Advances in trials in candidemia

Claudio Viscoli
Professor of Infectious Disease, University of Genova, Italy
Foreword

- There is no new randomized clinical trial for candidemia, as far as I know.
- The isavuconazole registration trial for the indication «Candidemia» or «Invasive Candidiasis» has just been completed by Astellas and it is being analysed.
- I can only talk to you about past RCT, but I think that it’s an interesting story anyway.
Why doing RTC for candidemia?

International Conference for the Development of a Consensus on the Management and Prevention of Severe Candidal Infections

Conference Chairman:
John E. Edwards, Jr.*

Conference Participants:
Gerald P. Bodey, Raleigh A. Bowden, Thomas Büchner, Ben E. de Pauw, Scott G. Filler, Mahmoud A. Ghannoun, Michel Glauser, Raoul Herbrecht, Carol A. Kauffman, Shigeru Kohno, Pietro Martino, Françoise Meunier, Takeshi Mori, Michael A. Pfaller, John H. Rex, Thomas R. Rogers, Robert H. Rubin, Joseph Solomkin, Claudio Viscoli, Thomas J. Walsh, and Mary White
Should all candidemic patients (either neutropenic or nonneutropenic) be treated with an antifungal?

Figure 1. Responses to the question “Should all candidemic patients (nonneutropenic and neutropenic) be treated with an antifungal agent?” A total of 20 investigators attending the consensus conference on candidal infections voted.
Why all patients with positive blood culture for Candida should be treated?

- We cannot predict who should and who should not require treatment; no accurate diagnostic test or clinical prediction rule is available.
- The risk for long-term sequelae is significant.
- There are non-toxic therapeutic options.
Literature Search: candidemia, RCT
An history which started only 15 years ago

1. Rex JH et al, NEJM 1994
3. Anaissie EJ, ICAAC 1996 and never published in extenso
6. Rex JH et al, CID 2003
A RANDOMIZED TRIAL COMPARING FLUCONAZOLE WITH AMPHOTERICIN B FOR THE TREATMENT OF CANDIDEMIA IN PATIENTS WITHOUT NEUTROPENIA

Fluconazole vs. D-AmB for candidemia in non-neutropenic patients
(Rex et al. NEJM, 1994)

<table>
<thead>
<tr>
<th></th>
<th>Fluco (n° =103)</th>
<th>AmB (n° = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td>70%</td>
<td>79%</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>2%</td>
<td>37%</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>14%</td>
<td>10%</td>
</tr>
<tr>
<td>Death</td>
<td>34%</td>
<td>40%</td>
</tr>
<tr>
<td><em>C. albicans</em></td>
<td>70%</td>
<td>63%</td>
</tr>
</tbody>
</table>
Table 3. Distribution of Infecting Species.*

<table>
<thead>
<tr>
<th>Species</th>
<th>Amphoterin B (N = 103)</th>
<th>Fluconazole (N = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>62</td>
<td>70</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>C. krusei</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>C. lusitaniae</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>C. lipolytica</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Multiple species</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>
Literature Search: candidemia, RCT
An history which started only 15 years ago

1. Rex JH et al, NEJM 1994
3. Anaissie EJ, ICAAC 1996 and never published in extenso
6. Rex JH et al, CID 2003
Management of Invasive Candidal Infections: Results of a Prospective, Randomized, Multicenter Study of Fluconazole Versus Amphotericin B and Review of the Literature

Elias J. Anaissie, Rabih O. Darouiche, Dina Abi-Said, Omrum Uzun, Jorge Mera, Layne O. Gentry, Temple Williams, Dimitrios P. Kontoyiannis, Cynthia L. Karl, and Gerald P. Bodey

From the Department of Medical Specialties, Section of Infectious Diseases, The University of Texas M. D. Anderson Cancer Center; the Veterans Affairs Medical Center; the Methodist Hospital; and St. Luke’s Episcopal Hospital, Houston, Texas

Clinical Infectious Diseases 1996;23:964–72
Table 2. Outcome of primary therapy for documented or presumed invasive candidiasis, among the 142 patients deemed evaluable.

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Amphotericin B (n = 67)</th>
<th>Fluconazole (n = 75)</th>
<th>Pearson $\chi^2$ or other value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 48 hours*</td>
<td>23 (34)</td>
<td>19 (26)</td>
<td>1.26</td>
<td>.26</td>
</tr>
<tr>
<td>In 5 days†</td>
<td>29 (51)</td>
<td>33 (50)</td>
<td>0.00</td>
<td>.92</td>
</tr>
<tr>
<td>At end of therapy</td>
<td>44 (66)</td>
<td>48 (64)</td>
<td>0.04</td>
<td>.84</td>
</tr>
<tr>
<td>Median no. of days to defervescence (range)</td>
<td>5 (1–33)</td>
<td>5 (1–29)</td>
<td>0.02†</td>
<td>.89</td>
</tr>
<tr>
<td>Survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 48 hours</td>
<td>67 (100)</td>
<td>74 (99)</td>
<td>...§</td>
<td>1.00</td>
</tr>
<tr>
<td>In 5 days‖</td>
<td>60 (91)</td>
<td>67 (93)</td>
<td>0.22</td>
<td>.64</td>
</tr>
<tr>
<td>At end of therapy</td>
<td>58 (87)</td>
<td>66 (88)</td>
<td>0.07</td>
<td>.80</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candidias</td>
<td>4 (6)</td>
<td>2 (3)</td>
<td>...§</td>
<td>.42</td>
</tr>
<tr>
<td>Other</td>
<td>5 (7)</td>
<td>7 (9)</td>
<td>0.16</td>
<td>.69</td>
</tr>
</tbody>
</table>

«Suspected» candidemias included
Literature Search: candidemia, RCT

1. Rex JH et al, NEJM 1994
3. Anaissie EJ, ICAAC 1996 and never published in extenso
6. Rex JH et al, CID 2003
ABLC vs. AmB in invasive candidiasis: the “phantom study”

<table>
<thead>
<tr>
<th>Response to treat</th>
<th>ABLC</th>
<th>AmB</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>81/124 (65%)</td>
<td>43/70 (61%)</td>
<td>0.642</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematol. malign.</td>
<td>14/28 (50%)</td>
<td>2/12 (17%)</td>
<td>0.079</td>
</tr>
<tr>
<td>Solid tumor</td>
<td>24/32 (75%)</td>
<td>17/25 (68%)</td>
<td>0.570</td>
</tr>
<tr>
<td>Major surgery</td>
<td>16/21 (76%)</td>
<td>7/10 (70%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Other</td>
<td>27/43 (63%)</td>
<td>17/23 (74%)</td>
<td>0.421</td>
</tr>
</tbody>
</table>

Anaissie EJ, et al. 35th ICAAC 1995 San Francisco
Literature Search: candidemia, RCT

1. Rex JH et al, NEJM 1994
3. Anaissie EJ, ICAAC 1996 and never published in extenso
6. Rex JH et al, CID 2003
Multicenter Randomized Trial of Fluconazole versus Amphotericin B for Treatment of Candidemia in Non-Neutropenic Patients

P. Phillips1, S. Shafran2, G. Garber3, C. Rotstein4, F. Smaill5, I. Fong6, I. Salit7, M. Miller8, K. Williams9, J.M. Conly9,10, J. Singer11, S. Ioannou12, for the Canadian Candidemia Study Group
<table>
<thead>
<tr>
<th>Organism</th>
<th>Fluconazole (n = 50)</th>
<th>Amphotericin B (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida albicans</td>
<td>40 (80)</td>
<td>33 (62)</td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>6 (12)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Candida parapsilosis</td>
<td>3 (6)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Candida tropicalis</td>
<td>0</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Candida guilliermondii</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>C. albicans &amp; C. glabrata</td>
<td>1 (2)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Saccharomyces or Rhodotorula</td>
<td>0</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>
### Table 5: Patient outcomes.

<table>
<thead>
<tr>
<th></th>
<th>Fluconazole group</th>
<th>Amphotericin B group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intention-to-treat analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total patients</td>
<td>50 (100)</td>
<td>53 (100)</td>
<td>0.39 (one-sided 95% CI, 8 ± 16.1%)</td>
</tr>
<tr>
<td>Successful treatment</td>
<td>25 (50)</td>
<td>31 (58)</td>
<td></td>
</tr>
<tr>
<td><strong>Efficacy evaluable</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total patients</td>
<td>42 (100)</td>
<td>42 (100)</td>
<td>0.66 (one-sided 95% CI, 5 ± 17.6%)</td>
</tr>
<tr>
<td>Successful treatment</td>
<td>24 (57)</td>
<td>26 (62)</td>
<td></td>
</tr>
<tr>
<td><strong>Mortality of intention-to-treat patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>7 (14)</td>
<td>5 (9)</td>
<td>0.68*</td>
</tr>
<tr>
<td>Day 14</td>
<td>13 (26)</td>
<td>11 (21)</td>
<td>0.69</td>
</tr>
<tr>
<td>Day 28</td>
<td>17 (34)</td>
<td>14 (26)</td>
<td>0.53</td>
</tr>
<tr>
<td>Day 60</td>
<td>19 (38)</td>
<td>18 (34)</td>
<td>0.82</td>
</tr>
<tr>
<td>Day 180</td>
<td>23 (46)</td>
<td>23 (43)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

* Chi-square test.
The situation at the end of the XX century

- Fluconazole 400 (w/out loading dose) drug of choice, despite concerns about its fungistatic activity and limited spectrum
- D-AmB more (too?) toxic, despite the relatively low dose (usually 0.6 mg/Kg/day)
- Lipid formulations not studied (company not interested)
- Combination fluco/AmB not studied because of concerns of in vitro antagonism
- C. albicans prevalent
- Response rates around 50-60% and mortality 30-40%
Literature Search: candidemia, RCT

1. Rex JH et al, NEJM 1994
3. Anaissie EJ, ICAAC 1996 and never published in extenso
6. Rex JH et al, CID 2003
COMPARISON OF CASPOFUNGIN AND AMPHOTERICIN B FOR INVASIVE CANDIDIASIS

Jorge Mora-Duarte, M.D., Robert Betts, M.D., Coleman Rotstein, M.D., Arnaldo Lopes Colombo, M.D., Luis Thompson-Moya, M.D., Juanita Smietana, B.S., Robert Lupinacci, M.S., Carole Sable, M.D., Nicholas Kartsonis, M.D., and John Perfect, M.D., for the Caspofungin Invasive Candidiasis Study Group*

Overall mortality 34% caspo vs 38% D-AmB
Caspofungin in candidiasis  
Efficacy Evaluation  

- **Main endpoint:** Favorable Overall Response at EOT  
  - Favorable Clinical Response: Complete resolution of signs and symptoms attributable to *Candida*,  
    - **AND**  
  - Favorable microbiological response: *Candida* eradication or presumptive eradication  
  - **Definition of non-inferiority:** 95.6% CI for the difference between the groups with respect to the proportion of patients with a favorable overall response to include 0 and the lower limit of the CI was above -20%
Caspofungin vs deoxycholate

AmB: all patients

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Caspofungin 70/50 mg</th>
<th>Amphotericin B 0.6-1.0 mg/kg</th>
<th>Estimated Difference Adjusted for Strata</th>
</tr>
</thead>
<tbody>
<tr>
<td>MITT (n=224)</td>
<td>80/109 (73.4)</td>
<td>71/115 (61.7)</td>
<td>12.7%*</td>
</tr>
<tr>
<td></td>
<td>n/m (%)</td>
<td>n/m (%)</td>
<td>(95.6% CI)</td>
</tr>
<tr>
<td>Evaluable Patients (n=185)</td>
<td>71/88 (80.7)</td>
<td>63/97 (64.9)</td>
<td>15.4%**</td>
</tr>
<tr>
<td></td>
<td>n/m (%)</td>
<td>n/m (%)</td>
<td>(1.1, 29.7)</td>
</tr>
</tbody>
</table>

* P value 0.0861
** P value 0.0346

Mora-Duarte, et al, NEJM 2002
### Causes of Failures or Relapses

<table>
<thead>
<tr>
<th></th>
<th>Caspofungin 70/50 mg (n=109)</th>
<th>Amphotericin B 0.6-1.0 mg/kg (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Failure (End of Rx)</strong></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Persistently (+) cultures</td>
<td>9 (8.3)</td>
<td>10 (8.7)</td>
</tr>
<tr>
<td>Persistent signs/symptoms</td>
<td>6 (5.5)</td>
<td>5 (4.3)</td>
</tr>
<tr>
<td>New lesions at distant sites</td>
<td>4 (3.7)</td>
<td>5 (4.3)</td>
</tr>
<tr>
<td>Toxicity requiring additional Rx *</td>
<td>3 (2.7)</td>
<td>19 (16.5)</td>
</tr>
<tr>
<td>Withdrawal ≤ 4 days/Indeterminate</td>
<td>7 (6.4)</td>
<td>5 (4.3)</td>
</tr>
<tr>
<td><strong>Relapse (6-8 weeks post-Rx)</strong></td>
<td>7 (6.4)</td>
<td>8 (7.0)</td>
</tr>
<tr>
<td>Recurrent candidemia</td>
<td>3 (2.7)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Non-blood <em>Candida</em> infection</td>
<td>2 (1.8)</td>
<td>0 NA</td>
</tr>
<tr>
<td>Received systemic antifungal Rx</td>
<td>1 (0.9)</td>
<td>6 (5.2)</td>
</tr>
<tr>
<td>Abscess (no culture and no Rx)</td>
<td>1 (0.9)</td>
<td>0 NA</td>
</tr>
</tbody>
</table>

* P value = 0.0277
Drug-related Clinical Adverse Experiences

- Chills: Caspofungin 5.3%, Amphotericin B 5.3%
- Fever: Caspofungin 26.4%, Amphotericin B 23.2%
- Phlebitis: Caspofungin 3.5%, Amphotericin B 4.8%
- Tachycardia: Caspofungin 10.4%, Amphotericin B 10.4%
- Tachypnea: Caspofungin 10.4%, Amphotericin B 0%

* P < 0.05
Literature Search: candidemia, RCT

1. Rex JH et al, NEJM 1994
3. Anaissie EJ, ICAAC 1996 and never published in extenso
6. Rex JH et al, CID 2003
A Randomized and Blinded Multicenter Trial of High-Dose Fluconazole plus Placebo versus Fluconazole plus Amphotericin B as Therapy for Candidemia and Its Consequences in Nonneutropenic Subjects


Clinical Infectious Diseases 2003;36:1221–8

Overall mortality 39% fluco/plac vs 40% fluco/AmB
Time to negative blood cultures was lower in the combination arm.
Literature Search: candidemia, RCT

1. Rex JH et al, NEJM 1994
3. Anaissie EJ, ICAAC 1996 and never published in extenso
6. Rex JH et al, CID 2003
Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial


Lancet 2005

Overall mortality 36% vorico vs 42% fluco/Amb
- Randomized, open label, comparative multicenter study
- Patients were randomized in a 2:1 ratio to either voriconazole or to amphotericin B followed by fluconazole
- Intravenous treatment required for at least the first 3 days, then patients could be switched to oral therapy
- Blinded external Data Review Committee (DRC) generated a single assessment of global response at the 12-week follow-up
- Patients not reaching the 12-week follow-up are failure by definition (very conservative approach)
Treatment

- **Voriconazole (IV for ≥ 3 days)**
  - Loading 6 mg/kg IV q12h on day 1, followed by 3 mg/kg IV q12h
  - After 3 days, allowed switch to oral tablets at 200 mg q12h

- **Amphotericin B → fluconazole**
  - Amphotericin B IV at 0.7-1.0 mg/kg/day
  - After 3-7 days, allowed switch to IV or oral fluconazole at 400 mg qd

- Treatment for at least 14 days after resolution of candidemia, up to 8 weeks

- Follow-up 12 weeks
Efficacy Endpoints

• Primary analysis
  - DRC successes at the 12-week follow-up timepoint only
    • All DRC successes at earlier timepoints, who did not reach the 12-week follow-up, were considered to be failures in this analysis

• Secondary analysis
  - DRC successes at the 12-week follow-up timepoint, plus DRC successes at any other timepoint
Primary and Secondary Analyses (MITT Population)

Primary analysis
- Voriconazole (N=248)
- Amphotericin B → fluconazole (N=122)

Secondary analysis
- Success rate (%)
  - Voriconazole: 40.72
  - Amphotericin B → fluconazole: 65.48

Success rate (%)
GLOBAL COMPARATIVE CANDIDEMIA STUDY

DRC-Assessed Success by Baseline Pathogen (MITT* Population)

- C. albicans: Voriconazole (43.0%), Amphotericin B (33.3%), Fluconazole (33.3%)
- C. glabrata: Voriconazole (47.6%), Amphotericin B (33.3%), Fluconazole (33.3%)
- C. parapsilosis: Voriconazole (53.3%), Amphotericin B (52.6%), Fluconazole (32.1%)
- C. tropicalis: Voriconazole (6.3%)

*MITT = Modified intention-to-treat.
### Median change in creatinine (μmol/L)

<table>
<thead>
<tr>
<th>Time since randomisation (weeks)</th>
<th>Voriconazole</th>
<th>Amphotericin B/fluconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>60</td>
</tr>
</tbody>
</table>

### Number of patients

<table>
<thead>
<tr>
<th></th>
<th>Voriconazole</th>
<th>Amphotericin B/fluconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>249</td>
<td>112</td>
</tr>
<tr>
<td>Number of samples</td>
<td>421</td>
<td>195</td>
</tr>
</tbody>
</table>

© by author
Literature Search: candidemia, RCT

1. Rex JH et al, NEJM 1994
3. Anaissie EJ, ICAAC 1996 and never published in extenso

6. Rex JH et al, CID 2003
Anidulafungin versus Fluconazole for Invasive Candidiasis

Annette C. Reboli, M.D., Coleman Rotstein, M.D., Peter G. Pappas, M.D., Stanley W. Chapman, M.D., Daniel H. Kett, M.D., Deepali Kumar, M.D., Robert Betts, M.D., Michele Wible, M.S., Beth P. Goldstein, Ph.D., Jennifer Schranz, M.D., David S. Krause, M.D., and Thomas J. Walsh, M.D., for the Anidulafungin Study Group

N ENGL J MED 356;24  WWW.NEJM.ORG  JUNE 14, 2007
Global Success* at End of IV Therapy
(Primary End Point; MITT Population)

- **Anidulafungin** (n=127): 76% successful* response
- **Fluconazole** (n=118): 60% successful* response

95% CI: 3.9-27.0
Lower limit of 95% CI: >0

*Success=clinical cure or improvement and documented or presumed microbiologic eradication.
Differences in Success* Rates at Primary and Secondary Time Points

*Success=cured or improved at the end of therapy and microbiological eradication.
†33 patients in each study arm switched to oral fluconazole after the end of IV therapy.
Success by species of Candida

<table>
<thead>
<tr>
<th>Species</th>
<th>success rate (total)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>77/81 (95%)</td>
<td>57/70 (81%)</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>15/20 (75%)</td>
<td>18/30 (60%)</td>
</tr>
<tr>
<td>C. krusei</td>
<td>EXCLUSION CRITERIA</td>
<td></td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>9/13 (69%)</td>
<td>14/16 (88%)</td>
</tr>
</tbody>
</table>

Reboli et al., NEJM 2007
Proportion of Patients With Positive Blood Cultures at Day 3 (MITT Population With Positive Culture at Baseline)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients with positive blood culture (%)</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anidulafungin</td>
<td>12.1%</td>
<td>14/116</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>20.4%</td>
<td>21/103</td>
</tr>
</tbody>
</table>
Success at End of IV Therapy by APACHE II Score (MITT Population)

Statistical analyses comparing response rates across multiple APACHE II scores were not conducted.
Rex, 2003
Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial

Ernst-Rüdiger Kuse, Ploenchan Chetchosakd, Clovis Arns da Cunha, Markus Ruhnke, Carlos Barrios, Digumarti Raghunadharao, Jagdev Singh Sekhon, Antonio Freire, Venkatasubramanian Ramasubramanian, Ignace Hemeyer, Marcio Nucci, Amorn Leelarasamee, Frédérique Jacobs, Johan Decruyenaere, Didier Pittet, Andrew D Ullmann, Luis Ostrosky-Zeichner, Olivier Lortholary, Sonja Kobliger, Heike Diekmann-Berndt, Oliver A Cornely, for the Micafungin Invasive Candidiasis Working Group*

Lancet 2007; 369: 1519-27
Double-blind comparison of micafungin with Ambisome in invasive candidiasis in adults

<table>
<thead>
<tr>
<th></th>
<th>Micafungin 100 mg</th>
<th>Ambisome 3 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number pts (MITT)</td>
<td>247</td>
<td>247</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Overall</td>
<td>74.1%</td>
<td>69.6%</td>
</tr>
<tr>
<td>- Neutropenic pts</td>
<td>19/32 (59.4%)</td>
<td>14/25 (56.0%)</td>
</tr>
<tr>
<td><strong>Deaths at Week12</strong></td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>Infusion related AEs</td>
<td>17.0%</td>
<td>28.8% p=.001</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>10.3%</td>
<td>29.9% p&lt;.0001</td>
</tr>
</tbody>
</table>

Micafungin has shown non-inferiority to Ambisome and better tolerance

*Kuse et al., Lancet 2007, 369 : 1519*
Mycafungin versus Caspofungin for Treatment of Candidemia and Other Forms of Invasive Candidiasis

Peter G. Pappas,¹ Coleman M. F. Rotstein,² Robert F. Betts,² Marcio Nucci,¹⁰ Deepak Talwar,¹¹ Jan J. De Waele,¹³ Jose A. Vazquez,³ Bertrand F. Dupont,¹⁴ David L. Horn,⁴ Luis Ostrosky-Zeichner,⁶ Annette C. Reboli,⁷ Byungse Suh,⁵ Raghunadharao Digumarti,¹² Chunzhang Wu,⁶ Laura L. Kovanda,³ Leah J. Arnold,⁹ and Donald N. Buell⁸

Clinical Infectious Diseases 2007; 45:883–93
Double-blind comparison of micafungin (100 mg or 150 mg) to caspofungin (70 D1 then 50 mg) in invasive candidiasis in adults

<table>
<thead>
<tr>
<th></th>
<th>Mica 100</th>
<th>Mica 150</th>
<th>Caspo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number pts (MITT)</td>
<td>191</td>
<td>168</td>
<td>188</td>
</tr>
</tbody>
</table>

**Response**
- Overall 87.4% 87.4% 87.2%
- Neutropenic pts 18/22 (82%) 9/17 (53%) 7/11 (64%)

**Mycological response**
- C. albicans 71/92 (77%) 71/102 (69.6) 61/83 (74%)
- C. glabrata 24/28 (86%) 30/34 (88%) 22/33 (67%)
- C. krusei 6/8 (75%) 5/8 (63%) 3/4 (75%)
- C. parapsilosis 22/29 (76%) 15/21 (71%) 27/42 (64%)

No difference in adverse events, in mortality, or in relapses

**Mica100 and Mica150 are non-inferior to caspo in invasive candidiasis**
No benefit to increase Mica dose to 150

*Pappas et al, CID 2007, 45 : 883*
Phase III study micafungin vs. caspofungin: treatment success by *Candida* species (mITT population)

![Bar chart showing treatment success rates for different *Candida* species with micafungin at 100 mg/day, 150 mg/day, and caspofungin at 50 mg/day.](image)

- **C. albicans**
  - Micafungin 100 mg/day (n = 191)
  - Micafungin 150 mg/day (n = 199)
  - Caspofungin 50 mg/day* (n = 188)
  - Treatment success rate: 80%
  - p = NS

- **Any non-albicans**
  - Treatment success rate: 70%
  - p = NS

- **C. glabrata**
  - Treatment success rate: 90%
  - p = 0.07

- **C. tropicalis**
  - Treatment success rate: 80%
  - p = NS

- **C. parapsilosis**
  - Treatment success rate: 70%
  - p = NS

- **C. krusei**
  - Treatment success rate: 80%
  - p = NS


*Loading dose 70 mg.*
Micafungin Versus Liposomal Amphotericin B for Pediatric Patients With Invasive Candidiasis

Substudy of a Randomized Double-Blind Trial

Flavio Queiroz-Telles, MD, * Eitan Berezin, MD, † Guy Leverger, MD, ‡ Antonio Freire, MD, § Annalie van der Vyver, MD, ¶ Taweel Chotpitayasunondh, MD, ‖ Josip Konja, MD, ** Heike Dickmann-Berndt, PhD, †† Sonja Koblinger, MD, ††† Andreas H. Groll, MD, ‡‡ and Antonio Arrieta, MD ‡‡‡ for the Micafungin Invasive Candidiasis Study Group

The Pediatric Infectious Disease Journal • Volume 27, Number 9, September 2008
Double-blind comparison of micafungin with Ambisome in invasive candidiasis in pediatric patients

<table>
<thead>
<tr>
<th></th>
<th>Micafungin</th>
<th>Ambisome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose</td>
<td>2 mg/kg</td>
<td>3 mg/kg</td>
</tr>
<tr>
<td>Number pts (ITT)</td>
<td>52</td>
<td>54</td>
</tr>
</tbody>
</table>

**Response**
- Overall: 69.2% vs. 74.1%
- Neutropenic pts: 5/7 (71.4%) vs. 10/13 (76.9%)

**Discontinuation for AE**
- 3.8% vs. 16.7%
Defining Responses to Therapy and Study Outcomes in Clinical Trials of Invasive Fungal Diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer Consensus Criteria

Brahm H. Segal,1 Raoul Herbrecht,22 David A. Stevens,110 Luis Ostrosky-Zeichner,1 Jack Sobel,7 Claudio Viscoli,28,29 Thomas J. Walsh,12 Johan Maertens,10 Thomas F. Patterson,6 John R. Perfect,2 Bertrand Dupont,22 John R. Wingard,8 Thierry Calandra,21 Carol A. Kauffman,6 John R. Graybill,6 Lindsey R. Baden,15 Peter G. Pappas,11 John E. Bennett,13 Dimitrios P. Kontoyiannis,3 Catherine Cordonnier,24 Maria Anna Viviani,27 Jacques Bille,26 Nikolaos G. Almyroudis,1 L. Joseph Wheat,14 Wolfgang Graninger,25,26 Eric J. Bow,16 Steven M. Holland,13 Bart-Jan Kullberg,1,12 William E. Dismukes,1 and Ben E. De Pauw17

Clinical Infectious Diseases 2008; 47:674–83
Table 1. General criteria for global responses to antifungal therapy.

<table>
<thead>
<tr>
<th>Outcome, response</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Success</strong></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>Survival within the prespecified period of observation, resolution of all attributable symptoms and signs of disease and radiological abnormalities, and mycological evidence of eradication of disease</td>
</tr>
<tr>
<td>Partial response</td>
<td>Survival within the prespecified period of observation, improvement in attributable symptoms and signs of disease and radiological abnormalities, and evidence of clearance of cultures or reduction of fungal burden, as assessed by a quantitative and validated laboratory marker</td>
</tr>
<tr>
<td><strong>Failure</strong></td>
<td></td>
</tr>
<tr>
<td>Stable response(^a)</td>
<td>Survival within the prespecified period of observation and minor or no improvement in fungal disease, but no evidence of progression, as determined on the basis of a composite of clinical, radiological, and mycological criteria</td>
</tr>
<tr>
<td>Progression of fungal disease</td>
<td>Evidence of progressive fungal disease based on a composite of clinical, radiological, and mycological criteria</td>
</tr>
<tr>
<td>Death</td>
<td>Death during the prespecified period of evaluation, regardless of attribution</td>
</tr>
<tr>
<td>Outcome, response</td>
<td>Criteria</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------</td>
</tr>
<tr>
<td><strong>Success</strong></td>
<td><strong>Complete response</strong>&lt;br&gt;Survival and resolution of all attributable symptoms and signs of disease; plus Documented clearance of pathogen from the blood in cases of candidemia; plus Documented clearance of infected sites that are accessible to repeated sampling (e.g., CSF) If additional cultures are not feasible (e.g., in cases of candidiasis involving visceral organs), survival and resolution of all attributable symptoms and signs of disease and radiological resolution can be equated with a complete response</td>
</tr>
<tr>
<td><strong>Partial response</strong>&lt;br&gt;Survival and improvement of attributable symptoms and signs of disease&lt;sup&gt;a&lt;/sup&gt;; plus Documented clearance of blood in cases of candidemia; plus Documented clearance of infected sites that are accessible to repeated sampling (e.g., CSF). If additional cultures are not feasible, survival and resolution of attributable symptoms and signs of disease and radiological improvement or stabilization can be equated with a partial response&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Death</strong>&lt;br&gt;New sites of disease or worsening of preexisting lesions radiologically (e.g., those observed in chronic disseminated candidiasis) in association with clinical deterioration</td>
<td>Death during the prespecified period of evaluation regardless of attribution</td>
</tr>
</tbody>
</table>
Problems for an adjudication group

- Clinical response difficult to evaluate because of the many concomitant bacterial infections
- Cause of death sometimes impossible to evaluate, even in the rare case of an autopsy
- Need to be consistent case by case
The situation in 2015

- Echinocandins first choice, but resistance appearing
- Fluconazole important for de-escalation (antifungal stewardship)
- D-AmB abandoned, but not everywhere
- Ambisome still there
- Combination AmB/fluco not taken in enough consideration by guidelines
- C. albicans $\leq 50\%$
- Response rates around 70\% or more, but mortality still around 40-50\% (difficult patients still die)
Thank you for your attention!
Phase III study micafungin vs. L-AmB: study design

- **Randomisation (1:1)**
  - **Micafungin 100 mg/day**
  - **L-AmB 3 mg/kg/day**

  **Treatment period†**
  - **2–4 weeks‡**

  **Post-treatment period**
  - **12 weeks**

*2.0 mg/kg/day in patients weighing ≤ 40 kg.
†Treatment continued until at least one week after resolution of clinical signs and symptoms and obtaining of two sequential negative blood cultures.
‡Maximum 8 weeks in chronic disseminated candidiasis, *Candida* osteomyelitis or *Candida* endocarditis.

Phase III study micafungin vs. L-AmB: inclusion and exclusion criteria

Inclusion criteria

- Age > 16 years
- Clinical signs of SCI
- Positive culture ≤ 4 days prior to first planned dose of study drug

Exclusion criteria

- Positive cultures only from oropharyngeal, oesophageal, urine, sputum, or bronchoalveolar lavage specimens, or from an indwelling catheter sample
- ≥ 3 days of systemic antifungal therapy within the previous week (except for patients with neutropenia, who were allowed antifungal prophylaxis)
- Clinically significant liver disease*

* Aminotransferase 10x upper limit of normal (ULN) or bilirubin 5x ULN.

Phase III study micafungin vs. L-AmB: study endpoints

- **Primary:** overall treatment success based on clinical and mycological response at end of therapy (EOT) as determined by investigator
- **Secondary:** clinical response; mycological response (plus others)
- **Safety:** adverse events (AEs), laboratory evaluations and change in estimated glomerular filtration rate (eGFR)

# Phase III study micafungin vs. L-AmB: baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>MICA (n = 264)</th>
<th>L-AmB (n = 267)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in years, median (range)</strong></td>
<td>54.5 (18–89)</td>
<td>56.0 (16–97)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>165 (63)</td>
<td>160 (60)</td>
</tr>
<tr>
<td><strong>Ethnic group, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>158 (60)</td>
<td>167 (63)</td>
</tr>
<tr>
<td>Black</td>
<td>14 (5)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>92 (35)</td>
<td>89 (33)</td>
</tr>
<tr>
<td><strong>Neutropenia (&lt; 500 cells/µL), n (%)</strong></td>
<td>34 (13)</td>
<td>28 (10)</td>
</tr>
<tr>
<td><strong>APACHE II score, mean SD</strong></td>
<td>15.8 8.4</td>
<td>15.6 8.1</td>
</tr>
<tr>
<td>&gt; 20, n (%)</td>
<td>66/240 (28)</td>
<td>56/233 (24)</td>
</tr>
</tbody>
</table>

Phase III study micafungin vs. L-AmB: overall treatment success

Treatment success rate, %

<table>
<thead>
<tr>
<th></th>
<th>Micafungin</th>
<th>L-AmB</th>
</tr>
</thead>
<tbody>
<tr>
<td>mITT</td>
<td>74.1</td>
<td>69.6</td>
</tr>
<tr>
<td>PPS</td>
<td>89.6</td>
<td>89.5</td>
</tr>
</tbody>
</table>

n = 247 n = 247 n = 202 n = 190

mITT = modified intent-to-treat; PPS = per-protocol set.

Phase III study micafungin vs. L-AmB: overall treatment success by infection site

Treatment success rate, %

- **Candidaemia**
  - Micafungin: 90.6%
  - L-AmB: 90.8%
  - n = 170

- **Invasive candidiasis**
  - Micafungin: 84.4%
  - L-AmB: 81.5%
  - n = 32

Phase III study micafungin vs. L-AmB: treatment success in patients with neutropenia

Treatment success rate, (%)

Difference in proportions: 4.9%
(95% CI: –3.0 to 12.8)

Difference in proportions: 0.7%
(95% CI: –5.3 to 6.7)

mITT = modified intent-to-treat; PPS = per-protocol set.
Phase III study micafungin vs. caspofungin: study design

- Patients were stratified by region and APACHE II score (≤ 20 or > 20)

Treatment period†: Max 4 weeks†

Post-treatment period: 6 weeks‡

*70 mg loading dose on Day 1.
†8 weeks in chronic disseminated candidiasis or Candida endophthalmitis; switch to oral fluconazole permitted after 10 days in patients meeting protocol-specified criteria.
‡Time from last dose day of protocol-defined antifungal therapy to final evaluation.


CAS = caspofungin.
Phase III study micafungin vs. caspofungin: inclusion and exclusion criteria

**Inclusion criteria**
- Patients aged ≥ 18 years with diagnosis of candidaemia or IC
- At least one of the following characteristics:
  - Fever (temperature ≥ 38°C)
  - Hypothermia (temperature < 36°C)
  - Hypotension (defined as a systolic blood pressure of < 90 mm Hg or a decrease of > 30 mm Hg from baseline)
  - Local signs and symptoms of inflammation, and/or radiological findings that suggested invasive candidiasis

**Exclusion criteria**
- Pregnant or breast-feeding
- Hepatic disease (Child–Pugh score > 9)
- Life expectancy < 5 days
- Proven or suspected *Candida* endocarditis, osteomyelitis, or meningitis
- Current cyclosporine treatment
- Echinocandin treatment ≤ 1 month before randomisation
- Systemic antifungal therapy for the current infection for > 48 hours

Phase III study micafungin vs. caspofungin: study endpoints

- **Primary:** treatment success, defined as achieving both clinical and mycological success at the end of blinded intravenous therapy, as determined by the investigators

- **Secondary:** emergent and recurrent fungal infections

- **Safety:** treatment-emergent adverse events and results of routine laboratory tests

Pappas PG, *et al.* *Clin Infect Dis* 2007; **45:**883–93
Phase III study micafungin vs. caspofungin: baseline characteristics and treatment information

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Micafungin 100 mg/day (n = 191)</th>
<th>Micafungin 150 mg/day (n = 199)</th>
<th>Caspofungin (n = 188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia at baseline, n (%)</td>
<td>22 (11.5)</td>
<td>17 (8.5)</td>
<td>11 (5.9)</td>
</tr>
<tr>
<td>Mean APACHE II score</td>
<td>14.9</td>
<td>14.8</td>
<td>13.9</td>
</tr>
<tr>
<td>Catheter at baseline, n (%)</td>
<td>167 (87.4)</td>
<td>186 (93.4)</td>
<td>175 (93.1)</td>
</tr>
<tr>
<td>Median duration of therapy with i.v. study drug, (days)</td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Protocol-defined switch to oral fluconazole, n (%)</td>
<td>41 (20.6)</td>
<td>30 (14.9)</td>
<td>41 (21.4)</td>
</tr>
<tr>
<td>Median duration of protocol-defined oral fluconazole therapy (days)</td>
<td>8.0</td>
<td>6.5</td>
<td>4.0</td>
</tr>
</tbody>
</table>


Phase III study micafungin vs. caspofungin: treatment success (mITT population)

- **Micafungin 100 mg/day**: 76.4%
- **Micafungin 150 mg/day**: 71.4%
- **Caspofungin 50 mg/day**: 72.3%

*n = 188*

*Loading dose 70 mg.*
Phase III study micafungin vs. caspofungin: treatment success by *Candida* species (mITT population)

- **Micafungin 100 mg/day** (n = 191)
- **Micafungin 150 mg/day** (n = 199)
- **Caspofungin 50 mg/day** (n = 188)

### Treatment Success Rate, %

- **C. albicans**
  - Micafungin 100 mg/day: 70%
  - Micafungin 150 mg/day: 70%
  - Caspofungin 50 mg/day: 60%
  - *p = NS*

- **Any non-albicans**
  - Micafungin 100 mg/day: 70%
  - Micafungin 150 mg/day: 80%
  - Caspofungin 50 mg/day: 70%
  - *p = NS*

- **C. glabrata**
  - Micafungin 150 mg/day: 90%
  - *p = 0.07*

- **C. tropicalis**
  - Micafungin 100 mg/day: 60%
  - Micafungin 150 mg/day: 60%
  - Caspofungin 50 mg/day: 60%
  - *p = NS*

- **C. parapsilosis**
  - Micafungin 100 mg/day: 60%
  - Micafungin 150 mg/day: 60%
  - Caspofungin 50 mg/day: 60%
  - *p = NS*

- **C. krusei**
  - Micafungin 100 mg/day: 60%
  - Micafungin 150 mg/day: 60%
  - Caspofungin 50 mg/day: 60%
  - *p = NS*

---


*Loading dose 70 mg.*
Paediatric sub-study to Phase III micafungin study vs. L-AmB: study design

- Almost identical to study design of adult trial
- Treatments dosed by body weight (micafungin: 2 mg/kg/day; L-AmB: 3 mg/kg/day)
- Dose increases permitted:
  - Micafungin: up to 4 mg/kg/day
  - L-AmB: up to 5 mg/kg/day
- Dose decrease of 50% permitted for L-AmB in cases of nephrotoxicity

Arrieta AC, et al. 17th ECCMID. Munich, Germany, 31 Mar – 3 Apr 2007; Presentation O-141
Paediatric sub-study micafungin vs. L-AmB: treatment success by neutropenic status

<table>
<thead>
<tr>
<th>Group</th>
<th>Overall Neutropenic patients</th>
<th>Overall Neutropenic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micafungin</td>
<td>69/52</td>
<td>71/41</td>
</tr>
<tr>
<td>L-AmB</td>
<td>74/54</td>
<td>77/42</td>
</tr>
<tr>
<td>ITT</td>
<td>85/41</td>
<td>88/42</td>
</tr>
<tr>
<td>PPS</td>
<td>100/5</td>
<td>90/10</td>
</tr>
</tbody>
</table>

Arrieta AC, et al. 17th ECCMID. Munich, Germany, 31 Mar – 3 Apr 2007; Presentation O-141
Paediatric sub-study micafungin vs. L-AmB: treatment success by Candida species

<table>
<thead>
<tr>
<th></th>
<th>Micafungin</th>
<th>L-AmB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Candida spp.</td>
<td>72</td>
<td>20</td>
</tr>
<tr>
<td>C. albicans</td>
<td>76</td>
<td>40</td>
</tr>
<tr>
<td>Non-albicans Candida</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>68</td>
<td>60</td>
</tr>
<tr>
<td>Any candida spp.</td>
<td>66</td>
<td>62</td>
</tr>
<tr>
<td>C. albicans</td>
<td>59</td>
<td>40</td>
</tr>
<tr>
<td>Non-albicans Candida</td>
<td>60</td>
<td>35</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>37</td>
<td>15</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>62</td>
<td>23</td>
</tr>
</tbody>
</table>

Figures inside bars = total n.

Paediatric sub-study micafungin vs. L-AmB: treatment success by primary infection site

- **Candidaemia**
  - Micafungin: ITT 72, PPS 87
  - L-AmB: ITT 75, PPS 88
- **Invasive candidiasis**
  - Micafungin: ITT 5, PPS 38
  - L-AmB: ITT 40, PPS 40

Figures inside bars = total n.


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Paediatric subset of Phase III trial micafungin vs. fluconazole: treatment success