanical ventilation – has become the cornerstone of empiric treatment of fungal infections in the ICU setting in order to reduce the high mortality rate associated with these infections.

Antifungals in the ICU

When?

Preemptive or empiric treatment?

Prophylaxis?

Risk factors for IC have been well recognized in the critical care setting by several studies. An effort is being made for a prediction rule to be formed based on identified risk factors and validated prospectively in multicenter studies.

Osrosky –Zeihner, Curr Opin Infect Dis 2003
Antifungals in the ICU

Frequently reported risk factors of invasive candidiasis in the critical care setting

Length of stay in the ICU
Broad spectrum antibiotics
Hemodialysis
CVC
Severity of illness
Total parenteral nutrition
GI perforation or surgery
Pancreatitis
Steroids or immunosuppression
Mechanical ventilation
Multiple transfusions
Candida colonization
D.M.

When?

ADULTS

Osrosky –Zeihner,Curr Opin Infect Dis 2003
Colonization Index (CI) = sides with colonization/ sides searched for colonization > 0.5

- Prolonged treatment with antibiotics
- APACHE II score

PPV of CI 66%
NPV of CI 100%

Pittet et al
Ann Surg 1994
Colonization

Colonization (particularly of many sites) should be regarded as nothing more than a risk factor, not as a disease that requires treatment on its own, because studies have shown there is no benefit to treating forms of colonization such as asymptomatic funguria in nonimmunocompromised patients.
DM
TPN
Under haemodialysis
Brad spectrum antibiotics

Se 83%
Sp 50%
PPV 11%
NPV 98%
Any systemic antibiotic (d1-3) OR presence of CVC

**AND 2 of the following**

- TPN (d 1-30)
- Any dialysis (d 1-3)
- Any major surgery (last 7 days)
- Pancreatitis (last 7 days)
- Steroids (last 7 days)
- Immunosuppression (last 7 days)

RR for candidemia 4.36
Se 34%
Sp 90%
PPV 10%
NPV 97%

**L. OSTROSKY-ZEICHNER, et al**

*Eur J Clin Microbiol Infect Dis 2007*
649 cases from Switzerland, France, US, and Australia.

Mean APACHE II score = 16. Mortality was 13%.

Mean hospital stay = 30 days. Mean ICU stay = 12 days.

*Candida* colonization identified in 66%. Median time to colonization = 4 days. Pts with proven IC = 12 (incidence 1.8%). Median time to IC = 16 days. 13% of pts with at least one antifungal

| SE 66% | SP 87% | PPV 9% | NPV 98% |

*L. OSTROSKY-ZEICHNER, et al, ICAAC 2008*
The Candida Bedside Score

- TPN +0.9(1)
- SURGERY +0.99(1)
- MULTIFOCAL COLONIZATION +1.11(1)
- SEVERE SEPSIS +2.038 (2)

A "Candida score" > 2.5 accurately selected patients who would benefit from early antifungal treatment.

Leon C et al EPCAN study group
CCM 2006; 34:730
Usefulness of the “Candida score” for discriminating between Candida colonization and invasive candidiasis in non-neutropenic critically ill patients: A prospective multicenter study

Cristóbal León, MD; Sergio Ruiz-Santana, MD, PhD; Pedro Sagreda, PhD; Beatriz Galván, MD; Armando Blanco, MD; Carmen Castro, MD; Carina Balasini, MD; Aránzazu Utané de Vázquez, MD; Francisco J. González de Molina, MD; Miguel A. Blasco Navalproa, MD; María J. López, MD; Pierre Emmanuel Charles, MD, PhD; Estrella Martín, PhD; María Adela Hernández-Viera, MD; on behalf of the Cava Study Group

1107 non neutropenics in ICU36 MEO

in Spain ,Argentina and France

Candida Score <3 in colonized pts hospitalized for > 7 days without antifungals correspond risk for candidiasis 2.3%

Crit Care Med 2009; 37:1624
Empirical fluconazole versus placebo for intensive care unit patients: a randomized trial

- Double blind comparative with placebo study
- 249 pts in ICU with fever non responding to antibiotics (26 centers)
- CVC and APACHE > 16
- Fluconazole 800mg vs placebo for 2 weeks
- No difference in the incidence of candidemia (<10%)
- No difference in the resolution of fever

preemptive or presumptive therapy?

Preemptive antifungal treatment is indicated in pts with several risk factors, fever non responding to antimicribials and significant colonization, especially if they are unstable.
Antifungals in the ICU

When?

PROPHYLAXIS?

Established criteria in recent guidelines for prophylaxis in the liver transplants with $\geq 2$ risk factors:

- Retransplantation
- Creatinine $>2$
- Choledochojejunostomy
- Intraoperative use of $\geq 40$ blood units
- Fungal colonization $\leq 2$ before and $\geq 3$ days after transplantation

10-20 mg/d Ampho B
1 mg/kg/d L-amb
Fluconazole 100 mg/d
Fluconazole 400 mg/d

CID 2004; 38:166
Key recommendations. Knowledge about this class of infections is evolving. The primary data showing utility of prophylaxis are from studies at single centers with high baseline rates of infections. The broader applicability of these rules in other ICUs remains a subject of significant debate. Institutions where high rates of invasive candidiasis in the adult or neonatal ICU persist despite standard infection-control procedures could consider fluconazole prophylaxis for carefully selected patients in these care areas (A-I).
Prophylaxis in non-febrile high-risk pts could be discussed if the incidence of candidemia in ICU is $\geq 10\%$. With the average incidence 3%, 100-200 pts should be receive prophylaxis to avoid one candidemia.

\textit{Curr Opin Infect Dis 2008;21;610}
Candidemia: General considerations

(Targeted treatment)

- Take into account any positive blood culture positive for Candida sp
- Treat even one positive blood culture
- Start treatment immediately
- Change or remove CVC
- Identify and test for sensitivity all Candida spp

# Candidemia – Targeted treatment

**Table 3. General patterns of susceptibility of Candida species.**

<table>
<thead>
<tr>
<th>Candida species</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Voriconazole</th>
<th>Flucytosine</th>
<th>Amphotericin B</th>
<th>Candins&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. albicans</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><em>C. parapsilosis</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S (to 1?)</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>S-DD to R&lt;sup&gt;b&lt;/sup&gt;</td>
<td>S-DD to R&lt;sup&gt;c&lt;/sup&gt;</td>
<td>S to I&lt;sup&gt;d&lt;/sup&gt;</td>
<td>S</td>
<td>S to I&lt;sup&gt;a&lt;/sup&gt;</td>
<td>S</td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>R</td>
<td>S-DD to R&lt;sup&gt;c&lt;/sup&gt;</td>
<td>S to I&lt;sup&gt;d&lt;/sup&gt;</td>
<td>I to R</td>
<td>S to I&lt;sup&gt;a&lt;/sup&gt;</td>
<td>S</td>
</tr>
<tr>
<td><em>C. lusitaniae</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S to R&lt;sup&gt;f&lt;/sup&gt;</td>
<td>S</td>
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</tbody>
</table>

**SDD**: maximum dosage requirements

*J Clin Microbiol* 2006;44:819  
*CID* 2004; 38: 161
<table>
<thead>
<tr>
<th>Antifungal</th>
<th>C. albicans</th>
<th>C. tropicalis</th>
<th>C. parapsilosis</th>
<th>C. glabrata</th>
<th>C. Kruzei</th>
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<tr>
<td>fluconazole</td>
<td>&gt;4</td>
<td>&gt;4</td>
<td>&gt;4</td>
<td>&gt;32</td>
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<td>itraconazole</td>
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<td>&gt;2</td>
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<tr>
<td>posaconazole</td>
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<td>&gt;2</td>
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</tr>
<tr>
<td>caspofungin</td>
<td>&gt;0.5</td>
<td>&gt;0.5</td>
<td>&gt;4</td>
<td>&gt;0.5</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>anidulafungin</td>
<td>&gt;0.5</td>
<td>&gt;0.5</td>
<td>&gt;4</td>
<td>&gt;0.5</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>micafungin</td>
<td>&gt;0.5</td>
<td>&gt;0.5</td>
<td>&gt;4</td>
<td>&gt;0.12</td>
<td>&gt;0.5</td>
</tr>
</tbody>
</table>

*Diagn Microbiol Infect Dis 2011;69: 45–50*
Candidemia – Targeted treatment

- If C. glabrata preferable echinocandins
- Alternative treatment: L-Amb
- Voriconazole not superior, comparable to fluconazole in sensitive strains. Oral treatment in C. kruzei or sensitive C. glabrata
- If possible de-escalation to fluconazole
- If C. parapsilosis avoid echinocandins

CID 2009; 48: 503 - 35
Choose treatment according to the local epidemiology, the severity of the disease and organ insufficiencies.

Available antifungals: Ampho B, fluconazole, echinocandins, voriconazole. Comparative clinical trials show non inferior

In stable pts without previous exposure to azoles high dose of fluconazole

In pts with previous exposure to azoles or moderate to severe clinical condition drug of choice echinocandins.
Candidemia: General considerations

- **Candidemia without organ involvement** continue treatment for 14 days after negative blood culture and resolution of symptoms.

- **All patients with candidemia should perform fundoscopy.**

- **If the patient is not responding to treatment** search for resistance, deep organ involvement, septic thrombophlebitis or other foreign bodies that need to be removed. Treatment is modified.
Candidemia: General considerations

- Preemptive therapy and prophylaxis are issues yet not clear and risk factors/surrogate markers for patient selection are yet to be clearly defined.
Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America

IDSA Clinical Infectious Diseases 2009; 48:503–35
ESCMID Diagnostic & Management Guideline for Candida Diseases 2011

Authors: Murat Akova, Maiken Arendrup, Sevtap Arikan-Akdagli, Matteo Bassetti, Jacque Bille, Thierry Calandra, Elio Castagnola, Oliver A. Cornely, Manuel Cuenca-Estrella, Peter Donnelly, Jorge Garbino, Andreas Groll, Raoul Herbrecht, William Hope, Henrik Elvang Jensen, Bart-Jan Kullberg, Cornelia Lass-Flörl, Olivier Lortholary, Wouter Meersseman, Georgios Petrikkos, Malcolm Richardson, Emmanuel Roilides, Andrew J. Ullmann, Paul Verweij, Claudio Viscoli

Main Coordinator: Andrew J. Ullmann
Proposed antifungal treatment of invasive candidiasis based on diagnostic stage in critical care settings.
Conclusions

• Several risk factors for IC are recorded in a large number of critically ill patients admitted to medical and surgical ICUs: a consistent proportion of them (ranging from 20% to 60%) become colonised during their hospital stay, but unlike immunocompromised neutropenic individuals, only a minority (1–5%) will develop IC.
Conclusions

• IFIs, especially in the critical care setting, have become an excellent target for prophylactic, empiric, and pre-emptive therapy interventions due to high morbidity and mortality rates, an increasing incidence, and their associated healthcare costs.
Conclusions

• The choice of antifungal drug must be based on the individual characteristics of the patient and a tailored therapy (de-escalation) must also be considered in the ICU setting. Importantly, echinocandins have become the firstline option when hemodynamic instability is present, for example in patients with severe sepsis.