Treatment of invasive aspergillosis

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The University of Manchester
Treatment
## Invasive aspergillosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Therapya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive pulmonary aspergillosis</td>
<td>Voriconazole (6 mg/kg IV every 12 h for 1 day, followed by 4 mg/kg IV every 12 h; oral dosage is 200 mg every 12 h)</td>
</tr>
</tbody>
</table>

\( ^a \) Refer to the IDSA guidelines. \( ^b \) Walsh et al. Clin Infect Dis 2008;46:327.
Invasive aspergillosis

There are few randomized trials on the treatment of invasive aspergillosis. The largest randomized controlled trial demonstrates that voriconazole is superior to deoxycholate amphotericin B (D-AMB) as primary treatment for invasive aspergillosis. **Voriconazole is recommended for the primary treatment of invasive aspergillosis in most patients (A-I).** Although invasive

Why most and not all?
Open study of 600 mg/day for 4 d, then 400 mg/d.
Treatment extended for ≥97 weeks, median 46

<table>
<thead>
<tr>
<th></th>
<th>12 weeks</th>
<th>End of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>5%</td>
<td>26%</td>
</tr>
<tr>
<td>Partial</td>
<td>26%</td>
<td>13%</td>
</tr>
<tr>
<td>Stable</td>
<td>34%</td>
<td>4%</td>
</tr>
<tr>
<td>Failure</td>
<td>32%</td>
<td>56% (30% other causes)</td>
</tr>
<tr>
<td>Deaths</td>
<td>--</td>
<td>31%</td>
</tr>
</tbody>
</table>
Randomised study of invasive aspergillosis with voriconazole versus amphotericin B

391 pts received either

1) Voriconazole 4 mg/d BID (after loading) for 12wks (or OLAT)
or 2) AmB 1.0 mg/kg/d for 12wks (or OLAT)

mITT analysis

<table>
<thead>
<tr>
<th></th>
<th>Success (%)</th>
<th>Severe AEs (%)</th>
<th>Renal tox (%)</th>
<th>Died (all) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vori</td>
<td>53</td>
<td>13</td>
<td>1</td>
<td>29</td>
</tr>
<tr>
<td>AmB</td>
<td>32</td>
<td>24</td>
<td>10</td>
<td>42</td>
</tr>
</tbody>
</table>

\{21\% \} \{13\% \}

Herbrecht, Denning et al, NEJM 2002;347:408
Survival after primary Rx with amphotericin B or voriconazole

Overall logrank test p = 0.015

Herbrecht, Denning et al, NEJM 2002;347:408
Impact of voriconazole in real life - France

5 other large case series demonstrating better outcomes with voriconazole for IA against all other therapies

\( P = .016 \)
Random voriconazole concentrations in adults receiving 3mg/Kg BID

Very small children may metabolise voriconazole very fast and need doses of 8mg/Kg BID, then TDM

Data from Denning et al, Clin Infect Dis 2002;34:563
Intrinsic and acquired resistance among the *Aspergilli*

**Amphotericin B resistance/insensitivity**

- *A. terreus*
- *A. nidulans*
- *A. flavus*

**Azole resistance**

- *A. fumigatus*
- *A. niger*

 Only itraconazole resistance
Randomised study of invasive aspergillosis with Amphocil versus amphotericin B

174 pts received either
   1) Amphocil 6 mg/d for >2wks after symptoms gone
or 2) AmB 1.0 - 1.5 mg/kg/d >2wks after symptoms gone
70/174 (40%) in high risk (HSCT, liver Tx, AIDS, brain)

ITT analysis

<table>
<thead>
<tr>
<th></th>
<th>Success (%)</th>
<th>Tox (%)</th>
<th>Renal tox (%)</th>
<th>Died (due to IA)(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphocil</td>
<td>13</td>
<td>83</td>
<td>23</td>
<td>59 (22)</td>
</tr>
<tr>
<td>AmB</td>
<td>15</td>
<td>83</td>
<td>41</td>
<td>67 (20)</td>
</tr>
</tbody>
</table>

Bowden et al Clin Infect Dis 2002;35:359
Randomised study of invasive aspergillosis with 2 doses of AmBisome

339 pts randomised to receive either

1) L-AmB 3 mg/d for 2+wks (169 randomised; 107 in MITT)
or 2) L-AmB 10 mg/d for 2+wks (162 randomised; 94 in MITT)
44/201 (22%) high risk (HSCT, AIDS)

MITT analysis

<table>
<thead>
<tr>
<th></th>
<th>CR + PR</th>
<th>Stop Rx</th>
<th>Renal tox</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-AmB 3</td>
<td>50%</td>
<td>20%</td>
<td>14%</td>
<td>28%</td>
</tr>
<tr>
<td>L-AmB 10</td>
<td>46%</td>
<td>32%</td>
<td>31%</td>
<td>41%</td>
</tr>
</tbody>
</table>
# Micafungin for invasive aspergillosis

## Table 3: Efficacy at end of therapy

<table>
<thead>
<tr>
<th></th>
<th>Primary (%)</th>
<th>Refractory/toxicity failure&lt;sup&gt;a&lt;/sup&gt; (%)</th>
<th>Total (%)&lt;br&gt;(N = 225)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Micafungin in combination (n = 17)</td>
<td>Micafungin alone (n = 12)</td>
<td>Micafungin in combination (n = 174)</td>
</tr>
<tr>
<td>Complete response</td>
<td>2 (11.8)</td>
<td>13 (7.5)</td>
<td>18 (8.0)</td>
</tr>
<tr>
<td>Partial response</td>
<td>3 (17.6)</td>
<td>47 (27.0)</td>
<td>62 (27.6)</td>
</tr>
<tr>
<td>Favorable response</td>
<td>5 (29.4)</td>
<td>60 (34.5)</td>
<td>80 (35.6)</td>
</tr>
<tr>
<td>Stabilization</td>
<td>3 (17.6)</td>
<td>17 (9.8)</td>
<td>25 (11.1)</td>
</tr>
<tr>
<td>Progression</td>
<td>9 (52.9)</td>
<td>97 (55.7)</td>
<td>120 (53.3)</td>
</tr>
<tr>
<td>Not successful</td>
<td>12 (70.6)</td>
<td>114 (65.5)</td>
<td>145 (64.4)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Four patients who had failed previous therapy due to toxicities are included in the micafungin-alone group.
Open study of invasive aspergillosis with caspofungin as primary therapy

61 pts with chemotherapy or auto HSCT received Caspofungin 70 then 50mg IV daily

Survival by day 84 = 33/61 (54%)

<table>
<thead>
<tr>
<th>Response</th>
<th>n</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>1</td>
<td>2 (0–9)</td>
</tr>
<tr>
<td>Partial</td>
<td>19</td>
<td>31 (20–44)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>9</td>
<td>15 (7–26)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>31</td>
<td>51 (38–64)</td>
</tr>
<tr>
<td>Not evaluable(^a)</td>
<td>1</td>
<td>2 (0–9)</td>
</tr>
</tbody>
</table>

\(^a\)Patient refused treatment.

Neutropenia at enrolment (not assessable in one case)

<table>
<thead>
<tr>
<th>Neutropenia at enrolment</th>
<th>No</th>
<th>Yes</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/9 (56)</td>
<td>15/51 (29)</td>
<td>0.14</td>
<td></td>
</tr>
</tbody>
</table>

Viscoli et al, JAC 2009;64:1274
Voriconazole versus amphotericin B

[Spectrum/activity]

Favours voriconazole

- Much more active for IA (~20% better)
- Active against *A. terreus*
- Active against *A. nidulans*
- More active *A. flavus*
- Active against *S. apiospermum*

Favours Amp B

- Mucorales possible
- Azole resistant *A. fumigatus*
Voriconazole versus echinocandin

[Spectrum/activity]

Favours voriconazole

Much more active for IA (~20% better)

Active against *A. terreus*

Active against *A. nidulans*

More active *A. flavus*

Active against *S. apiospermum*

Favours micafungin/caspofungin

Azole resistant *A. fumigatus*
# Cytochrome P450 Interactions

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Fluc</th>
<th>Itra</th>
<th>Posa</th>
<th>Vori</th>
</tr>
</thead>
<tbody>
<tr>
<td>2C19</td>
<td>+</td>
<td></td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>2C9</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>3A4</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Fluc</th>
<th>Itra</th>
<th>Posa</th>
<th>Vori</th>
</tr>
</thead>
<tbody>
<tr>
<td>2C19</td>
<td></td>
<td></td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>2C9</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3A4</td>
<td>+++</td>
<td></td>
<td></td>
<td>+</td>
</tr>
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</table>
13 years and counting
Over 2M pages read monthly in >125 countries
Supported by the Fungal Research Trust – 20 year anniversary in 2011

New section on drug interactions which you can search very quickly
Combination therapy (voriconazole + caspofungin)

Retrospective AmB failures
Most HSCT
30/47 proven IA

Multivariate analysis
P=0.008 for combination and survival

Combination therapy may be useful for a short time early during voriconazole treatment to allow confirmation of adequate voriconazole concentrations, especially in children.
Arguments for not using voriconazole?

1. Amphotericin B is a broader spectrum agent - No
2. AmBisome is equivalent to voriconazole in IA - No
3. Patient was on itraconazole prophylaxis - No
4. The patient has cerebral aspergillosis - No (be sure interactions, especially phenytoin)
5. The patient might have azole resistant Aspergillus - maybe
6. Major drug interactions - yes sometimes
7. Renal failure - only if IV therapy needed for any duration
8. My patient is a young child and I am worried about blood levels - yes use 9mg/Kg BD (200mg BD orally) and consider combination therapy with an echinocandin and measure levels
Choice of antifungal for invasive aspergillosis

Priority sequence

• Voriconazole (unless drug interaction)
• Micafungin/caspofungin (if not neutropenic)
  OR
• AmBisome 3mg/Kg (if not ‘nephro-critical’)

3. Posaconazole (oral only, if no drug interactions)

4. Itraconazole
When not to use voriconazole as primary therapy?

Absolute contraindications
- Drug interactions (ie rifampicin, carbamazepine, phenytoin etc)
- Voriconazole used as prophylaxis (but not itraconazole or posaconazole)
- Resistance to voriconazole (esp zygomycosis, *A. lentulus* or azole resistance in *A. fumigatus*)

Relative contraindications
- Renal failure (IV only)
- Young children (need higher dose ?+ other agent)
- Severe hepatic dysfunction
- Interacting drugs (ie sirolimus)
Conclusions

- Voriconazole is the treatment of choice for invasive aspergillosis
- For those with toxicity, significant drug interactions or azole resistance, an echinocandin or lipid AmB is appropriate
- Current treatments are partially successful but more oral therapies are needed
- Isolates of *Aspergillus* should be susceptibility tested, if treatment given