Management of Candidemia in non-neutropenic patients

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A Friday afternoon in the ICU

- The ICU patient with a blood culture positive for yeasts
- Species and susceptibility yet unknown
- Is antifungal therapy required?
- Which initial therapy?

Should all patients with candidemia be treated?

- Yes,
- Transient, self-limited candidemias do exist
- However, we are unable to identify those patients who may have a transient candidemia, or those who have disseminated disease
- All patients with a positive blood culture should receive antifungal therapy
What Do Clinical Data Support?

5 Studies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole 400 mg/d</td>
<td>72%&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Amphotericin B 0.7-0.9 mg/kg/d</td>
<td>79%&lt;sup&gt;1&lt;/sup&gt;, 62%&lt;sup&gt;2&lt;/sup&gt;, 71%&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Caspofungin 70/50 mg/d</td>
<td>74%&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Voriconazole 3-6 mg/kg q12h</td>
<td>65%&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

No studies with:
- Lipid-associated Amphotericin B
- Amphotericin B + flucytosine (5-FC)
- Itraconazole

Initial treatment

- What drives the choice of initial antifungal therapy?
  - efficacy?
    - candidacidal vs. candidastatic drugs?
  - host status?
    - neutropenic vs. non-neutropenic?
      - hemodynamically stable vs. instable?
  - spectrum of activity?
    - Candida species?
Microbial Factors

- *Candida* species drives selection of antifungal agent.

- Fear of *C. glabrata* drives the drug selection process.

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Initial therapy for candidemia of unknown species/susceptibility

**Initial therapy**

- Fluconazole-susceptible strain likely
  - yes
  - Fluconazole
  - Initial extended-spectrum antifungal

- colonized
- fluconazole-exposed
- high-incidence area
- unstable patient

**C. albicans**

<table>
<thead>
<tr>
<th></th>
<th>Sentry (EU)</th>
<th>ECMM (EU)</th>
<th>ECMM (D)</th>
<th>PEG (D)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>54%</td>
<td>56%</td>
<td>68%</td>
<td>55%</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>16%</td>
<td>14%</td>
<td>13%</td>
<td>22%</td>
</tr>
</tbody>
</table>

* Dr M Borg-Von Zepelin, PEG 15.04.05
Initial treatment

- Initial broad-spectrum therapy to maximize spectrum of activity
- Step-down to limit toxicity guided by species and susceptibility
  - Amphotericin B followed by fluconazole
  - Caspofungin
  - Voriconazole

Echinocandins
Echinocandins

- Poor oral bioavailability - always iv
- Generally, few side effects & interactions
- Fungistatic for Aspergillus
- Fungicidal for Candida

Does this help?

Caspofungin invasive candidiasis trial
Overall Efficacy Results

Randomized, double-blind, multicenter study
Caspofungin vs. Amphotericin B

<table>
<thead>
<tr>
<th></th>
<th>Caspofungin 70/50 mg n (%)</th>
<th>Amphotericin B 0.6-1.0 mg/kg n (%)</th>
<th>Estimated Difference Adjusted for Strata % (95.6% CI; P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success (MITT) n=224</td>
<td>73%</td>
<td>62%</td>
<td>12.7% (–0.7, 26.0; P=0.09)</td>
</tr>
<tr>
<td>Evaluable Patients n=185</td>
<td>81%</td>
<td>65%</td>
<td>15.4% (1.1, 29.7; P=0.033)</td>
</tr>
<tr>
<td>Crude Mortality</td>
<td>34%</td>
<td>30%</td>
<td>P=0.53</td>
</tr>
<tr>
<td>Side effects Discontinuations</td>
<td>3%</td>
<td>23%</td>
<td>P=0.03</td>
</tr>
</tbody>
</table>

Caspofungin invasive candidiasis trial

Time to First Negative Blood Culture

Caspofungin (N=92) vs Amphotericin B (N=94)

Day 4:
- Caspofungin: 19.6%
- Amphotericin B: 19.1%

Day 7:
- Caspofungin: 12.0%
- Amphotericin B: 9.0%

Day 9:
- Caspofungin: 6.5%
- Amphotericin B: 6.4%

Reasons for failure:

<table>
<thead>
<tr>
<th></th>
<th>Caspofungin</th>
<th>Amphotericin B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistently positive cultures</td>
<td>9 (9%)</td>
<td>10 (9%)</td>
</tr>
<tr>
<td>New disseminated disease</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Clinical failure</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Relapse</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Other/unknown reasons</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Withdrawal due to AE</td>
<td>3 (2.8%)</td>
<td>19 (16.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>36 (33.0%)</td>
<td>52 (45.2%)</td>
</tr>
</tbody>
</table>
Voriconazole for candidemia?

- Extended-spectrum azole, active against fluconazole-resistant *Candida*, including *C. glabrata* and *C. krusei*

- Proof of concept: double blind randomized trial 98% efficacy in Candida esophagitis

- Salvage treatment for refractory candidiasis: 
  ✓ Overall success 52%
  ✓ In fluconazole R (MIC ≥64) species: 74%

* Ally et al, Clin Infect Dis 2001
**Ostrosky & Kullberg, EJCMID 2003

Global Comparative Candidemia Study

- To demonstrate safety and efficacy of voriconazole for treatment of serious *Candida* infections

- Largest prospective, randomized, comparative clinical trial of candidemia ever conducted

- Anticipated large proportion of patients with non-albicans *Candida* infections

- Voriconazole compared to a realistic comparator regimen
Comparator Arm Strategy

Initiate Treatment With Conventional Amphi B

3–7 Days

Maximize Spectrum

Is Candida Species Fluconazole-Susceptible?

NO

Continue Conventional Amphi B

YES

Switch to Fluconazole

Minimize Toxicity

Voriconazole candidemia trial

- 2:1 randomization
  - Voriconazole
    3 mg/kg bid IV (loading 6 mg/kg)
    After 3 days, allowed switch to oral tablets at 200 mg bid
  - AmB -> 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

- Outcome assessed by blinded Data Review Committee (DRC)

Kullberg et al, ECCMID 2004
Baseline *Candida* species (MITT Population)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>N=370 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Candida albicans</em></td>
<td>170 (45)</td>
</tr>
<tr>
<td>Non-<em>albicans</em>:</td>
<td>211 (55)</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>57 (15)</td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td>69 (19)</td>
</tr>
<tr>
<td><em>C. parapsilosis</em></td>
<td>64 (17)</td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>5 (1)</td>
</tr>
<tr>
<td>Other non-<em>albicans</em></td>
<td>16 (4)</td>
</tr>
<tr>
<td>Mixed <em>Candida</em> spp</td>
<td>15 (4)</td>
</tr>
</tbody>
</table>

Note: Patients can have more than one baseline pathogen.

**Efficacy Endpoints**

**Primary analysis**

- **Sustained successes (DRC) at the 12-week post end-of-treatment follow-up time point only**
  - All patients (even treatment successes) who did not reach the 12 week visit for any reason were considered failures in this analysis
Primary and Secondary Analyses
(MITT Population)

Secondary analysis
- DRC successes at the last evaluable follow-up study visit

<table>
<thead>
<tr>
<th></th>
<th>Voriconazole (N=248)</th>
<th>Amphotericin B → fluconazole (N=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success rate (%)</td>
<td>40.72</td>
<td>40.70</td>
</tr>
<tr>
<td>P</td>
<td>0.25</td>
<td></td>
</tr>
</tbody>
</table>

14-weeks mortality

Voriconazole 36%
Amphotericin B / fluconazole 42%

Hazard ratio 0.822
suggesting an 18% survival benefit for voriconazole (N.S.)
95% CI: (0.582, 1.161)
DRC Success Rates Compared

- Candidemia III
  - Voriconazole: 66%
  - Amphotericin B -> Fluconazole: 71%
  - Amphotericin: 70%

- Candidemia I
  - Fluconazole: 79%
  - Amphotericin + Fluconazole: 69%

Kullberg, ECCMID 2004
Rex, NEJM 1994
Rex, CID 2003

Time to First Negative Blood Culture

- Median:
  - Voriconazole: 2.0 days
  - Amphotericin B / fluconazole: 2.0 days

- Days 1-4:
  - No difference between Voriconazole ("fungistatic" in vitro)
  - and Amphotericin B ("fungicidal" in vitro)

  *No clinical relevance of fungicidal/fungistatic properties in vitro*
Safety

- Patients on voriconazole had significantly
  - Fewer treatment-related adverse events
  - Fewer serious adverse events
  - Fewer infusion-related adverse events
  - Fewer renal adverse events

- Patients on voriconazole had
  - Visual side effects in 4.1%

- No difference between study arms in
  - Dermatologic adverse events
  - Liver enzyme elevations

Summary

- Voriconazole is as effective as the strategy of amphotericin B → fluconazole in treating nonneutropenic patients with candidemia

- Response rates for voriconazole were similar to that of amphotericin B for Candida albicans and non-albicans infections

- Success rates in the secondary analysis are similar to previously published data

- Voriconazole was able to clear the blood of Candida as quickly as amphotericin B

- Voriconazole caused fewer adverse events

- Survival was comparable between the two treatment arms
Management of Candidemia