Second Interactive Session
Management of Candidemia

Speakers:
Patricia Muñoz
Emilio Bouza
Manuel Cuenca Estrella
In a patient with candidemia, which antifungal would be your first choice before knowing the Candida species?
Antifungal of choice before knowing species

1.- I would wait for the full identification of the microorganism before starting any antifungal.

2.- Voriconazole.

3.- Fluconazole or a candin.

4.- Liposomal Amphotericin B.

5.- Posaconazole.
1. I would wait for the full identification of the microorganism before starting any antifungal.

2. Voriconazole.

3. Fluconazole or a candin.

4. Liposomal Amphotericin B.

5. Posaconazole.
# Targeted Treatment of Candidaemia Polyenes

<table>
<thead>
<tr>
<th>Compound</th>
<th>So</th>
<th>Qo</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B, lipid complex</td>
<td>C</td>
<td>II&lt;sub&gt;a&lt;/sub&gt;</td>
<td>Anaissie ICAAC 1995 Ito CID 2005</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B, colloidal dispersion</td>
<td>D</td>
<td>II&lt;sub&gt;u&lt;/sub&gt;</td>
<td>Noskin CID 1998</td>
<td>• Mostly immunocompromised patients (HCT, haem/onc or SOT) rather than ICU patients</td>
</tr>
</tbody>
</table>

HCT, haematopoietic stem cell transplantation; SOT, solid organ transplantation.
# Targeted Treatment of Candidaemia Echinocandins

<table>
<thead>
<tr>
<th>Compound</th>
<th>So</th>
<th>Qo</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anidulafungin 200/100</td>
<td>A</td>
<td>I</td>
<td>Reboli NEJM 2007</td>
<td>• Broad spectrum</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Resistance rare</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Fungicidal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Local epidemiology</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• C. parapsilosis, C. krusei</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Safety profile</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Less drug-drug interactions than caspofungin</td>
</tr>
<tr>
<td>Caspofungin 70/50</td>
<td>A</td>
<td>I</td>
<td>Mora-Duarte NEJM 2002</td>
<td>• Largely as above</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pappas CID 2007</td>
<td></td>
</tr>
<tr>
<td>Micafungin 100</td>
<td>A</td>
<td>I</td>
<td>Kuse Lancet 2007</td>
<td>• Largely as above</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pappas CID 2007</td>
<td>• Consider EMA warning label</td>
</tr>
</tbody>
</table>
## Targeted Treatment of Candidaemia Azoles

<table>
<thead>
<tr>
<th>Compound</th>
<th>So</th>
<th>Qo</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>C</td>
<td>I</td>
<td>Anaissie CID 1996 Rex NEJM 1994 Rex CID 2003 Philips EJCMID 1995</td>
<td>• Limited spectrum&lt;br&gt;• Inferiority to anidulafungin (especially in the subgroup with high APACHE scores),&lt;br&gt;• <em>C. parapsilosis</em></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>D</td>
<td>IIa</td>
<td>Tuil CCM 2003 (abstract)</td>
<td></td>
</tr>
<tr>
<td>Posaconazole</td>
<td>D</td>
<td>III</td>
<td>No reference found</td>
<td>• PO only</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>B</td>
<td>I</td>
<td>Kullberg Lancet 2005 Ostrosky EJCMID 2003 Perfect CID 2003</td>
<td>• Limited spectrum compared to echinocandins&lt;br&gt;• Drug-drug interactions&lt;br&gt;• IV in renal impairment&lt;br&gt;• Need for TDM</td>
</tr>
</tbody>
</table>

TDM, Therapeutic drug monitoring.
Please, choose the right answer among the following statements:
Candida and resistance

1.- *Candida glabrata* is frequently resistant to fluconazole.

2.- *Candida krusei* is always resistant to fluconazole.

3.- *Candida parapsilosis* is associated to catheter infection.

4.- *Candida albicans* is usually susceptible to fluconazole.

5.- All of the above are correct.
Candida and resistance

1.- *Candida glabrata* is frequently resistant to fluconazole.

2.- *Candida krusei* is always resistant to fluconazole.

3.- *Candida parapsilosis* is associated to catheter infection.

4.- *Candida albicans* is usually susceptible to fluconazole.

5.- All of the above are correct.
<table>
<thead>
<tr>
<th>Species</th>
<th>AMB</th>
<th>FLU</th>
<th>FLC</th>
<th>ITC</th>
<th>VRC</th>
<th>POS</th>
<th>EQUIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida albicans</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Candida parapsilosis</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S-I</td>
</tr>
<tr>
<td>Candida tropicalis</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>S</td>
<td>S</td>
<td>I-R</td>
<td>S-I-R*</td>
<td>S-I-R*</td>
<td>S-I-R*</td>
<td></td>
</tr>
<tr>
<td>Candida krusei</td>
<td>S</td>
<td>R</td>
<td>R</td>
<td>S-I-R**</td>
<td>S-I-R**</td>
<td>S-I-R**</td>
<td>S</td>
</tr>
<tr>
<td>Candida guilliermondii</td>
<td>S</td>
<td>S</td>
<td>I-R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S-I</td>
</tr>
<tr>
<td>Candida lusitaniae</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Cryptococcus spp.</td>
<td>S</td>
<td>S-I</td>
<td>S-I-R**</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
</tr>
</tbody>
</table>
Microbiology informs you that there are yeasts in the Gram stain of a blood culture.
Yeast reported in blood cultures

1. You start antifungal treatment immediately.

2. You wait to see in how many bottles they grow.

3. You wait to see the final microbiological identification.

4. You remove the catheters and take new blood cultures.

5. You request a cryptococcal serology.
Yeasts reported in blood cultures

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4. You remove the catheters and take new blood cultures.

5. You request a cryptococcal serology.
Emerging opportunistic yeast infections.

Miceli et al. Lancet Infect Dis 2011

- **Trichosporon**
  - 2º cause of fungemia in oncohematology (after Candida spp)
  - *T. asahii, T.asteroides, T.cutaneum, T.inkin, T. mucoides, T.ovoides (T. beigeli)*
  - Leukemia, AIDS, burn, valvulopathy
  - **Resistance** to Anfot-B and echinocandins

- **Rhodotorula**
  - Cryptococccaceae. Asia-Pacific
  - Catheter-related sepsis, endocarditis
  - HIV, BMT, Abdominal surgery, cirrhosis, burns, autoimmune disease

- **Cryptococcus neoformans**
  - HIV, cancer and transplant

- **Geotrichum, Hansenula, Malassezia and Saccharomyces**
  - Severe immunosuppressed
Any number of BC, obtained from a peripheral vein, with *Candida* is significant.

Preliminary data: In patients with CVC 3/3 + BC suggest a CRC.
Impact on mortality of early antifungal therapy

158 candidemic patients
In-hospital mortality: 31.8%

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted odds ratio</th>
<th>95% Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II score (one-point increments)</td>
<td>1.24</td>
<td>1.18–1.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior antibiotic treatment</td>
<td>4.05</td>
<td>2.14–7.65</td>
<td>0.028</td>
</tr>
<tr>
<td>Delay in antifungal treatment</td>
<td>2.09</td>
<td>1.53–2.84</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Importancia del tratamiento precoz en la UCI

![Graph showing mortality rates]

- All patients
  - Delay: 33.1%
  - No delay: 11.1%

Morrell M et al. Antimicrob Agents Chemother 2005
How can I optimize antifungal therapy in critically ill patients?

- Early therapy
- Appropriate antifungal agent
- Adequate dosing
- Interventions on the source
  - Catheter withdrawal
  - Surgical drainage
Candidemia: just the beginning

- Disseminated candidiasis?
- Catheter related candidemia?
- Candidemia from other origin?
- Transient candidemia?

© by author
Treatment related mortality risk

1. Retention of CVC
2. Inadequate initial fluconazole dose
3. Therapy delayed > 48 hrs

Impact of catheter withdrawal

- Conflicting effect on mortality (Almirante 05, Kuse 08)
- In others, difference disappears when adjusted to severity
- Raad
  - Impact only in CRC and when done early (<72h)

Raad. CID 2004
Catheter removal in studies of micafungin

- Catheter removal by 24 or 48 hours after treatment initiation had no effect on:
  - Overall treatment success
  - Mortality
  - Mycological eradication

- Possible effect of removal after 48 hours was not assessed.

Kaplan–Meier plots of time to mycological eradication by catheter removal status: CVC24 (top) and CVC48 (bottom).

Nucci. CID 2010
6. Microbiology informs you that yeast have been seen in the blood culture.
   a) You start antifungal drugs immediately
   b) You wait till knowing how many bottles are positive
   c) You wait till knowing what is cultured
   d) You remove the catheters and order new blood cultures
   e) You order Crypto serology

30% wait!!!
In a CR-Candidemia if you try to keep the line. What is your opinion regarding the present and future of lock therapy in patients with Candidemia related to the catheter?
Lock-therapy with antifungal agents

1. I don’t use Amphotericin B for locks
2. I don’t trust azoles for lock therapy
3. I prefer candins for lock therapy
4. Experimental models suggest that Micafungin is going to be the choice candin for lock therapy
5. Lock therapy with anti-fungals is not established yet and should be considered in research phase
Lock-therapy with antifungal agents

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3. I prefer candins for lock therapy
4. Experimental models suggest that Micafungin is going to be the choice candin for lock therapy
5. Lock therapy with anti-fungals is not established yet and should be considered in research phase
Catheter removal is recommended for CRBSI due to S. aureus and Candida species, instead of treatment with antibiotic lock and catheter retention, unless there are unusual extenuating circumstances (e.g., no alternative catheter insertion site).

Mermel L. C.I.D. 2009
Lock-therapy for Candida

In vitro effectiveness of antifungal lock solutions on catheters infected with *Candida* species

In vitro antibiotic Lock-Model
Infected catheters *C. albicans* and *C. parapsilosis*
AmphoB, Caspo, Fluco, Itra, Vori.
300, 500, 1000 fold MIC
1, 3, 5, 7 days

Oncu S. J.Infect.Chemother. 2011
Lock for Candida

*C. albicans*

*C. parapsilosis*

**Ampho B**
Lock for Candida

C. albicans

C. parapsilosis

Caspofungin
Lock for Candida

C. albicans

C. parapsilosis

Fluconazole
Lock for Candida

\[ C. \text{ albicans} \quad \text{and} \quad C. \text{ parapsilosis} \]

Itraconazole

Oncu S. J. Infect. Chemother. 2011
Lock for Candida

C. albicans

C. parapsilosis

Voriconazole
How long would you treat patients with Catheter-Related candidemia?
How long would you treat?

1. For 2 weeks after first positive blood cultures

2. For 2 weeks after the first negative follow up blood cultures

3. For 2 weeks after negative BC's but with a long-term follow up

4. For 4-6 weeks if TEE is not available or if retinal lesions were present and with a long term follow up

5. I don't have an opinion on this point
How long would you treat?

1.- For 2 weeks after first positive blood cultures

2.- For 2 weeks after the first negative follow up blood cultures

3.- For 2 weeks after negative BC's but with a long-term follow up

4.- For 4-6 weeks if TEE is not available or if retinal lesions were present and with a long term follow up

5.- I don't have an opinion on this point
Choose an echinocandin for moderately severe to severe illness and for patients with recent azole exposure. Transition to fluconazole after initial echinocandin is appropriate in many cases. Remove all intravascular catheters, if possible. Treat 14 days after first negative blood culture result and resolution of signs and symptoms associated with candidemia. Ophthalmological examination recommended for all patients.
What is your attitude in patients with catheter tips colonized with Candida, without concomitant fungemia?
Candida Colonized Catheters (CCC)

1.- I do not prescribe antifungals on the basis of Candida colonization of the catheter tips and do not perform follow-up BC's.

2.- I do not prescribe antifungals on the basis of Candida colonization of the catheter tips but carefully follow-up BC's.

3.- I treat the patient as if BC's were positive.

4.- I treat the patients with antifungals until follow-up cultures return negative.

5.- I never saw a patient in that situation.
Candida Colonized Catheters (CCC)

1.- I do not prescribe antifungals on the basis of Candida colonization of the catheter tips and do not perform follow-up BC’s.

2.- I do not prescribe antifungals on the basis of Candida colonization of the catheter tips but carefully follow-up BC’s.

3.- I treat the patient as if BC’s were positive.

4.- I treat the patients with antifungals until follow-up cultures return negative.

5.- I never saw a patient in that situation.
Is *Candida* colonization of central vascular catheters in non-candidemic, non-neutropenic patients an indication for antifungals?

We were unable to demonstrate that antifungal therapy was an independent variable influencing outcome (OR 0.82; 95% CI, 0.27–2.47; P = 0.73). Conclusions: Our data suggest that, in non-neutropenic critically ill patients with no concomitant candidemia and with CVC tips colonized by *Candida*, antifungal therapy does not seem to have a significant influence on clinical outcome.

Pérez-Parra A, Bouza E. Intensive Care Med. 2009
Candida colonization of the CVC tip

Hospital: 1,750 beds
Adult ICU’s: 60 beds
February 2003 to February 2007

Patients with Candida in the CVC tip
Blood cultures without candidemia

Clinical improvement
Poor outcome

Pérez-Parra A, Bouza E. Intensive Care Med. 2009
During the follow-up of candidemic patients, it is advised to:
Follow-up of candidemic patients

1.- Get blood cultures after 3-7 days of antifungal treatment.

2.- Exclude infective endocarditis by transesophageal echocardiography.

3.- Consider sequential treatment switching to an oral azole.

4.- Perform an eye fundus examination.

5.- All of the above are true.
Follow-up of candidemic patients

1. Get blood cultures after 3-7 days of antifungal treatment.

2. Exclude infective endocarditis by transesophageal echocardiography.

3. Consider sequential treatment switching to an oral azole.

4. Perform an eye fundus examination.

5. All of the above are true.
Treatment of Candidaemia in Non-Neutropenic Patients: IDSA Guidelines

Treatment recommendations:
- Fluconazole or an echinocandin
- Choose an echinocandin for patients with moderately severe to severe illness or with recent azole exposure

The recommended duration of therapy for candidemia without obvious metastatic complications is for 2 weeks after documented clearance of Candida from the bloodstream and resolution of symptoms attributable to candidemia (A-III).

Should we do an echocardiogram in all candidemias?

<table>
<thead>
<tr>
<th>Microbiological Alerts</th>
<th>Nº patients</th>
<th>Echocardi done</th>
<th>TEE</th>
<th>IE</th>
<th>Yield TEE in IE episodes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>317</td>
<td>227 (72%)</td>
<td>126 (55%)</td>
<td>23 (7%)</td>
<td>23/126 (18%)</td>
</tr>
<tr>
<td>C.N.S.</td>
<td>347</td>
<td>136 (39%)</td>
<td>48 (35%)</td>
<td>7 (2%)</td>
<td>7/48 (14%)</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>215</td>
<td>139 (64%)</td>
<td>65 (47%)</td>
<td>14 (6%)</td>
<td>14/65 (21%)</td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td>122</td>
<td>89 (70%)</td>
<td>39 (45%)</td>
<td>10 (8%)</td>
<td>10/39 (25%)</td>
</tr>
<tr>
<td>Candida spp.</td>
<td>103</td>
<td>71 (69%)</td>
<td>33 (46%)</td>
<td>7 (7%)</td>
<td>7/33 (21%)</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
<td>8 (47%)</td>
<td>3 (37%)</td>
<td>3 (17%)</td>
<td>3/3 (100%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1121</td>
<td>667 (59%)</td>
<td>314 (47%)</td>
<td>64 (6%)</td>
<td>64/314 (20%)</td>
</tr>
</tbody>
</table>

**Candida Endocarditis:**

Yield of Echocardiogram in Patients with Candidemia


Hospital General Universitario Gregorio Marañón-REIPI, Madrid, Spain
Candida ENDOPHTHALMITIS

- All patients with candidemia should have at least 1 dilated retinal examination (A-II).
- AmB-d + 5-F for advancing lesions or lesions threatening the macula (A-III)
- Fluco less severe endophthalmitis (B-III)
- Rescue: LFAmB, voriconazole, or an echinocandin

<table>
<thead>
<tr>
<th></th>
<th>Brain (µg/g)</th>
<th>CSF (µg/ml)</th>
<th>Choroid (µg/ml)</th>
<th>Vitreous humor (µg/ml)</th>
<th>Aqueous humor (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.08 ± 0.01</td>
<td>ND</td>
<td>0.012 ± 0.014</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>0.10 ± 0.00</td>
<td>ND</td>
<td>0.061 ± 0.039</td>
<td>0.015 ± 0.025</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>0.18 ± 0.02</td>
<td>ND</td>
<td>0.162 ± 0.096</td>
<td>0.034 ± 0.032</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Groll AH et al. AAC. 2001; 45: 3322-3327
Management of Invasive Candidiasis in the Intensive Care Unit

E. Geoffrey Playford,¹² Jeff Lipman³⁴ and Tania C. Sorrell⁵⁶

- **Initial:** IV. Correct doses

- **Evolution**
  - Consider origin and septic metastases
  - Evaluate response and confirm negative BC (only 68%)
    - If no response consider:
      - Resistance
      - Persistence or development intravascular or deep focus (Eyes exam only 36% in ICU pts- 13% +)
      - No control of source (Cath removed in 80%)

- **De-escalate if susceptible strain and patient stable**

Drugs 2010; 70 (7): 823-839; Marriott DJ Critical Care 2009
## DRUGS for Invasive candidiasis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical situation</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echinocandin</strong></td>
<td>Before <em>Candida</em> species is known</td>
<td>AI</td>
</tr>
<tr>
<td><strong>(anidula, caspo or mica)</strong></td>
<td>Moderate or severely ill</td>
<td>AIII</td>
</tr>
<tr>
<td></td>
<td>Previous therapy with azoles</td>
<td>AIII</td>
</tr>
<tr>
<td></td>
<td><em>C. glabrata</em> infection</td>
<td>BIII</td>
</tr>
<tr>
<td><strong>Fluconazole</strong></td>
<td>Before <em>Candida</em> species is known</td>
<td>AI</td>
</tr>
<tr>
<td></td>
<td>Clinically stable patient</td>
<td>AIII</td>
</tr>
<tr>
<td></td>
<td><em>C. parapsilosis</em> infection</td>
<td>BIII</td>
</tr>
<tr>
<td></td>
<td><strong>Sequential therapy in stable patients</strong></td>
<td>AIII</td>
</tr>
<tr>
<td><strong>AMB</strong></td>
<td>Alternative to fluconazole in areas of scarce resources</td>
<td>AI</td>
</tr>
<tr>
<td><strong>Voriconazole</strong></td>
<td><em>C. krusei</em> infection</td>
<td>BIII</td>
</tr>
<tr>
<td></td>
<td><strong>Sequential therapy in stable patients</strong></td>
<td>AIII</td>
</tr>
</tbody>
</table>

*IDSA Guidelines 2008: candidemia in non-neutropenic patient*
When you are informed of the isolation of Candida in a urine sample of one of your patients, you......
In patients with Candiduria you...

1. Start antifungal treatment in all cases.

2. Start antifungal treatment if the colony count is $>10^4$ cfu/ml.

3. Start antifungal treatment if the colony count is $>10^5$ cfu/ml.

4. Start antifungal treatment if the patient has an indwelling bladder catheter.

5. Start antifungal treatment only in some cases.
In patients with Candiduria you...

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2. Start antifungal treatment if the colony count is $>10^4$ cfu/ml.

3. Start antifungal treatment if the colony count is $>10^5$ cfu/ml.

4. Start antifungal treatment if the patient has an indwelling bladder catheter.

5. Start antifungal treatment only in some cases.
Candida in different samples
Candiduria: classify your patient

- Systemic candidosis
  - 90% renal involvement
- Peritoneal candidosis
- Pyelonephritis
- Cystitis
- Colonization
  - IBC

Hematogenous

Ascending

Candiduria in non-critical pts

Most probably: colonized
- 6.5-20% hospitalized patients
- Risk factors: IBC, antibiotics, age
- Therapy has no impact: eliminate predisposing factors
- Exceptions: FLU, AMB:
  - Obstructive uropathy, UT manipulation
  - Kidney Tx, low birth weight born, neutropenics?
- 10% candidemias (structural abnormalities)

Nassoura. J Trauma 93
Ang BS. CID 93
Sobel JD. CID 2000;30:19
Image the kidneys to exclude “fungus balls”
Abscess and urologic abnormalities
Guidelines

- **Cystitis**
  - FLU-S: Flu 200 mg/d 2 wks (A-III)
  - FLU-R: AMB-d 0.3-0.6 mg/k/d 1-7 d or 5F 25 mg/kg/6h 7-10 d (B-III)

- **Pyelonephritis**
  - FLU-S: Flu 200-400mg/d 2 wks ±5F (B-III)
  - FLU-R: AMB-d 0.3-0.6 mg/k/d 1-7 d or 5F 25 mg/kg/6h 7-10 d (B-III)

- **Fungus ball**
  - Surgery in nonneonates (BIII). FLU or AMB±5F (B-III) or irrigation with AmB-d 50 mg/L until symptoms resolve and culture negative
Candiduria in critical patients

- Never ignore candiduria in a septic patient
  - Blood cultures
  - Ultrasonogram
  - Eye exam
- Possible marker of invasive candidiasis

Sobel JD. CID 2000;30:19
Lundstrom T. CID 2001; 32:1602
Candida colonization in ICU

- Mouth: 63%
- IV catheters: ?
- Gut: 11%
- Urine: 25%
Anatomic site of Candida colonization and IC

- 182 SICU patients
- 2851 surveillance fungal cultures (urine, oropharynx, tracheal and gastric aspirates, and rectum or ostomy drainage)
- Statistically significant differences in:
  - Urine: (13.2% vs 2.8%, p = 0.02),
  - Respiratory samples (8.0% vs 1.2%, p = 0.04)
  - Rectum/Ostomy (8.4% vs 0%, p = 0.01)
- Patients with negative rectum/ostomy cultures and patients with both negative urine and respiratory tract cultures did not develop IC.

Regarding therapy with azoles and candins, which of the following statement is true?
Regarding azoles and candins?

1.- Candins can be used as empirical treatment before knowing the antifungal susceptibility of yeasts.

2.- Voriconazole is used to treat infections due to fluconazole-resistant Candida and is preferred to a candin.

3.- Voriconazole does not have significant interactions with other drugs so it is preferred to a candin.

4.- Candins are superior to fluconazole in the treatment of candidemia due to fluconazole-susceptible species.

5.- Posaconazole is the first choice treatment for fluconazole-resistant Candida.
Empirical Therapy in Non-Neutropenic Patients: IDSA Guidelines

- **Patients who will benefit:**
  - Critically ill patients with risk factors for invasive candidiasis and no known cause of fever

- **Treatment recommendations:**
  - Consider host and local epidemiology
  - Echinocandins preferred in:
    - haemodynamically unstable patients
    - patients previously exposed to an azole
    - patients colonized with azole-R species
  - If fluconazole is used: 12 mg/kg

Pappas PG et al. *Clin Infect Dis* 2009; *Curr Opin Crit Care* 2010; 16; *Playford Drugs* 2010
# DRUGS for Invasive candidiasis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical situation</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echinocandin</strong></td>
<td>Before <em>Candida</em> species is known</td>
<td>AI</td>
</tr>
<tr>
<td>(anidula, caspo or mica)</td>
<td>Moderate or severely ill</td>
<td>AIII</td>
</tr>
<tr>
<td></td>
<td>Previous therapy with azoles</td>
<td>AIII</td>
</tr>
<tr>
<td></td>
<td><em>C. glabrata</em> infection</td>
<td>BIll</td>
</tr>
<tr>
<td><strong>Fluconazole</strong></td>
<td>Before <em>Candida</em> species is known</td>
<td>AI</td>
</tr>
<tr>
<td></td>
<td>Clinically stable patient</td>
<td>AIII</td>
</tr>
<tr>
<td></td>
<td><em>C. parapsilosis</em> infection</td>
<td>BIll</td>
</tr>
<tr>
<td></td>
<td>Sequential therapy in stable patients</td>
<td>AIII</td>
</tr>
<tr>
<td><strong>AMB</strong></td>
<td>Alternative to fluconazole in areas of scarce resources</td>
<td>AI</td>
</tr>
<tr>
<td><strong>Voriconazole</strong></td>
<td><em>C. krusei</em> infection</td>
<td>BIll</td>
</tr>
<tr>
<td></td>
<td>Sequential therapy in stable patients</td>
<td>AIII</td>
</tr>
</tbody>
</table>

IDLSA Guidelines 2008: candidemia in non-neutropenic patient
## Interactions and dose adjustment

<table>
<thead>
<tr>
<th>Fluconazole</th>
<th>Caspo</th>
<th>Anidula</th>
<th>Micafungin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interactions</strong></td>
<td>Benzodiazepines, opioids, calcium antagonists, rifampin, cimetidine, tolbutamide, warfarin, phenytoin, cyclosporin A, tacrolimus .....</td>
<td>Cyclosporin A, tacrolimus, rifampin, efavirenz, phenytoin, dexamethasone, carbamazepine</td>
<td>No</td>
</tr>
<tr>
<td><strong>Dose adjustment</strong></td>
<td>Renal and liver insufficiency</td>
<td>Liver insufficiency</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Antifungals: Metabolism and Drug Interactions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Amphotericin B formulations</th>
<th>Itraconazole</th>
<th>Fluconazole</th>
<th>Voriconazole</th>
<th>Caspofungin</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP substrate</td>
<td>No</td>
<td>3A4</td>
<td>3A4</td>
<td>2C19</td>
<td>No</td>
</tr>
<tr>
<td>CYP inhibited</td>
<td>No</td>
<td>3A4, ↑serum conc.</td>
<td>2C9/3A4, ↑serum conc.</td>
<td>2C9/3A4, ↑serum conc.</td>
<td>No</td>
</tr>
<tr>
<td>CYP inducers</td>
<td>No effect</td>
<td>↓serum conc.</td>
<td>↓serum conc.</td>
<td>↓serum conc.</td>
<td>No</td>
</tr>
<tr>
<td>CsA metabolism</td>
<td>No inhibition</td>
<td>↑CsA exposure</td>
<td>↑ CsA exposure doses &gt;200 mg</td>
<td>↑ CsA exposure 1.7x</td>
<td>CsA exposure 35%</td>
</tr>
<tr>
<td>Tacrolimus metabolism</td>
<td>No inhibition</td>
<td>↑Tacrolimus exposure</td>
<td>↑ Tacrolimus exposure at higher doses</td>
<td>↑ Tacrolimus trough 10x</td>
<td>Tacrolimus exposure 20%</td>
</tr>
<tr>
<td>PK</td>
<td>Linear</td>
<td>Non-Linear</td>
<td>Linear</td>
<td>Non-linear</td>
<td>Linear</td>
</tr>
</tbody>
</table>

**Note:**
- **↑** denotes increase.
- **↓** denotes decrease.
- **CsA** refers to Cyclosporine A.
- **Tacrolimus** refers to Tacrolimus.
Cytochrome P450 (CYP) 2C19 and CYP3A4 are the major enzymes responsible for voriconazole elimination.

<table>
<thead>
<tr>
<th>Type of interaction, drug</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreases voriconazole levels</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Long-acting barbiturates</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Levels increased by voriconazole</td>
<td></td>
</tr>
<tr>
<td>Azole antifungals, salicylates</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Ergot alkaloids</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Monitor prothrombin time</td>
</tr>
<tr>
<td>Decreases voriconazole levels and increases other drug levels</td>
<td></td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Double voriconazole dosage and monitor for increased phenytoin levels</td>
</tr>
<tr>
<td>Levels likely increased by voriconazole: sulfonylureas, statins, vinca alkaloids, calcium channel blockers, benzodiazepines</td>
<td>Monitor effects of drug and consider decreasing dosage when voriconazole is added</td>
</tr>
</tbody>
</table>
### Comparative studies in candidemia

<table>
<thead>
<tr>
<th>Design</th>
<th>Endpoint</th>
<th>Success</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rex 94</td>
<td>F vs AMB</td>
<td>Wk 12</td>
<td>70% vs 79%</td>
</tr>
<tr>
<td>Rex 03</td>
<td>F vs AMB+F</td>
<td>Wk 12</td>
<td>56% vs 69%</td>
</tr>
<tr>
<td>Tuil 03</td>
<td>F vs Itra</td>
<td>Wk 12</td>
<td>41% vs 35%</td>
</tr>
<tr>
<td>Kullberg 05</td>
<td>V vs AMB/F</td>
<td>End IV Tx</td>
<td>70% vs 74%</td>
</tr>
<tr>
<td>Mora 02</td>
<td>Cas vs AMB</td>
<td>End IV Tx</td>
<td>73% vs 62%</td>
</tr>
<tr>
<td>Reboli 07</td>
<td>Ani vs F</td>
<td>End IV Tx</td>
<td>75% vs 60%</td>
</tr>
<tr>
<td>Kuse 07</td>
<td>Mic vs AMB-L</td>
<td>End IV Tx</td>
<td>89% vs 89%</td>
</tr>
<tr>
<td>Pappas 07</td>
<td>Mica vs Cas</td>
<td>End IV Tx</td>
<td>76% vs 72%</td>
</tr>
</tbody>
</table>
In which of the following scenarios would you choose Amphotericin B as your first choice?
When is Amphotericin B the first choice?

1. In the empirical treatment of candidemia.

2. In a proven invasive aspergillosis.

3. In an unspecified invasive filamentous fungal infection.

4. In patients intolerant to fluconazole.

5. In infections due to fluconazole resistant Candida.
When is Amphotericin B the first choice?

1. In the empirical treatment of candidemia.

2. In a proven invasive aspergillosis.

3. In an unspecified invasive filamentous fungal infection.

4. In patients intolerant to fluconazole.

5. In infections due to fluconazole-resistant Candida.
Clinical indications of AMB

- Invasive candidiasis fluconazole resistant
  - Alternative to echinocandins
  - Neutropenic patients (first line)
- Severe cryptococcosis (plus flucytosine)
- Endemic mycoses (severe or IC)
  - Histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis,
- Aspergillosis, zygomycosis and other emerging mycoses
- Febrile neutropenia
In which of the following clinical scenarios would you start anti-Candida prophylaxis?
Prophylaxis anti Invasive Candidiasis

1.- In an ICU patient colonized by Candida.

2.- In an ICU patient not colonized by Candida but having an indwelling bladder catheter, a central venous catheter and recent surgery.

3.- In Liver transplant recipients.

4.- In Acute Myeloid Leukemia patients on induction chemotherapy.

5.- In all of the above circumstances.
## Treatment strategies

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>High-risk patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No signs of infection yet</td>
</tr>
</tbody>
</table>

| Preemptive        | Colonized and fungal blood marker or with high scores |

<table>
<thead>
<tr>
<th>Empiric Tx</th>
<th>Signs of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No etiologic diagnosis yet</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Guided therapy</th>
<th>Demonstrated Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Etiologic confirmation</td>
</tr>
</tbody>
</table>
Fungal infections in Spanish ICUs. Antifungal therapy

1,655 pts 409 treated  
21 %

EPCAN. IC: 5.5%

72 %

7 %

1,107 pts 224 treated  
22 %

CAVA-I. IC: 5.2%

76 %

2 %

Dr. Cristobal León
PROPHYLAXIS

- Allogeneic transplantation A-I
- Burned patients
- Complicated surgical patients
  - Liver or pancreas transplantation
- ICU patients?
  - Groups with >10% incidence
Recommendations for Prophylaxis in IDSA Guidelines

- **Solid-organ transplant recipients**
  - Post-operative prophylaxis with fluconazole 200–400 mg/day or LAmB 1–2 mg/day for at least 7–14 days (A-I – B-III, depending on transplant type)

- **ICU patients**
  - In high-risk patients in adult units with a high incidence of invasive candidiasis, use fluconazole 400 mg/day (B-I)

- **Chemotherapy-induced neutropenia**
  - Fluconazole 400 mg/day (A-I), posaconazole 200 mg 3 times daily (A-I) or caspofungin 50 mg/day (B-II) during induction chemotherapy for the duration of neutropenia

- **Stem cell transplant recipients with neutropenia**
  - Fluconazole 400 mg/day, posaconazole 200 mg 3 times daily or micafungin 50 mg/day during the period of risk of neutropenia (A-I)

322 neonates < 1500 g: placebo or flu 3 or 6 mg/Kg till + 30

Weekly cultures

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>3 mg/kg</th>
<th>6 mg/Kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonization</td>
<td>29.2</td>
<td>9.8%</td>
<td>7.7%</td>
</tr>
<tr>
<td>IC</td>
<td>13.2%</td>
<td>3.8%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Death /RD</td>
<td>9.4% / 2%</td>
<td>8% / 0%</td>
<td>8% / 0%</td>
</tr>
</tbody>
</table>

NNT 8
(5 if< 1 kg)
Fluconazole prophylaxis in critically ill surgical patients: A meta-analysis*

Andrew F. Shorr, MD, MPH; Kevin Chung, MD; William L. Jackson, MD; Paige E. Waterman, MD; Marin H. Kollef, MD


![Mortality Diagram](image)
Patients with recent abdominal surgery AND recurrent gastrointestinal perforations or anastomotic leakages either suspected or confirmed by surgery.

Posaconazole vs. Fluconazole or Itraconazole as Prophylaxis in Patients with Neutropenia

Cornely OA et al. NEJM 2007.
Posaconazole vs. Fluconazole as Prophylaxis in Patients with Severe Graft-Versus-Host Disease


*112 days or until protocol-specified end point;
†period from first dose of study drug to 7 days after last dose
Prophylaxis in HSCT Recipients: RCT of Micafungin vs. Fluconazole

<table>
<thead>
<tr>
<th>Treatment Success (%)</th>
<th>Micafungin</th>
<th>Fluconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>425</td>
<td>457</td>
</tr>
<tr>
<td>p</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>

*Absence of proven, probable, or suspected systemic fungal infection through the end of prophylaxis therapy and absence of a proven or probable systemic fungal infection through the end of the 4-week post-treatment period

Comparison of approved indications in Europe

<table>
<thead>
<tr>
<th>Indication</th>
<th>Micafungin&lt;sup&gt;1*&lt;/sup&gt;</th>
<th>Caspofungin&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Anidulafungin&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Invasive candidiasis</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes†</td>
</tr>
<tr>
<td>Neutropenic patients</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Pediatric patients</td>
<td>Yes†</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Neonates</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Prophylaxis in HSCT or high-risk neutropenia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Pediatric patients</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Neonates</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Esophageal candidiasis in adults</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Invasive aspergillosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rescue</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

†Anidulafungin has been evaluated mainly in pts with candidemia and only in a few patients with other forms of IC. Little experience with no albicans species.
Manuel Cuenca Estrella

In your opinion, the best choice for Candida prophylaxis is?
Best choice for Candida prophylaxis is?

1.- Fluconazole in most of the cases.

2.- Candins.

3.- Liposomal Amphotericin B.

4.- Voriconazole.

5.- None of the above.
Best choice for Candida prophylaxis is?

1. Fluconazole in most of the cases.
2. Candins.
3. Liposomal Amphotericin B.
4. Voriconazole.
5. None of the above.
# Prophylaxis: Which Agents?

<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 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 surgical patients with an expected length of ICU stay ≥ 3d</td>
<td>As above</td>
<td>Caspofungin 70/50mg/d</td>
<td>C</td>
<td>IIu</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 delay the time to fungal infection</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></td>
<td>To prevent invasive candidiasis / candidaemia</td>
<td>Fluconazole 100mg/d (in the context of SDD)</td>
<td>C</td>
<td>I</td>
<td>Garbino ICM 2002</td>
<td>Placebo, N=204</td>
</tr>
</tbody>
</table>