Antifungal therapy (combination, step-down, salvage)

Hossein Khalili, Pharmacotherapy, TUMS
Combination therapy (advantages)

- Additive or synergic effects
- Resistant fungi
- Coverage
- Dose reduction
Combination therapy (disadvantages)

- Antagonism
- Interactions
- Toxicity
- Cost
<table>
<thead>
<tr>
<th>Organism</th>
<th>Drugs</th>
<th>Effect</th>
<th>Reference, yr</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Candida albicans, Candida pseudotropicalis, Candida glabrata, Saccharomyces cerevisiae</em></td>
<td>Amphotericin B ± miconazole or clotrimazole</td>
<td>Antagonism</td>
<td>10, 1978</td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>Amphotericin B ± miconazole or ketoconazole</td>
<td>Antagonism (short-term incubation); potentiation (long-term incubation)</td>
<td>7, 1982</td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>Amphotericin B ± miconazole, ketoconazole, itraconazole, or fluconazole</td>
<td>Antagonism of polyene effect by all azoles</td>
<td>18, 1991</td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>Amphotericin B ± fluconazole</td>
<td>Antagonism</td>
<td>15, 1994</td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>Amphotericin B ± ketoconazole</td>
<td>Antagonism</td>
<td>29, 1982</td>
</tr>
<tr>
<td><em>Aspergillus fumigatus</em></td>
<td></td>
<td>Antagonism</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence

<table>
<thead>
<tr>
<th>Mycosis</th>
<th>Animal model; organism</th>
<th>Drug regimen(s)</th>
<th>Results</th>
<th>Reference, yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillosis</td>
<td>Intravenous injection of neutropenic mice; <em>Aspergillus fumigatus</em> (two strains)</td>
<td>Amphotericin B ± ketoconazole</td>
<td>Antagonism of polyene effect</td>
<td>29, 1982</td>
</tr>
<tr>
<td></td>
<td>Intravenous injection of immunosuppressed mice; <em>Aspergillus fumigatus</em></td>
<td>Amphotericin B ± itraconazole</td>
<td>Antagonism of polyene effect</td>
<td>19, 1987</td>
</tr>
<tr>
<td></td>
<td>Immunosuppressed rat, invasive pulmonary; <em>Aspergillus fumigatus</em></td>
<td>Amphotericin B ± ketoconazole; amphotericin B followed by itraconazole or SCH 39304</td>
<td>Antagonism, sequential use, no antagonism</td>
<td>30, 1991</td>
</tr>
<tr>
<td></td>
<td>Immunosuppressed rabbit, invasive pulmonary; <em>Aspergillus fumigatus</em></td>
<td>Fluconazole, amphotericin B</td>
<td>No antagonism, no positive effect</td>
<td>12, 1993</td>
</tr>
<tr>
<td></td>
<td>Intravenous injection of immunosuppressed mice</td>
<td>Amphotericin B ± itraconazole</td>
<td>Antagonism of amphotericin B with concurrent or sequential treatment</td>
<td>28, 1993</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>Intravenous injection of immunosuppressed mice; <em>Candida albicans</em></td>
<td>Amphotericin B ± itraconazole</td>
<td>Indifferent or weak antagonism</td>
<td>19, 1987</td>
</tr>
<tr>
<td></td>
<td>Intravenous inoculation of immunocompetent mice; <em>Candida albicans</em></td>
<td>Amphotericin B ± SCH 39304</td>
<td>No antagonism, additive or synergistic</td>
<td>37, 1991</td>
</tr>
<tr>
<td></td>
<td>Intravenous inoculation of immunocompetent mice; <em>Candida albicans</em></td>
<td>Amphotericin B ± saperconazole</td>
<td>No antagonism</td>
<td>39, 1994</td>
</tr>
<tr>
<td></td>
<td>Intravenous inoculation of immunocompetent and immunosuppressed mice; <em>Torulopsis glabrata</em></td>
<td>Amphotericin B ± DO870</td>
<td>No antagonism, additive</td>
<td>4, 1994</td>
</tr>
<tr>
<td></td>
<td>Intravenous inoculation of immunocompetent and immunosuppressed mice; <em>Candida albicans</em></td>
<td>Amphotericin B ± fluconazole</td>
<td>No antagonism, additive</td>
<td>38, 1994</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>Intravenous injection of mice; <em>Cryptococcus neoformans</em></td>
<td>Amphotericin B ± itraconazole</td>
<td>Indifferent or weak antagonism</td>
<td>19, 1987</td>
</tr>
<tr>
<td></td>
<td>Intracranial injection of immunocompetent mice; <em>Cryptococcus neoformans</em></td>
<td>Amphotericin B ± SCH 39304</td>
<td>No antagonism, additive or synergistic</td>
<td>1, 1991</td>
</tr>
<tr>
<td></td>
<td>Immunocompetent and immunosuppressed guinea pigs, meningeal and disseminated infection; <em>Cryptococcus neoformans</em></td>
<td>Amphotericin B ± itraconazole</td>
<td>No antagonism, combination was additive or synergistic</td>
<td>43 (abstract only), 1992</td>
</tr>
</tbody>
</table>
What need to know before selecting an antifungal agent?

Molecular characteristics and structure-related activity
<table>
<thead>
<tr>
<th>Drug</th>
<th>Molecular weight</th>
<th>Polarity</th>
<th>lipophilicity</th>
<th>Permeability</th>
<th>Protein binding</th>
<th>Vd</th>
<th>T1/2(h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>705</td>
<td>101</td>
<td>4.89</td>
<td>1.85</td>
<td>99.8%</td>
<td>11</td>
<td>34-42</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>700</td>
<td>112</td>
<td>4.41</td>
<td>1.94</td>
<td>&gt;98</td>
<td>7- 25</td>
<td>29</td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>437</td>
<td>88</td>
<td>3.62</td>
<td>4.03</td>
<td>&gt;99</td>
<td>6</td>
<td>110</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>349</td>
<td>76</td>
<td>2.13</td>
<td>4.5</td>
<td>58</td>
<td>4.6</td>
<td>6</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>306</td>
<td>81</td>
<td>0.82</td>
<td>4.06</td>
<td>12</td>
<td>0.7</td>
<td>30</td>
</tr>
</tbody>
</table>
Azole’ chemical structure

Fig. 5. Fluconazole (24) structure optimizations.
<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drug class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell membrane</td>
<td>Azoles (14-α-demethylase inhibitors)</td>
<td>Imidazoles</td>
</tr>
<tr>
<td></td>
<td>Polyenes (ergosterol binding)</td>
<td>Ketoconazole, miconazole, Fluconazole, itraconazole, voriconazole posaconazole, isavuconazole*</td>
</tr>
<tr>
<td></td>
<td>Allylamines (squalene monoxygenase)</td>
<td>Amphotericin B</td>
</tr>
<tr>
<td></td>
<td>Echinocandins (β-1,3-β-glucan synthesis inhibitors)</td>
<td>Terbinafine</td>
</tr>
<tr>
<td>Cell wall</td>
<td>Mannoproteins and α-glucans</td>
<td>Anidulafungin, caspofungin, micafungin</td>
</tr>
<tr>
<td>Intracellular</td>
<td>β-1,3-β-glucan synthesis</td>
<td>Flucytosine</td>
</tr>
<tr>
<td></td>
<td>Echinocandins</td>
<td>Griseofulvin</td>
</tr>
</tbody>
</table>
1. **Amphotericin B** interacts hydrophobically with ergosterol in the fungal cell membrane, forming a pore.

2. Potassium and other small molecules are lost through the pore, causing cell death.

**Lanosterol**

- **Fluconazole** inhibits P450, disrupting ergosterol synthesis, which decreases membrane function and increases permeability.
Interactions between antifungals depend on:

- Type of drug (itraconazole vs. voriconazole)
- Antifungal half-life
- Administration interval (at least 12 hours)
- Type of fungus (cryptococcosis vs. aspergillosis)
- Fungus structure (ergosterol or lanosterol content)
Step-down therapy

- De-escalation
Salvage therapy

- Refractory
- Progressive
Invasive Aspergillosis

<table>
<thead>
<tr>
<th>Initial therapy</th>
<th>Combination therapy</th>
<th>Step-down therapy</th>
<th>Salvage therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Voriconazole</td>
<td>Voriconazole + Echinocandin</td>
<td>Voriconazole</td>
<td>- Voriconazole + Echinocandin - Liposomal amphotericin B + Echinocandin</td>
</tr>
<tr>
<td>- Posaconazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Isavoconazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>6 to 12 weeks (minimum)</td>
<td>10 to 14 days combination therapy then step-down to Voriconazole</td>
<td></td>
</tr>
</tbody>
</table>
Azole choice:

- Organ dysfunction
- Toxicities
- Tolerability
- Need for initial intravenous therapy
Azole choice:

- Posaconazole and isavuconazole are the preferred alternatives for patients who cannot tolerate voriconazole.
- Both have been shown to be as effective as voriconazole.
- However, clinical experience with these agents is limited.
Posaconazole over voriconazole

• In patients who have sustained visual disturbances, other neurologic disturbances, or dermatologic toxicity with voriconazole
Isavuconazole over voriconazole

- In patients with a prolonged QTc
- Patients who require intravenous therapy but cannot receive intravenous voriconazole due to its cyclodextrin vehicle
Amphotericin B over azoles

- Patients with severe hepatotoxicity
- There is a concern for drug interactions with azoles
Resistance?

- Mucorales are intrinsically resistant to voriconazole
- A. terreus has high MICs to amphotericin B
- Combination therapy
### Invasive candidiasis

<table>
<thead>
<tr>
<th>Initial therapy</th>
<th>Combination therapy</th>
<th>Step-down therapy</th>
<th>Salvage therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Echinocandin -Azoles</td>
<td>-Amphotericin B+Flucytosin -Posaconazole +Caspofungin -Amphotericin B+ Fluconazole</td>
<td>-High-dose Fluconazole (C.glabrta) -Voriconazole</td>
<td>-Echinocandin -Flucytosine -Voriconazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td><strong>Continue treatment for 14 days after negative B/C culture</strong></td>
<td><strong>5 to 7 days after inanition B/C negative Fluconazole (oral)</strong></td>
<td></td>
</tr>
</tbody>
</table>
# Mucormycosis

- **Initial therapy**: Amphotericin B
- **Combination therapy**: Amphotericin B + Posaconazole
- **Step-down therapy**: Isavuconazole, Posaconazole
- **Salvage therapy**: Posaconazole, Isavuconazole

<table>
<thead>
<tr>
<th>Duration</th>
<th>Induction therapy minimum for 4 weeks</th>
<th>After improvement in the clinical conditions then for several weeks</th>
<th></th>
</tr>
</thead>
</table>

**Table**: Therapy for Mucormycosis

<table>
<thead>
<tr>
<th>Initial therapy</th>
<th>Combination therapy</th>
<th>Step-down therapy</th>
<th>Salvage therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>Amphotericin B + Posaconazole</td>
<td>Isavuconazole, Posaconazole</td>
<td>Posaconazole, Isavuconazole</td>
</tr>
</tbody>
</table>

**Note**:
- Duration of induction therapy is minimum for 4 weeks.
- Therapy is continued until improvement in clinical conditions and for several weeks.
- salvage therapy is used when initial therapy fails.