Complexities of Antifungal Therapy Made Simple

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There are no relationships to disclose related to this presentation.

Unlabeled/unapproved uses of antifungal drugs will be discussed.
Objectives

**Pharmacists:**
1. Discuss differences in antifungal spectrums of activity for the most commonly used antifungals.
2. Differentiate the antifungals based on their adverse effect profile.
3. Explain the need for antifungal therapeutic drug monitoring and apply this knowledge to clinical practice.

**Technicians:**
1. Recognize the different classes of antifungal agents.
2. Describe the adverse effects of antifungal agents.
3. Explain the need for antifungal therapeutic drug monitoring.
Fungal Classification

Yeast
- Candida species
- Cryptococcus species

Molds
- Dimorphic molds
  - Histoplasma
  - Coccidioides
  - Blastomyces
  - Paracoccidioides
- Septated hyphae
  - Aspergillus species
- Non-septated hyphae
  - Zygomycetes
    - Mucorales (Rhizopus, Mucor, Rhizomucor, Absidia)
The Big Five

Candida sp.
Aspergillus sp.
Zygomycetes
Cryptococcus neoformans
Pneumocystis jirovecii
## Risk Factors for Fungal Infections

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Fungal colonization</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Prolonged mechanical ventilation</td>
</tr>
<tr>
<td>Recent or current use of antibiotics</td>
<td>Prolonged ICU stay</td>
</tr>
<tr>
<td>Central venous catheters</td>
<td>High disease severity</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Immunosuppression</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>Chemotherapy/radiation</td>
</tr>
<tr>
<td>TPN</td>
<td>Mucositis</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Prolonged neutropenia</td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td></td>
</tr>
</tbody>
</table>

Invasive Fungal Infections (IFIs) in the ICU

Extended Prevalence of Infection in Intensive Care (EPIC II)
- 19% of isolated pathogens were fungi → 88% Candida

Candida sp. 3rd most common cause of bloodstream infections in the ICU (10%)

Attributable mortality of candidemia 5-71%
- Candidemia associated with ↑ LOS and hospital costs
- Delays in therapy associated with ↑ mortality

IFIs in Solid Organ Transplant

<table>
<thead>
<tr>
<th>IFI type</th>
<th>Kidney (n = 332)</th>
<th>Liver (n = 378)</th>
<th>Pancreas (n = 128)</th>
<th>Lung (n = 248)</th>
<th>Heart (n = 99)</th>
<th>Small bowel (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidiasis</td>
<td>164 (49%)</td>
<td>256 (68%)</td>
<td>97 (76%)</td>
<td>56 (23%)</td>
<td>48 (49%)</td>
<td>19 (85%)</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>47 (14%)</td>
<td>42 (11%)</td>
<td>6 (5%)</td>
<td>109 (44%)</td>
<td>23 (23%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Zygomycosis</td>
<td>8 (2%)</td>
<td>9 (2%)</td>
<td>0 (0%)</td>
<td>9 (3%)</td>
<td>3 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other mold</td>
<td>10 (3%)</td>
<td>9 (2%)</td>
<td>4 (3%)</td>
<td>49 (19%)</td>
<td>7 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Unspecified mold</td>
<td>7 (2%)</td>
<td>8 (2%)</td>
<td>0 (0%)</td>
<td>7 (2%)</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>49 (15%)</td>
<td>24 (6%)</td>
<td>8 (6%)</td>
<td>6 (2%)</td>
<td>10 (10%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Endemic mycoses</td>
<td>33 (10%)</td>
<td>17 (5%)</td>
<td>8 (6%)</td>
<td>3 (1%)</td>
<td>3 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pneumocystosis</td>
<td>5 (1%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>4 (2%)</td>
<td>3 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other yeast</td>
<td>6 (1.8%)</td>
<td>9 (2.4%)</td>
<td>5 (3.9%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Unspecified yeast</td>
<td>3 (0.9%)</td>
<td>5 (1.3%)</td>
<td>1 (0.8%)</td>
<td>6 (2.4%)</td>
<td>0 (0)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

IFIs in Stem Cell Transplant

43% invasive aspergillosis
  ◦ Median onset 99 days

28% invasive candidiasis
  ◦ Median onset 61 days

8% mucormycosis

Choosing an Antifungal

Spectrum

Toxicities

Dose
Fungal Cell Membrane and Cell Wall

- Mannoproteins
- \( \beta-(1,6)-\text{glucan} \)
- \( \beta-(1,3)-\text{glucan} \)
- Chitin

Cell Wall

Cell Membrane

- Ergosterol
- \( \beta-(1,3)-\text{glucan synthase} \)

Ergosterol Synthesis Pathway

- Azoles
- Amphotericin-B
- Echinocandins
- Flucytosine

Slide adapted from R. Lewis; posted at www.doctorfungus.org.
Activities of Antifungal Agents against *Candida* species

<table>
<thead>
<tr>
<th>Species</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Voriconazole</th>
<th>Posaconazole</th>
<th>Isavuconazole</th>
<th>Amphotericin B</th>
<th>Echinocandins</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. albicans</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><em>C. parapsilosis</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S to R</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>S-DD to R</td>
<td>S-DD to R</td>
<td>S-DD to R</td>
<td>S-DD to R</td>
<td>S-DD to R</td>
<td>S to I</td>
<td>S</td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>R</td>
<td>S-DD to R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S to I</td>
<td>S</td>
</tr>
<tr>
<td><em>C. lusitaniae</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S to R</td>
<td>S</td>
</tr>
<tr>
<td><em>C. auris</em></td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S to R</td>
<td>S to R</td>
</tr>
</tbody>
</table>

S: susceptible; S-DD: susceptible dose-dependent; I: intermediate; R: resistant

## Activity of Antifungals against non-*Candida* Species

<table>
<thead>
<tr>
<th>Fungus</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Voriconazole</th>
<th>Posaconazole</th>
<th>Isavuconazole</th>
<th>Amphotericin B</th>
<th>Echinocandins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus spp.</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓ (not A. terreus)</td>
<td>✓</td>
</tr>
<tr>
<td>Fusarium</td>
<td>X</td>
<td>X</td>
<td>✓ (breakthrus)</td>
<td>Conflicting data</td>
<td>X</td>
<td>✓ occas R</td>
<td>X</td>
</tr>
<tr>
<td>Scedosporium</td>
<td>X</td>
<td>+/-</td>
<td>✓</td>
<td>+/-</td>
<td>+/-</td>
<td>✓ occas R</td>
<td>X</td>
</tr>
<tr>
<td>Zygomycetes</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
</tr>
</tbody>
</table>

X = no in vitro activity  
✓ = in vitro activity  
R = resistance  

Choosing an Antifungal

**Spectrum ✓**

**Toxicities**

**Dose**
Adverse Reactions

**Amphotericin B**
- Renal toxicity
- Electrolyte abnormalities
- Infusion-related reactions

**Azoles**
- **Hepatotoxicity**: itraconazole >> voriconazole >> posaconazole, isavuconazole > fluconazole
- **QTc prolongation**: all, EXCEPT isavuconazole
- **CNS effects**: voriconazole
- **Photosensitivity/Skin**: increased risk with voriconazole

**Flucytosine**
- Bone marrow suppression
- Hepatotoxicity

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Beware of Added Toxicities

Hepatotoxicity
- Terbinafine combination, macrolides, anti-mycobacterial therapy

QTc
- Psychotropics, macrolides, quinolones

Renal toxicity
- Vancomycin, aminoglycosides, TMP/SMX, colistin/polymyxin B, calcineurin inhibitors (post-transplant)
Long Term Safety?

Voriconazole associated with most data
- Squamous cell carcinomas and melanomas (3.1-39.5%)
- Periostitis (10%)
- Peripheral neuropathies (9%)

Peripheral neuropathies also reported with itraconazole (17%), posaconazole (1 case), isavuconazole (1 case)

Squamous cell carcinoma reported in 2 cases with isavuconazole

Choosing an Antifungal

- Spectrum ✓
- Toxicities ✓
- Dose
Getting the Dose Right

Factors ↓ concentrations
- Younger Age
- PK changes
- Drug interactions
- Pharmacogenomics

Factors ↑ concentrations
- Drug interactions
- End organ function
- Pharmacogenomics
## Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Voriconazole</th>
<th>Posaconazole</th>
<th>Isavuconazole</th>
<th>Amphotericin B</th>
<th>Echinocandins</th>
<th>Flucytosine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral bioavailability</strong></td>
<td>&gt;90%</td>
<td>30% (caps) 50% (soln)</td>
<td>&gt;90%</td>
<td>8-47% (dose-dependent)</td>
<td>98%</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>10%</td>
<td>&gt;99%</td>
<td>58%</td>
<td>&gt;98%</td>
<td>98%</td>
<td>&gt;95%</td>
<td>85-99%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Food effect</strong></td>
<td>↓ Absorption</td>
<td>↑ Absorption (caps)</td>
<td>↓ Absorption</td>
<td>↑ Absorption</td>
<td>None</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>CSF penetration</strong></td>
<td>&gt; 52%</td>
<td>&lt;1%</td>
<td>60%</td>
<td>5-22%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>75%</td>
</tr>
<tr>
<td><strong>Urine penetration</strong></td>
<td>90%</td>
<td>1-10%</td>
<td>&lt;2%</td>
<td>&lt;2%</td>
<td>&lt;1%</td>
<td>≤5%</td>
<td>&lt;2%</td>
<td>90%</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Minor hepatic (CYP3A4)</td>
<td>Hepatic (CYP3A4)</td>
<td>Hepatic (CYP2C19/2C9)</td>
<td>Hepatic (UDP glucuronidation)</td>
<td>Hepatic (CYP3A4)</td>
<td>Minimal</td>
<td>None Hepatic</td>
<td>Minor intestinal</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Renal</td>
<td>Hepatic</td>
<td>Renal</td>
<td>Feces</td>
<td>Feces</td>
<td>Minor</td>
<td>Urine Feces</td>
<td>Renal</td>
</tr>
</tbody>
</table>

Dodds Ashley E. J Fungi (Basel) 2019; 5: 97.
PK Challenges

Absorption
- Itraconazole: dependent on formulation, food, pH
- Voriconazole: dependent on age (↓50% in children), patient population (lung transplant F24-63%)
- Posaconazole: saturable absorption, dependent on food, pH
  - Oral solution: needs fatty supplement
  - Oral delayed-release tabs: ↑50% with fatty meal, not affected by pH

Elimination
- Voriconazole: non-linear PK in adults (↑dose 1.7-fold → ↑AUC 3.1-fold)
Genetic Polymorphisms

CYP2C19 impacts voriconazole metabolism and concentrations

Voriconazole Concentrations

CYP450 Drug Interactions

Cytochrome P450 most common drug metabolizing enzymes
Substrates: drug metabolized by CYP450 enzyme

Substrate

Inhibitor

Metabolism of Substrate

Concentrations of Substrate

Toxicity

Substrate

Inducer

Metabolism of Substrate

Concentrations of Substrate

Efficacy
## Azoles as Inhibitors and Substrates

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Voriconazole</th>
<th>Posaconazole</th>
<th>Isavuconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>+</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>P-glycoprotein</td>
<td>-</td>
<td>yes</td>
<td>-</td>
<td>-</td>
<td>yes (mild)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Voriconazole</th>
<th>Posaconazole</th>
<th>Isavuconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>P-glycoprotein</td>
<td>yes</td>
<td>yes</td>
<td>-</td>
<td>yes</td>
<td>-</td>
</tr>
</tbody>
</table>

Clinical Implications of Interactions

Azoles as **TARGETS** of drug interactions
- Itraconazole, voriconazole, isavuconazole

Azoles as the **CAUSE** of drug interactions
- Fluconazole, itraconazole, voriconazole, posaconazole

Heightened vigilance with rifamycins, antiepileptics, immunosuppressants, psychotropics, statins, warfarin, HIV antiretrovirals

Children

Fluconazole
- ↑ clearance → half-life 20 hrs vs 30 hrs in adults
- Children require 6-12 mg/kg/d for similar adult exposure

Voriconazole
- Linear PK
- Exposure most affected by weight
- 7 mg/kg q12h comparable to 4 mg/kg q12h in adults

Echinocandins
- ↑ CL and shorter half-life compared to adults
- Caspofungin: BSA dosing
- Micafungin: CL inversely related to age (premature infants require 3-fold higher dosing than adults)

## Azole Therapeutic Drug Monitoring

<table>
<thead>
<tr>
<th></th>
<th>Pharmacokinetic variability</th>
<th>TDM range defined</th>
<th>Narrow therapeutic window</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>✓</td>
<td>✓</td>
<td>?</td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>✓</td>
<td>X</td>
<td>?</td>
</tr>
</tbody>
</table>

- **Voriconazole**
  - TDM range: 2-6 mcg/mL (troughs)
  - Troughs >6 mcg/mL associated with hallucinations, hepatotoxicity, neurotoxicity

- **Posaconazole**
  - TDM range: >1 mcg/mL (troughs)

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Therapeutic Drug Monitoring

J.R. is a 27 yo woman (wt 50 kg) with CF, s/p lung transplant who is initiated on voriconazole 300 mg PO q12h x 2 doses, then 200 mg PO q12h for Aspergillus fumigatus on a respiratory culture. Five days after starting therapy a voriconazole trough level is checked and returns at 0.9 mg/L. The nurses have been administering the voriconazole on an empty stomach. Her LFTs are within normal range.

What are best next steps for her voriconazole therapy?

A. Continue voriconazole at current dose
B. Stop voriconazole and check a QTc
C. Increase voriconazole dose to 300 mg PO q12h
D. Decrease voriconazole dose to 150 mg PO q12h
Choosing an Antifungal

Spectrum ✔️
Toxicities ✔️
Dose ✔️
Candidiasis

T.R. is a 58 yo man with short gut syndrome requiring chronic TPN, DM with chronic renal insufficiency admitted with new fever, chills, hypotension. WBC 22,000. Scr 2.7 mg/dL.

Likely line infection
Blood cx +yeast x2

Which of the following would be the most appropriate empiric antifungal therapy?

A. Fluconazole
B. Voriconazole
C. Micafungin
D. Liposomal amphotericin B
"Fluconazole or an echinocandin is recommended as initial therapy (AI). The Expert Panel favors an echinocandin for patients with moderately severe to severe illness or for patients who have had recent azole exposure (A-III)."

For infection due to *Candida glabrata*, an echinocandin is preferred (B-III).

For infection due to *Candida parapsilosis*, treatment with fluconazole is recommended (B-III).

Therapy = source control and early initiation of effective systemic antifungal therapy
Fluconazole vs Echinocandins

IV vs PO, species, site of infection, toxicity drive treatment choice

Distribution:

<table>
<thead>
<tr>
<th>Fluconazole</th>
<th>Echinocandins</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF levels &gt;60% serum levels</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>90% excreted unchanged in the urine</td>
<td>&lt;2% excreted unchanged in the urine</td>
</tr>
<tr>
<td>Aqueous &amp; vitreous humor levels ≥ 70% serum</td>
<td>0%</td>
</tr>
</tbody>
</table>

# Activities of Antifungal Agents against *Candida* species

<table>
<thead>
<tr>
<th>Species</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Voriconazole</th>
<th>Posaconazole</th>
<th>Isavuconazole</th>
<th>Amphotericin B</th>
<th>Echinocandins</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. albicans</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><em>C. parapsilosis</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S to R</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>S-DD to R</td>
<td>S-DD to R</td>
<td>S-DD to R</td>
<td>S-DD to R</td>
<td>S-DD to R</td>
<td>S to I</td>
<td>S</td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>R</td>
<td>S-DD to R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S to I</td>
<td>S</td>
</tr>
<tr>
<td><em>C. lusitaniae</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S to R</td>
<td>S</td>
</tr>
<tr>
<td><em>C. auris</em></td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S to R</td>
<td>S to R</td>
</tr>
</tbody>
</table>

*S*: susceptible; *S-DD*: susceptible dose-dependent; *I*: intermediate; *R*: resistant

Candidiasis

T.R.’s blood culture is identified as Candida parapsilosis. He was empirically started on Micafungin, his line was removed/replaced, and he was de-escalated to fluconazole 200 mg PO daily. Five days into his fluconazole course, his QTc increased from 480 msec to 537 msec (normal QRS).

What is the best option to complete T.R.’s antifungal therapy?

A. Continue fluconazole PO
B. Change back to micafungin IV
C. Change to isavuconazole PO
D. Change to voriconazole PO
Isavuconazole Versus Caspofungin in the Treatment of Candidemia and Other Invasive Candida Infections: The ACTIVE Trial

Isavuconazole did not meet non-inferiority criteria

- Overall response at EOI VT: successful outcome 60.3% in isavuconazole group vs. 71.1% in caspofungin group (adjusted difference: -10.8%; 95% CI -19.9—-1.8)
- Overall response rates at 2 weeks after EOT and mortality were similar

Invasive Aspergillosis

Risk factors
- Profound and persistent neutropenia
- Repeated cycles of prolonged neutropenia
- Corticosteroids
- GVHD
- HSCT (allo > auto)
- Hematologic malignancies
- SOT (lung > liver > heart)
  - Reoperation/retransplant
  - Rejection
  - CMV infection
  - Renal failure (especially requiring hemodialysis)
  - Aspergillus colonization

Most common species
- A. fumigatus
- A. flavus
- A. niger
- A. terreus
Invasive Aspergillosis

A.F. is a 67 yo woman with AML. She is neutropenic on broad-spectrum antimicrobials, with fever and new respiratory symptoms. A CT scan is obtained and is suggestive of invasive fungal infection with a halo-sign. Invasive aspergillosis is strongly suspected.

Based on the IDSA guidelines, which antifungal regimen should be initiated in A.F.?

A. Liposomal amphotericin B
B. Fluconazole
C. Voriconazole
D. Micafungin
E. Voriconazole plus anidulafungin
**Primary** | Alternatives
---|---
Voriconazole 6 mg/kg q12h x2, then 4 mg/kg q12h | • L-AMB 3-5 mg/kg/d, isavuconazole
• ABLC 5 mg/kg/d
• Caspofungin
• Micafungin
• Posaconazole
• Itraconazole

<table>
<thead>
<tr>
<th>12-week survival (%)</th>
<th>Voriconazole (144)</th>
<th>Amphotericin B (133)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>70.8</td>
<td>57.9</td>
</tr>
<tr>
<td>12-week complete/partial response (%)</td>
<td>52.8</td>
<td>31.6</td>
</tr>
<tr>
<td>Treatment duration (days)</td>
<td>77</td>
<td>10</td>
</tr>
</tbody>
</table>

### Voriconazole 6 mg/kg q12h x2, then 4 mg/kg q12h

**Alternatives**
- L-AMB 3-5 mg/kg/d
- ABLC 5 mg/kg/d
- Caspofungin
- Micafungin
- Posaconazole
- Itraconazole

**Comments**
Primary combination therapy is not routinely recommended based on lack of clinical data; addition of another agent or switch to another drug class for salvage therapy may be considered in individual patients.

Combination Therapy

Slide adapted from R. Lewis; posted at www.doctorfungus.org.
## Initial Combination Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Sample size</th>
<th>Design</th>
<th>Regimen-Combo</th>
<th>Regimen-Monotherapy</th>
<th>Outcome measure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kontoyiannis, et al (Cancer 2005)</td>
<td>Heme Malignancy</td>
<td>112 (11 C, 101 M)</td>
<td>Cohort</td>
<td>Lipid ampho + Itra IV/PO</td>
<td>Lipid ampho</td>
<td>Favorable response (EOT)</td>
<td>NO BENEFIT 0% combo vs. 10% mono (p=ns)</td>
</tr>
<tr>
<td>Singh, et al (Transplantation 2006)</td>
<td>Solid Organ Transplant</td>
<td>87 (40 C, 47 M)</td>
<td>Cohort</td>
<td>Vori + Caspo</td>
<td>Lipid ampho</td>
<td>Mortality (3 mos)</td>
<td>NO BENEFIT 68% combo vs. 51% mono (p=0.117)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Beneficial in subset with renal failure or A. fumigatus infection</strong></td>
<td></td>
</tr>
<tr>
<td>Upton, et al (CID 2007)</td>
<td>HSCT</td>
<td>405 (33 C, 372 M)</td>
<td>Cohort</td>
<td>Vori + Caspo (33)</td>
<td>Voriconazole (58)</td>
<td>Mortality (3 mos)</td>
<td>NO BENEFIT Unadj HR 2.3 (0.6-9.4; p=0.23)</td>
</tr>
<tr>
<td>Raad, et al (Leukemia 2008)</td>
<td>Heme Malignancy</td>
<td>143 (38 C, 105 M)</td>
<td>Cohort</td>
<td>Lipid ampho (≥ 7.5 mg/kg/d) + caspo (38)</td>
<td>Posaconazole (53)</td>
<td>Favorable Response (EOT or 3 mos)</td>
<td>BENEFIT 11% combo vs. 40% mono (p=0.002)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mortality (3 mos)</td>
<td>74% combo vs. 43% mono (p=0.004)</td>
</tr>
<tr>
<td>Caillot, et al (Cancer 2007)</td>
<td>Heme Malignancy</td>
<td>30 (15 C, 15 M)</td>
<td>Open, RCT</td>
<td>Lipid ampho (3 mg/kg/d) + caspo</td>
<td>Lipid ampho (10 mg/kg/d)</td>
<td>Favorable response (EOT)</td>
<td>BENEFIT 67% combo vs. 27% mono (p=0.028)</td>
</tr>
</tbody>
</table>
Combination Vori/Anidulafungin vs. Vori Monotherapy – Primary Therapy

Prospective, randomized double-blind
- Allo-HSCT/heme malignancy patients
- 142 monotherapy vs. 135 combination
- Combination therapy x 2-4 weeks, at 2 weeks could switch to monotherapy

Primary endpoint: survival at 6 weeks

Take home → combination therapy may be of benefit in patients with clinical symptoms plus galactomannan positive AND combination therapy may only be necessary for 2 weeks

Isavuconazole vs. Voriconazole for IA

Primary treatment

Primary endpoint: no difference in all-cause mortality at day 42 in ITT population
- 19% in isavuconazole groups vs. 20% in voriconazole group (adjusted treatment difference –1.0%, 95% CI –7.8 to 5.7)

Less treatment emergent adverse events in isavuconazole group
- Lower frequency of hepatobiliary disorders, eye disorders, and skin/subcutaneous tissue disorders

No altered/TDM dosing of voriconazole

Posaconazole vs. Voriconazole for IA

Primary treatment

Primary endpoint: no difference in all-cause mortality at day 42 in ITT population
- 15% for posaconazole group vs. 21% for voriconazole group (treatment difference −5.3%, 95% CI −11.6 to 1.0)

Fewer drug-related adverse events with posaconazole
- Eye disorders, psychiatric disorders

More hypokalemia and decreased appetite with Posaconazole

No altered/TDM dosing of voriconazole

Zygomycetes

Manifestations: rhinocerebral, pulmonary, gastrointestinal, cutaneous, and disseminated

Most common species
- Rhizopus
- Rhizomucor
- Mucor
- Absidia

Aggressive, fast growing, non-septate molds
- Tissue necrosis common

Risk factors
- Hematologic malignancy
- Prolonged and profound neutropenia
- Poorly controlled diabetes mellitus
- Prolonged corticosteroid use
- Iron overload
- Malnutrition
- Illicit intravenous drug use
- Premature birth

Mortality 44% in DM, 35% in patients with no underlying conditions, and 66% in patients with malignancies
- 96% mortality with disseminated infections

Zygomycetes

Treatment = Surgical debridement + Antifungal Treatment
Zygomycetes Antifungal Therapy

**Liposomal amphotericin B (5-10 mg/kg/d)**
- Improved survival rate compared to conventional amphotericin B (67% vs. 39%)
- Liposomal > ABLC
- Limited by nephrotoxicity

**Isavuconazole**
- Compared to historical amphotericin B data
- Day-42 crude all-cause mortality 33% of 21 isavuconazole cases similar to 39% of 33 amphotericin B-treated matched controls
- Limited by small sample size, external control matching

**Posaconazole**
- Not considered first-line
- Posaconazole relatively ineffective in pre-clinical animal models
- Breakthroughs during posaconazole prophylaxis
- Limited to salvage therapy (~60% response rate)

Cryptococcus neoformans

Encapsulated yeast
- Grows naturally in environment
- Found in pigeons nests, droppings

*C. neoformans var neoformans*
- Immunocompromised
- Mortality rate 12-28% overall

Pulmonary and disseminated/CNS diseases most common
Cryptococcus neoformans

Amphotericin B = main therapy

Combination with fluycytosine
- Combination most potent fungicidal regimen with faster CSF sterilization and fewer relapses, lower attributable mortality

Fluconazole
- Substitute for flucytosine
- Fungistatic effect on Cryptococcus sp.
- Associated with increased mortality
- Monotherapy in consolidation and maintenance therapy

Flucytosine

Synthesized in 1957 as an anti-tumor agent

Active against *Candida* sp and *Cryptococcus* sp.

Mechanism: converted to 5-FU which causes RNA miscoding and inhibits DNA synthesis

Significant bone marrow suppression
- Prolonged high serum levels >100 mg/L
- 75-100 mg/kg/d
- Renal elimination, often used with ampho B
- Check 2-hr post dose level: goal 30-80 mg/L

Antifungal Stewardship

Delays in diagnosis and appropriate therapy $\rightarrow$ poorer outcomes

Increased antifungal utilization especially ICUs and transplant centers

Emerging antifungal resistance

Opportunities
- Diagnostics
- De-escalation
- Limiting combination therapy
- Therapeutic drug monitoring
- Drug-drug interaction management
- Guidelines / Education
- IV to PO conversion

Summary

Appropriately assess risk factors for fungal disease in at-risk populations

Choice of antifungal agents based on likely pathogens, pharmacokinetics, toxicity and drug interaction potential

Optimize dosing based on therapeutic drug monitoring

Explore opportunities for antifungal stewardship
Assessment Question #1

Which of the following azole antifungals is not associated with QTc-prolongation?

A. Fluconazole
B. Voriconazole
C. Posaconazole
D. Isavuconazole
Assessment Question #2

Which of the following infusion-related adverse effects to you most expect to see while monitoring a patient receiving intravenous amphotericin B?

A. Anemia
B. Fever and chills
C. Hypokalemia
D. Diarrhea
Assessment Question #3

Which of the following antifungals causes clinically significant drug-drug interactions through inhibition of CYP2C9 or CYP2C19?

A. Micafungin
B. Isavuconazole
C. Voriconazole
D. Posaconazole
Assessment Question #4

Which of the following *Candida* species is notable for its resistance to azole antifungals, persistence in the environment, and association with healthcare-associated infections?

A. *Candida albicans*
B. *Candida lusitaniae*
C. *Candida glabrata*
D. *Candida auris*
Assessment Question #5

Minimal drug interactions and side effects with limited clinical utility in genitourinary and central nervous system fungal infections best characterizes which of the following antifungal classes?

A. Azoles
B. Polyenes
C. Echinocandins
D. Allylamines
Complexities of Antifungal Therapy Made Simple

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