Antifungal Therapy in Leukemia Patients

UPDATE ECIL 4, 6 September 2011

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Patricia Ribaud, Anne Thiebaut, Catherine Cordonnier
The logo on top of a slide means that recommendations has be updated with either a change of grading, an addition or a confirmation of a previous grading.
Background

- Despite recent advances in antifungal therapy there is still a high failure rate in invasive aspergillosis and a 30 to 40% 3-month mortality rate in both candidemia and aspergillosis.

- In the past decades few options were available and there was no place to discuss the best primary or salvage therapy.

- With the development of new agents and strategies, there is now a need for guidelines.
Questions

• What is the optimal
  – first line antifungal therapy of candidemia / aspergillosis?
  – second line antifungal therapy of candidemia / aspergillosis?
  – duration of antifungal therapy in candidemia / aspergillosis?

• Should *in vitro* susceptibility testing be recommended to guide the choice of antifungals in candidemia / aspergillosis?

• Current indications for combination therapy in candidemia / aspergillosis?
Methods

- Questionnaire on practice in Europe
- Literature review
  - Pubmed
  - Cochrane
  - ICAAC, ECCMID, ASH, ASCO, and EBMT
- CDC grading (I-III, A-E)
Invasive aspergillosis
Questionnaire
Summer 2005
Questionnaire on current practice (38 responses)
First line therapy in invasive aspergillosis

Results of the ECIL Questionnaire, September 2005
Questionnaire on current practice (38 responses)
Circumstances for use of combination therapy

Results of the ECIL Questionnaire, September 2005
Questionnaire on current practice (38 responses)
Type of combination

In most cases AmB = Ambisome

Results of the ECIL Questionnaire, September 2005
Questionnaire on current practice (38 responses)
Second line therapy for aspergillosis

• Equally distributed between monotherapy and combination

• For monotherapy
  – Caspofungin: 50 to 75%
  – Ambisome: 15 to 18%
  – Voriconazole: 25 to 35%

• For combination
  – Caspofungin + Voriconazole: ≈ 40%
  – Caspofungin + AmB: ≈ 35%
Literature search
Aspergillosis: 1st line therapy with Voriconazole

Randomized, open label comparison (voriconazole versus amphotericin B deoxycholate)
277 probable / proven IA for 391 pts randomized
Allo HSCT ≈ 25% ; Leukemia ≈ 43%

<table>
<thead>
<tr>
<th></th>
<th>Vori</th>
<th>Ampho B</th>
<th>Significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>144</td>
<td>133</td>
<td></td>
</tr>
<tr>
<td>Dose (mg/kg/d)</td>
<td>7.87</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>CR + PR</td>
<td>53%</td>
<td>32%</td>
<td>yes</td>
</tr>
<tr>
<td>Survival (week 12)</td>
<td>71%</td>
<td>58%</td>
<td>yes</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>13%</td>
<td>24%</td>
<td>yes</td>
</tr>
<tr>
<td>Most frequent SAE</td>
<td>liver</td>
<td>renal</td>
<td></td>
</tr>
</tbody>
</table>

Herbrecht et al. NEJM, 2002
Aspergillosis: 1st line with liposomal amphotericin B (Ambisome)

Double blind comparison of Ambisome 3mg/kg and Ambisome 10 mg/kg in primary therapy (Ambiload study)

<table>
<thead>
<tr>
<th></th>
<th>Ambisome 3</th>
<th>Ambisome 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number pts (ITT)</td>
<td>107</td>
<td>94</td>
</tr>
<tr>
<td>Median duration therapy</td>
<td>15 d</td>
<td>14 d</td>
</tr>
<tr>
<td>Response at EOT*</td>
<td>50%</td>
<td>46%</td>
</tr>
<tr>
<td>Survival at Wk 12</td>
<td>72%</td>
<td>59%</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>14%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Ambisome is effective in invasive aspergillosis
No benefit to increase the dose to 10 mg/kg

No detailed indication on partial response in main paper and loose definition in reply to Denning et al. (CID 2007, 45:1109)

Cornely et al., CID 2007, 44: 1289
Aspergillosis: 1st line therapy with amphotericin B colloidal dispersion (ABCD)

Randomized, double-blind comparison (ABCD versus amphotericin B deoxycholate)
174 possible, probable, proven IA
Allo HSCT ≈ 42% ; Leukemia ≈ 70%

<table>
<thead>
<tr>
<th></th>
<th>ABCD</th>
<th>Ampho B</th>
<th>Significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (ITT population)</td>
<td>88</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>Dose (mg/kg/d)</td>
<td>6</td>
<td>1 to 1.5</td>
<td></td>
</tr>
<tr>
<td>CR + PR</td>
<td>13%</td>
<td>15%</td>
<td>no</td>
</tr>
<tr>
<td>Survival (week 12)</td>
<td>50%</td>
<td>45%</td>
<td>no</td>
</tr>
<tr>
<td>Doubling creatinine</td>
<td>11%</td>
<td>33%</td>
<td>yes</td>
</tr>
<tr>
<td>Most frequent AE</td>
<td>Chills</td>
<td>Creatinine</td>
<td></td>
</tr>
</tbody>
</table>

Bowden R et al. Clin Infect Dis, 2002
Caspofungin for primary therapy of invasive aspergillosis

- Two strata in an exploratory study. Results presented separately.
  2. Allogeneic hematopoietic stem cell transplantations: Herbrecht et al., Bone Marrow Transplantation, in press
Caspofungin for primary therapy of invasive aspergillosis

Hematological malignancies

- 129 patients enrolled
- 61 patients eligible, all with a mycologically documented IA (probable or proven)
- Treated with standard dose of caspofungin
- Mostly acute leukemia; 85% neutropenic
- CR or PR: 20 / 61 (33%); (expected response rate at least 35%)
- 12-week survival: 53%

Viscoli et al., J Antimicrob Chemother, 2009
Caspofungin for primary therapy of invasive aspergillosis

Allogeneic HSCT recipients

- 42 patients enrolled
- 24 patients eligible, all with a mycologically documented IA (probable or proven)
- Early termination due to slow accrual
- Treated with standard dose of caspofungin
- CR or PR : 10 / 24 (42%)
- 12-week survival: 50%

Herbrecht et al., Bone Marrow Transplantation, in press
Caspofungin for primary therapy of invasive aspergillosis

Considering

– that study conducted in pts with hematological malignancies was well designed, that expected accrual was obtained and that response rate was below expectation
– that study in alloHSCT pts was stopped prematurely with only 24 pts

C II grading for primary therapy with caspofungin (previously caspofungin was graded C III for primary therapy)
Papers also considered (1)

**ABLC versus liposomal AmB monotherapy for invasive aspergillosis in patients with hematologic malignancy. Hachem et al., Cancer 2008**

- Retrospective study of 381 consecutive patients with proven or probable invasive aspergillosis between Jun 93 and Dec 05
- 158 received primary therapy (106 L-AMB and 52 ABLC) and 81 received salvage therapy (51 L-AMB and 30 ABLC)
- Advanced stage and severity of underlying diseases in all groups
- Poor response rates (7.7 to 15.8%) to primary or salvage therapy in both study drug groups regardless of treatment modality.
- High mortality rates in all groups
- Higher nephrotoxicity with ABLC than L-AMB

No change in grading for

| Liposomal AmB: | B I for first line and B III for salvage |
| ABLC: | B II for first line and B III for salvage |
Papers also considered (2)
Safety and efficacy of a caspofungin-based combination therapy for treatment of proven or probable aspergillosis in pediatric hematologic pts. Cesaro et al. BMC Infect Dis 2007

- Retrospective analysis of caspofungin-based combination therapy in 40 pediatric pts (median age 11 y; range: 1-17 y)
- Mostly HSCT recipients and leukemia pts
- Probable IA in 20 (50%) and proven in 20 (50%) pts
- Caspofungin + liposomal AmB (n=18) or caspofungin + voriconazole (n=9) or both sequentially (n=9). Information is missing for 4 pts treated for < 7 days.
- Primary therapy: 20 cases; salvage therapy: 20 cases
- Favorable response in 21 pts (53%). No difference according to type of combination
- Probability of 100-day survival was 70%

No change in grading for combination therapy (previously D III for first line and C II for salvage)
Papers also considered (3)

Treatment of invasive pulmonary aspergillosis in neutropenic patients by additional bronchoscopic amphotericin B instillation. *Winkler et al, Respiration 2007*

- 20 patients treated between February 1996 and October 2002
- First line therapy with AmB deoxycholate (8 pts) or AmB deoxycholate followed by liposomal AmB (10 pts) or liposomal AmB (23 pts)
- Most pts received in addition flucytosine, fluconazole or itraconazole
- Paper not further considered as reference for primary therapy of invasive aspergillosis has changed since this study

No recommendation
Aspergillosis: salvage therapy

- Only open-label, non comparative studies
- Pts failing or intolerant of ampho B or itraconazole
  - Ambisome, ABLC, ABCD, voriconazole, posaconazole, caspofungin are effective in 30 to 50% of the cases
  - Insufficient data for itraconazole
- Pts failing caspofungin
  - Voriconazole was effective in 8 / 12 patients (67%)

Posaconazole in aspergillosis

- Paper published in CID (Walsh et al, 2007)
- Previously graded on abstract presented at ASH (Blood 2003, supplement)
- No change
  - No data in first line
  - B II for salvage
Aspergillosis: combination in 1st line

- Ampho B + placebo versus Ampho B + terbinafine
  - Results never published; Higher mortality with combination
- Ambisome + anidulafungin
  - Efficacy results not yet presented or published
  - No unexpected AEs but 57% (17 / 30) deaths
- Itra + lipid ampho B (n=11) compared retrospectively to lipid Ampho B alone (n = 101)
  - No response (0%) in combination therapy compared to 10% in monotherapy group
- Ambisome + caspofungin
  - 9 / 17 (53%) response in possible, probable, proven cases

**References:**
Steinbach et al, CID, 2003; Herbrecht et al., ASBMT, 2004; Kontoyiannis et al., Cancer, 2005; Kontoyianis et al., CID, 2003
Aspergillosis: Salvage combination therapy

- Vori + caspo (n=16) versus historical control group of vori alone (n=31) after failure or ampho B or itra
  - Higher 3-month survival in patients receiving combination (HR 0.42)

- Ambisome + caspo (n=31) after failure of Ambisome
  - 57% response in possible, 18% in probable or proven cases

- Ambisome (or ampho B) + caspo in possible, probable or proven aspergillosis failing ampho B
  - 18 / 30 favorable response (60%); 67% survival to discharge

Marr et al., 2004; Kontoyiannis et al., 2003; Aliff et al., 2003; Maertens et al., 2006
Combination therapy in aspergillosis

Caspofungin with another antifungal agent (Maertens et al. Cancer 2007)
- 53 patients, salvage therapy
- Response rate at end of combination: 55%
- Day 84 survival: 55%

Lipid Amphotericin B + caspofungin (59 pts) or Voriconazole + caspofungin (33 pts) as salvage therapy (Raad et al, ICAAC, 2007)
- 12-week survival: 48% for Voriconazole + caspofungin compared to 25% for Lipid-Amphotericin B + caspofungin
- Retrospective comparison; High rate of *Aspergillus terreus*

Updated grading of combination therapy as salvage for invasive aspergillosis: C II instead C III at ECIL 1
Aspergillosis

- Efficacy of caspofungin as salvage therapy for invasive aspergillosis compared to standard therapy in a historical cohort. 
  Hiemenz et al. Eur J Clin Microbiol Infect Dis, 2010
  - Comparison of the 83 pts of the Caspofungin Salvage Invasive Aspergillosis Study (Maertens et al., Clin Infect Dis 2004) to a historical control group of 214 pts with documented IA refractory or intolerant to standard therapy (AmB, lipid-AmB, itra)
  - Favorable response rates: 45% with caspo and 16% in control group

  Maertens et al. BMC Infect Dis, 2010
  - Prospective observational registry in 11 countries
  - 101 proven or probable invasive aspergillosis; caspo salvage therapy
  - Favorable response: 56%

No change in recommendation for caspofungin for salvage therapy: B II
Aspergillosis

• Caspofungin plus posaconazole as salvage therapy of invasive fungal infections in immunocompromised patients.  
  Lellek et al. Mycosis, 2011, 54 Suppl 1
  – Retrospective, monocentric
  – 31 HSCT patients with refractory IA
  – Combination of caspofungin 50 mg/d and posaconazole 800 mg/d
  – Favorable response rate: 77%

• Micafungin alone or in combination with other systemic antifungal therapies in HSCT recipients with invasive aspergillosis  
  Kontoyiannis et al., Transpl Infect Dis. 2009
  – 87 HSCT recipients with IA refractory (prior therapy mostly lipid AmB)
  – Micafungin 75 mg/d, mostly in combination with lipid-AmB
  – Successful response: 24%

No change in recommendation for combination therapy in second line: C II
Recommendations
Aspergillosis
Invasive pulmonary aspergillosis: 1st line

<table>
<thead>
<tr>
<th>Agent</th>
<th>Grade</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voriconazole</td>
<td>A I</td>
<td>2x6 mg/kg D1 then 2x4 mg/kg (initiation with oral: CIII)</td>
</tr>
<tr>
<td>Ambisome</td>
<td>B I</td>
<td>dose 3 – 5 mg/kg</td>
</tr>
<tr>
<td>ABLC</td>
<td>B II</td>
<td>dose 5 mg/kg</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>C II</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>C III</td>
<td>start with iv</td>
</tr>
<tr>
<td>ABCD</td>
<td>D I</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>D I</td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>D III</td>
<td></td>
</tr>
</tbody>
</table>

In the absence of data in 1st line, posaconazole has not been graded
## Invasive aspergillosis: salvage

<table>
<thead>
<tr>
<th>Agent</th>
<th>Grade</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambisome</td>
<td>B III</td>
<td>no data in voriconazole failure</td>
</tr>
<tr>
<td>ABLC</td>
<td>B III</td>
<td>no data in voriconazole failure</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>B II</td>
<td>no data in voriconazole failure</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>B II</td>
<td>no data in voriconazole failure</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>B II</td>
<td>if not used in 1st line</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>C III</td>
<td>Insufficient data</td>
</tr>
</tbody>
</table>
Invasive pulmonary aspergillosis: antifungal combinations

- **First line**
  - Not recommended  
  - DIII

- **Salvage**
  - Caspofungin + lipid ampho B  
    - C II
  - Caspofungin + voriconazole  
    - C II
  - Ampho B (any formulation) + azole:  
    - no data

UPDATE ECIL 3, 2009
Aspergillosis

- Surgery (CIII) in case of
  - Lesion contiguous to a large vessel
  - Hemoptysis from a single lesion (embolization is an alternative)
  - Localized extrapulmonary lesion including central nervous system lesion (on case by case)
Aspergillosis: unsolved questions

• Duration of therapy
  • No fixed duration

• Drug monitoring, especially for azoles, may be indicated in case of failure or of adverse events

• In vitro testing
  • Filamentous fungi are not routinely tested for susceptibility
  • No correlation between susceptibility testing and outcome
  • Identification to the species level is recommended: C III
Invasive candidiasis
Questionnaire
Summer 2005
Questionnaire on current practice (38 responses)
Therapy in candidemia (before species identification)

Results of the ECIL Questionnaire, September 2005
Questionnaire on current practice (38 responses)
Therapy in candidemia (after species identification)

Results of the ECIL Questionnaire, September 2005
Literature search
Neutropenia and Candidemia

The following 12 studies were analyzed:

- Kullberg BJ et al. Clinical Microbiology and Infection, 2004
- Kartsonis NA et al. J Antimicrob Chemother, 2004
- DiNubile et al. J Infect 2005
### Three Studies Including Neutropenic Patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Study design</th>
<th>Antifungals</th>
<th>Success</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaissie EJ</td>
<td>217 neutropenic, 257 non neutropenic</td>
<td>retrospective</td>
<td>Fluconazole vs Amphotericin B</td>
<td>all patients, 71% Fluconazole, 73% Amphotericin B</td>
<td>neutropenic patients more likely tt Ampho B</td>
</tr>
<tr>
<td>Mora-Duarte J.</td>
<td>24 neutropenic, 200 non neutropenic</td>
<td>randomized</td>
<td>Caspofungin vs Amphotericin B</td>
<td>(24 neutropenic), Caspofungin 6/8, Amphotericin B 3/8</td>
<td>tt at least 5d</td>
</tr>
<tr>
<td>Ostrosky-Zeichner</td>
<td>13 neutropenic, 52 non neutropenic</td>
<td>compassionate use</td>
<td>Voriconazole</td>
<td>13 neutropenic, Voriconazole 6/13</td>
<td>83% previous tt with azole</td>
</tr>
</tbody>
</table>

**Success**
- all patients
- 71% Fluconazole
- 73% Amphotericin B
- 13 neutropenic
- 13 neutropenic
- Amphotericin B 3/8

**Comments**
- neutropenic patients
- more likely tt Ampho B
- tt at least 5d

**tt**: Treatment

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Efungumab (Mycograb)

- A human recombinant antibody (Fv fragment) that binds to HSP90 of Candida

- Double-blind, placebo-controlled, randomized, multicentre study of patients with culture-confirmed candidiasis
  - Pilot study (n=21) and a confirmatory study (n=137)
    - All patients received AmBisome (3mg/kg/d) or Abelcet (5mg/kg/d)
    - Patients were randomized to received Efungumab (1 mg/kg bid) or placebo
      - Only very limited number of neutropenic patients
      - Some methodological concerns
      - So far not approved. Sofar not graded by the ECIL

Pachl et al. CID 2006, 42: 1404
Anidulafungin in candidiasis

Double-blind comparison of anidula 200 mg then 100 with fluco. 800 mg then 400 in invasive candidiasis in adults

<table>
<thead>
<tr>
<th></th>
<th>Anidulafungin</th>
<th>Fluconazole</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number pts (MITT)</td>
<td>118</td>
<td>127</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- End of therapy</td>
<td>74.0%</td>
<td>56.8%</td>
<td></td>
</tr>
<tr>
<td>- Limited number of neutropenic patients: 3 and 4 respectively</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycological eradication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- C albicans</td>
<td>77/81 (95%)</td>
<td>57/70 (81%)</td>
<td></td>
</tr>
<tr>
<td>- C glabrata</td>
<td>15/20 (75%)</td>
<td>18/30 (60%)</td>
<td></td>
</tr>
<tr>
<td>- C krusei</td>
<td>EXCLUSION</td>
<td>CRITERIA</td>
<td></td>
</tr>
<tr>
<td>- C parapsilosis</td>
<td>9/13 (69%)</td>
<td>14/16 (88%)</td>
<td></td>
</tr>
</tbody>
</table>

All cause mortality 23% 31% 0.13

Anidulafungin has shown non-inferiority to fluconazole

Reboli et al., NEJM 2007
Micafungin in candidiasis (1)

Double-blind comparison of micafungin with Ambisome in invasive candidiasis in adults

<table>
<thead>
<tr>
<th>Micafungin 100 mg</th>
<th>Ambisome 3 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number pts (MITT)</td>
<td>247</td>
</tr>
</tbody>
</table>

**Response**

- Overall 74.1% 69.6%
- Neutropenic pts 19/32 (59.4%) 14/25 (56.0%)

**Mycological persistence at EOT**

- *C. albicans* 9/85 (11%) 8/73 (11%)
- *C. glabrata* 3/22 (14%) 3/15 (20%)
- *C. krusei* 1/6 (17%) 1/5 (20%)
- *C. parapsilosis* 5/35 (14%) 3/29 (10%)

Deaths at Week12 40% 40%
Infusion related AEs 17.0% 28.8%  p=.001
Nephrotoxicity 10.3% 29.9%  p<.0001

Micafungin has shown non-inferiority to Ambisome and better tolerance

Kuse et al., Lancet 2007, 369 : 1519
## Micafungin in candidiasis (2)

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>Micafungin 100</th>
<th>Micafungin 150</th>
<th>Caspofungin</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% (Micafungin 100), 87.4% (Micafungin 150), 87.2% (Caspofungin)
- 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*

Micafungin 100 mg and micafungin 150 mg are non-inferior to caspofungin in invasive candidiasis

*No benefit to increase micafungin dose to 150 mg*

Pappas et al, CID 2007, 45 : 883
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%
High dose caspofungin in candidiasis

- Double-blind comparison of two doses of caspofungin in invasive candidiasis.
  - 104 pts received standard dose (SD): 70 mg on d1 then 50 mg/d
  - 100 pts received high dose (HD): 150 mg/d
  - 60 pts with active malignancy but only 15 neutropenic and 10 transplant recipients
  - 42% C. albicans, 21% C. parapsilosis, 10% C. glabrata

Betts et al., Clin Infect Dis, 2009
High dose caspofungin in candidiasis

Safety outcomes

<table>
<thead>
<tr>
<th></th>
<th>SD (n=104)</th>
<th>HD (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat. duration</td>
<td>14.5 d</td>
<td>14.2 d</td>
</tr>
<tr>
<td>Drug related AE</td>
<td>20 (19%)</td>
<td>19 (19%)</td>
</tr>
<tr>
<td>- leading to discontin.</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

No differences in frequency and type of events

Betts et al., Clin Infect Dis, 2009
# High dose caspofungin in candidiasis

## Efficacy outcomes

<table>
<thead>
<tr>
<th></th>
<th>SD (n=102)</th>
<th>HD (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favorable response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>73/102 (72%)</td>
<td>74/95 (78%)</td>
</tr>
<tr>
<td>Neutropenic pts</td>
<td>2/6 (33%)</td>
<td>4/7 (57%)</td>
</tr>
</tbody>
</table>

No differences in
- time to clear blood cultures
- in 8 weeks mortality rate (33 and 38% respectively)

Betts et al., Clin Infect Dis, 2009

No change in grading for caspofungin
(previously: A I in overall population
B II in hematological pts)
Candidemia

- Monotherapy with caspofungin for candidaemia in adult patients with cancer: a retrospective, single institution study
  
  *Sipsas et al. Int J Antimicrob Agents, 2009*
  
  - Retrospective, non-comparative, single center
  - 63 adults with cancer and candidemia; caspofungin monotherapy
  - Clinical response rate 78%

- Caspofungin for the treatment of candidaemia in patients with haematological malignancies.
  
  *Pagano et al. Clin Microbiol Infect, 2010*
  
  - Prospective, non-comparative, 11 hematology centers
  - 24 neutropenic patients with candidemia treated with caspofungin
  - Favorable overall response rate: 58%

No change in recommendation for caspofungin
A I (overall population), B II (hematological pts)
Recommendations Candidiasis
Candidemia in hematologic patients before species identification

<table>
<thead>
<tr>
<th></th>
<th>Overall population</th>
<th>Hematological pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micafungin</td>
<td>A I</td>
<td>B II</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>A I</td>
<td>B II</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>A I</td>
<td>B II</td>
</tr>
<tr>
<td>Ambisome</td>
<td>A I</td>
<td>B II</td>
</tr>
<tr>
<td>Other lipid-AmB</td>
<td>A II</td>
<td>B II</td>
</tr>
<tr>
<td>AmB deoxycholate</td>
<td>A I *</td>
<td>C III *</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>A I **</td>
<td>C III</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>A I ***</td>
<td>B II</td>
</tr>
</tbody>
</table>

* DIII if concomitant nephrotoxic drug and EIII if renal impairment

** Not in severely ill patients or in patients with previous azole prophylaxis

** Not in patients with previous azole prophylaxis
### Candidemia after species identification (1/2)

<table>
<thead>
<tr>
<th></th>
<th>Overall population</th>
<th>Hematological pts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Micafungin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C. albicans</em></td>
<td>A I</td>
<td>B II</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>B I</td>
<td>B II</td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>B I</td>
<td>B II</td>
</tr>
<tr>
<td><strong>Anidulafungin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C. albicans</em></td>
<td>A I</td>
<td>B II</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>B I</td>
<td>B II</td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>B I</td>
<td>B II</td>
</tr>
<tr>
<td><strong>Caspofungin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C. albicans</em></td>
<td>A I</td>
<td>B II</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>B I</td>
<td>B II</td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>B I</td>
<td>B II</td>
</tr>
</tbody>
</table>
# Candidemia after species identification (2/2)

<table>
<thead>
<tr>
<th></th>
<th>Overall population</th>
<th>Hematological pts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ambisome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C albicans</em></td>
<td>A I</td>
<td>B II</td>
</tr>
<tr>
<td><em>C glabrata</em></td>
<td>B I</td>
<td>B II</td>
</tr>
<tr>
<td><em>C krusei</em></td>
<td>B I</td>
<td>B II</td>
</tr>
<tr>
<td><strong>Other lipid-AmB</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C albicans</em></td>
<td>A II</td>
<td>B II</td>
</tr>
<tr>
<td><em>C glabrata</em></td>
<td>B II</td>
<td>B II</td>
</tr>
<tr>
<td><em>C krusei</em></td>
<td>B II</td>
<td>B II</td>
</tr>
<tr>
<td><strong>AmB deoxycholate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C albicans</em></td>
<td>A I</td>
<td>C III</td>
</tr>
<tr>
<td><em>C glabrata</em></td>
<td>B I</td>
<td>C III</td>
</tr>
<tr>
<td><em>C krusei</em></td>
<td>B I</td>
<td>C III</td>
</tr>
<tr>
<td><strong>Fluconazole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C albicans</em></td>
<td>A I</td>
<td>C III</td>
</tr>
<tr>
<td><em>C glabrata</em></td>
<td>C III</td>
<td>D III</td>
</tr>
<tr>
<td><em>C krusei</em></td>
<td>E III</td>
<td>E III</td>
</tr>
<tr>
<td><strong>Voriconazole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C albicans</em></td>
<td>A I</td>
<td>C III</td>
</tr>
<tr>
<td><em>C glabrata</em></td>
<td>C III</td>
<td>C III</td>
</tr>
<tr>
<td><em>C krusei</em></td>
<td>B I</td>
<td>C III</td>
</tr>
</tbody>
</table>

* DIII if concomitant nephrotoxic drug and EIII if renal impairment
Duration of antifungal therapy in candidemia
Duration of antifungal therapy in candidemia: overview of selected studies

- 12 studies 1994 – 2005
- 3/12 prospective, randomized & double-blinded
- Duration of AFT designed *a priori* in 4 studies
- Total effective duration of therapy 10-21 d. except for «salvage» studies (30-60 d.)
- No specific study in leukemia / neutropenia
- No well-designed trial specifically studying duration of therapy
### Duration of antifungal therapy in candidemia: current guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Duration recommended</th>
<th>Specific guidelines in neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany 2003</td>
<td>2 w. OR 10-14 d. after 1st –ve BC with adapt. to possible organ manif.</td>
<td>None</td>
</tr>
<tr>
<td>Spain 2003</td>
<td>2 w. after last +ve BC AND resol. of symp. AND &gt; 4 w. if dissem.</td>
<td>None</td>
</tr>
<tr>
<td>France 2004</td>
<td>2 w. after last +ve BC AND resol. of symp.</td>
<td>≥ 7 d. after resolution of neutropenia</td>
</tr>
<tr>
<td>U.S.A. 2004</td>
<td>2 w. after last +ve BC AND resol. of signs &amp; symp. of infection</td>
<td>2 w. after resolution of neutropenia</td>
</tr>
</tbody>
</table>
Recommendations for duration of therapy in candidemia
Duration of antifungal therapy in candidemia: recommendations

Non-neutropenic adults: at least 14 days after the last +ve blood culture and resolution of signs and symptoms: B III

Neutropenic patients: at least 14 days after the last +ve blood culture and resolution of signs and symptoms and resolved neutropenia: C III

Importance of an active search for dissemination of infection in leukemic patients following neutrophil recovery (ocular fundus + abdominal imaging)
Antifungal susceptibility testing in candidemia
Antifungal susceptibility testing in candidemia: *in vitro* / clinical correlation

- 11 studies 1988-2005
- 7/11 prospective (or data extracted from prospective studies)
- Heterogeneous populations
- Various number of episodes analyzed (24 – 262)
- Amphotericin B and/or fluconazole
- Attempts to correlate *in vitro* AFST or inappropriate AF therapy and outcome (death or clinical / microbiologic treatment failure)
<table>
<thead>
<tr>
<th>Ref</th>
<th>Method</th>
<th>N</th>
<th>AF</th>
<th>Method</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powderly 88</td>
<td>retrosp</td>
<td>29</td>
<td>Ampho</td>
<td>Tube dil.</td>
<td>Yes (MIC – mortality)</td>
</tr>
<tr>
<td>Rex 95</td>
<td>prosp.</td>
<td>232</td>
<td>Ampho /FCZ</td>
<td>NCCLS</td>
<td>No</td>
</tr>
<tr>
<td>Nguyen 98</td>
<td>prosp.</td>
<td>105</td>
<td>Ampho</td>
<td>NCCLS</td>
<td>Yes (MLC - microb. failure)</td>
</tr>
<tr>
<td>Clancy 99</td>
<td>prosp.</td>
<td>99</td>
<td>Ampho</td>
<td>E-test</td>
<td>Yes (MIC – microb. failure)</td>
</tr>
<tr>
<td>Kovacicova 00</td>
<td>?</td>
<td>262</td>
<td>FCZ</td>
<td>Agar E-test</td>
<td>Yes (attributable mortality)</td>
</tr>
<tr>
<td>Lee 00</td>
<td>prosp.</td>
<td>32</td>
<td>FCZ</td>
<td>NCCLS</td>
<td>Yes (success rate)</td>
</tr>
<tr>
<td>Wenisch 01</td>
<td>prosp.</td>
<td>24</td>
<td>Ampho /FCZ</td>
<td>NCCLS</td>
<td>Yes (AFST by flow cytometry – outcome)</td>
</tr>
<tr>
<td>Antoniadou 03</td>
<td>Retros Mult an</td>
<td>80 272</td>
<td>Ampho /FCZ</td>
<td>NCCLS</td>
<td>Yes (inappr. AFT – outcome)</td>
</tr>
<tr>
<td>Baddley 04</td>
<td>prosp.</td>
<td>119</td>
<td>FCZ</td>
<td>NCCLS</td>
<td>Yes (AFST - outcome)</td>
</tr>
<tr>
<td>Chen 05</td>
<td>retrosp</td>
<td>56</td>
<td>Ampho /FCZ</td>
<td>E-test</td>
<td>No</td>
</tr>
<tr>
<td>Clancy 05</td>
<td>prosp.</td>
<td>32</td>
<td>FCZ</td>
<td>NCCLS</td>
<td>Yes (MIC &amp; dose/MIC - outcome)</td>
</tr>
</tbody>
</table>
## Antifungal susceptibility testing in candidemia: current « guidelines »

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
<th>Comment on choice of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany 2003</td>
<td>None</td>
<td>NA</td>
</tr>
<tr>
<td>Spain 2003</td>
<td>AFST (not graded)</td>
<td>None</td>
</tr>
<tr>
<td>France 2004</td>
<td>Routine E-test (B-II)</td>
<td>None</td>
</tr>
<tr>
<td>U.S.A. 2004</td>
<td>NCCLS M27A &amp; FCZ</td>
<td>Helpful in case of lack of clinical response</td>
</tr>
<tr>
<td></td>
<td>Not a standard of care</td>
<td>May support oral switch to azole (long-term therapies)</td>
</tr>
<tr>
<td></td>
<td>Helpful in deep or hematogenous infection</td>
<td></td>
</tr>
</tbody>
</table>

Not graded
Recommendations

for antifungal susceptibility testing
Antifungal susceptibility testing (AFST)

AFST should be performed in hematological patients on isolates from blood or normally sterile sites, in order to:

- evaluate a possible cause of lack of clinical response or microbiologic eradication  \ A II
- support a change in initial antifungal therapy  \ B II
- support a switch from an IV antifungal to an oral azole  \ A II
Recommendations for catheter removal in candidemia
Candidemia: catheter removal

- Removal of central venous line
  - is a consensus recommendation for the non-hematological patients
  - in hematology patients the quality of evidence is lower
  - removal is always recommended when *C parapsilosis* is isolated