How To Best Use Antifungal Agents

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Roadmap

- Epidemiology
- Diagnosis
- Antifungal drugs and therapy
Trends in fungal diseases

• Increasing cases of invasive fungal infections
• Clinical signs/symptoms are non specific: a continuum of clinical presentations
• Poor diagnostic tools
• Replacement of sensitive species by resistant ones
• Increasing use of prophylaxis and empirical therapy
• Increasing drug and hospitalisation costs
• New hosts

Hope, 2005; Denning, 2006; Lass-Flörl, 2007
Fungal infections

Fungi can be both, colonizers and pathogens, hence vigilance is required in the interpretation of:

- superficial cultures
- antigen tests, PCR screening, presence of antibodies and/or metabolites

Conventional methods for the laboratory diagnosis of fungal infections might be insensitive and timeconsuming!

## Non culture techniques

<table>
<thead>
<tr>
<th>Tests</th>
<th>Fungus identification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galactomannan</td>
<td>Aspergillus species</td>
</tr>
<tr>
<td>1-3-β-D-Glucan</td>
<td>Candia species, Aspergillus species, Pneumocystisjiroveci</td>
</tr>
<tr>
<td>Glucurono-xylo-mannan</td>
<td>Cryptococcus neoformans, Cryptococcus gattii</td>
</tr>
<tr>
<td>Antibody</td>
<td>Histoplasma and Coccidiodes</td>
</tr>
<tr>
<td>PCR</td>
<td>Genus or species-specific</td>
</tr>
</tbody>
</table>

Lass-Flörl, Mycoses 2009
Diagnosis of fungal infections

• Blood cultures
Sensitivity: Candida 35% - 60%

• Antibody
Sensitivity: Candida 50%, chron. Aspergillose 80%

• (1,3)-β-D-Glucan
No difference between yeasts and molds

• Mannan - Candida
Sensitivity 34%-85%, Specificity 76% -94%

• Galactomannan - Aspergillus
Sensitivity 50%-83%, Specificity 64% -94%

• PCR Polymerase chain reaction
Sensitivity 45%-85%, Specificity 56% -94%
Possible Infection

Commensal Flora

Proven Infection
Sterile specimen

Superficial Cultures
Sputum, TS, BAL

Infection

Blood
Aspiration

Biopsy
„Puzzle diagnosis“

- Clinical features
- Microscopic Examination
- CT, Radiology
- Serology tests
Genus and Species Distribution
- what are the concerns?

• C. glabrata: panazole resistant
• C. parapsilosis: MIC↑ echinocandins
• Aspergillus spp: (pan) azole resistant
• A. terreus: Ampho B resistant
• Zygomyzetes: susceptible to POS and AMPHO B
• Scedosporium prolificans: multidrug resistant
• Fusarium solani: multidrug resistant
<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis</td>
<td>Administration of the antifungal agent at a period of high risk of infection</td>
</tr>
<tr>
<td>Empirical treatment</td>
<td>Initiation antifungal in persistently febrile patients with neutropenia (generally 4–7 days in duration) - without a known source and is unresponsive to antibacterial agents</td>
</tr>
<tr>
<td>Preemptive therapy</td>
<td>Aims to treat a suspected early IFI but uses radiologic studies, laboratory markers, or both</td>
</tr>
<tr>
<td>Treatment of proven IFI</td>
<td>European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria: proven IFI</td>
</tr>
</tbody>
</table>
The echinocandin class

• The three sisters. All are IV only
  – Caspofungin
  – Anidulafungin
  – Micafungin

• Mostly similar
  – Safety: Consistently very clean
  – Non-renal clearance (no adjust in renal fail)
    • Hepatic failure:
      – C: 35 mg/d for moderate, no data for severe
  – Drug interactions: More with caspofungin
    • P450 inducers: No effect (A, M), some ↓ (C)
    • Cyclosporine: No effect (A, M), caution (C)
    • Tacrolimus: No effect (A, M), some ↑ (C)

• Caspofungin: 70 mg load then 50 mg/d
• Anidulafungin: 200 mg load then 100 mg/d (IC);
• Micafungin: 50 mg/d. Not approved yet for IC; dose likely 100/d
The azoles

- Fluconazole
  - Renal clearance (dose per creatinine)
  - IV and PO: forms are interchangeable
- Voriconazole
  - Hepatic clearance (↓ dose 50% with mild to moderate failure, no data in severe)
  - IV uses cyclodextrin carrier that is cleared by kidneys. Avoid in renal failure

Safety: Both are quite good
- Hepatic injury is main risk

Drug interactions
- Both have typical range of P450/cytochrome azole problems
  - Voriconazole is more difficult

- Flu: 100-200 mg/d (EC) and 400/d (IC). Load with 2x daily dose.
- Vori: Load with 6 mg/kg q12h x 2 doses. Then, 3-4 mg/kg qd (IC). Oral is 200 mg q12h x 2 dose then 200/d (IC & EC).
Voriconazole

- Oral and iv formulations

- Therapy of choice: Aspergillus
- Increasingly used as prophylaxis and empiric therapy in neutropenia and bone marrow/stem cell transplant
  - Are we selecting for Zygomycosis infections?

- Adverse drug effects: hepatotoxicity – follow LFTs! visual disturbances
  void IV in pts with CrCl < 50 ml/min
Posaconazole

- **Very broad spectrum**
  - Candida spp, Aspergillus, Zygomyces, hyahyphomycetes, Fusarium, endemic fungi

- **Currently approved indications based on clinical trials**
  - Antifungal prophylaxis:
    - patients with HCST and severe GVHD
    - Patients with hematologic malignancies and profound neutropenia secondary to chemotherapy

- **Other uses: salvage therapy of Zygomycosis and other mould infections**
The amphotericinines

- Amphotericin B deoxycholate
  - Fungizone™
- Liposomal amphotericin B
  - AmBisome™
- Amphotericin B lipid complex
  - ABLC, Abelcet™
- Amphotericin B colloidal dispersion
  - ABCD, Amphocil™, Amphotec™

The names matter
- Side-effects & dosages are different
- “Lipid amphi B” does not describe anything at all!
- Broadest antifungal activity

Some patients tolerate one but not another
Lipid Amphotericin B Formulations

Abelcet® ABLC
- Ribbon-like particles
- Carrier lipids: DMPC, DMPG
- Particle size (µm): 1.6-11

Amphotec® ABCD
- Disk-like particles
- Carrier lipids: Cholesteryl sulfate
- Particle size (µm): 0.12-0.14

Ambisome® L-AMB
- Unilaminar liposome
- Carrier lipids: HSPC, DSPG, cholesterol
- Particle size (µm): 0.08

DMPC-Dimyristoyl phosphatidylcholine
DMPG- Dimyristoyl phosphatidylglycerol
HSPC-Hydrogenated soy phosphatidylcholine
DSPG-Distearoyl phosphatidylcholine

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Efficacy of Liposomal AmB (L-AmB) in Invasive Mycoses: AmBiLoad Trial

14 day loading dose of L-AmB 3 or 10 mg/kg/d followed by L-AmB 3 mg/kg/d

Proven/Probable Invasive Fungal Infection

<table>
<thead>
<tr>
<th>Condition</th>
<th>L-AmB 3</th>
<th>L-AmB 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPA</td>
<td>96%</td>
<td>97%</td>
</tr>
<tr>
<td>CT Halo</td>
<td>58</td>
<td>60</td>
</tr>
<tr>
<td>Allo-SCT</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>71</td>
<td>76</td>
</tr>
<tr>
<td>Survival</td>
<td>72</td>
<td>59</td>
</tr>
<tr>
<td>Toxicity</td>
<td>20</td>
<td>32</td>
</tr>
</tbody>
</table>

Note: L-AmB=liposomal amphotericin B; CR+PR=complete & partial responses; EOT=End of Therapy; IPA=invasive pulmonary aspergillosis; Allo-SCT=allogeneic stem cell transplant

Cornely et al, 2007
Yeasts (blood cultures)

Non-neutropenic

No azole prophylaxis

- Fluconazole
  - Fluconazole: C. parapsilosis
  - Candine: C. glabrata

Azole prophylaxis

Neutropenic

- Candine Polyene

Severe sepsis-septic shock

Candine Polyene

IDSA Guidelines for Candida 2009
Other mold infections IDSA-Guidelines 2009

Invasive Mold Infection

Aspergillus
- First Line/Alternative
  - Voriconazol (i.v.)
  - L-Ampho B
- Salvage therapy
  - Itraconazol
  - Posaconazol
  - Polyene*
  - Candine**

Non-Aspergillus
- Mucormycetes
- Polyene*
- Posaconazol
- Salvage therapie
- Polyene*
- targetted therapy
  - Spezies and resistance

* Polyene: AmphoB, L-AmphoB, ABLC, ABCD
** Candine: Caspofungin
Invasive Aspergillosis

Probable or proven

Voriconazol
L-Ampho B*

Ampho B ABCD

Caspofungin
Mycafungin**

Itraconazol

Resistance

Posaconazol

Ampho B L-Ampho B ABCD ABLC

Empiric Treatment: L-Aampho B, Caspofungin

Prophylaxis: Noxafil, Micafungin**

ABCD: colloidal form
*L-Ampho B: liposomal Ampho B, ECIL 2 Guidelines and DGHO (AII)
ABLC: Lipid complex
** In some countries not licensed for IA
Antifungal Combination Therapy: Considerations

**PRO**
- Increased activity
- More rapid response
- Broader spectrum
- Prevention of resistance development
- Better tissue distribution
- Reduced toxicity?

**CON**
- Potential antagonism
- Drug interactions
- Increased toxicity?
  - Higher costs
# Antifungal Treatment Recommendations for Cryptococcal Meningoencephalitis in Human Immunodeficiency Virus-Infected Individuals

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AmBd (0.7-1.0 mg/kg per day) plus flucytosine (100 mg/kg per day)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 weeks</td>
<td>A-I</td>
</tr>
<tr>
<td>Liposomal AmB (3-4 mg/kg per day) or ABLC (5 mg/kg per day, with renal function concerns) plus flucytosine (100 mg/kg per day)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 weeks</td>
<td>B-II</td>
</tr>
<tr>
<td>AmBd (0.7-1.0 mg/kg per day) or liposomal AmB (3-4 mg/kg per day) or ABLC (5 mg/kg per day, for flucytosine-intolerant patients)</td>
<td>4-6 weeks</td>
<td>B-II</td>
</tr>
<tr>
<td><strong>Alternatives for induction therapy&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AmBd plus fluconazole</td>
<td>...</td>
<td>B-I</td>
</tr>
<tr>
<td>Fluconazole plus flucytosine</td>
<td>...</td>
<td>B-II</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>...</td>
<td>B-II</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>...</td>
<td>C-II</td>
</tr>
<tr>
<td><strong>Consolidation therapy:</strong> fluconazole (400 mg per day)</td>
<td>8 weeks</td>
<td>A-I</td>
</tr>
<tr>
<td><strong>Maintenance therapy:</strong> fluconazole (200 mg per day)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≥ 1 year&lt;sup&gt;c&lt;/sup&gt;</td>
<td>A-I</td>
</tr>
<tr>
<td><strong>Alternatives for maintenance therapy&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole (400 mg per day)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>≥ 1 year&lt;sup&gt;c&lt;/sup&gt;</td>
<td>C-I</td>
</tr>
<tr>
<td>AmBd (1 mg/kg per week)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>≥ 1 year&lt;sup&gt;c&lt;/sup&gt;</td>
<td>C-I</td>
</tr>
</tbody>
</table>

ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmBd, amphotericin B deoxycholate; HAART, highly active antiretroviral therapy.

<sup>a</sup> Begin HAART 2-10 weeks after the start of initial antifungal treatment.

<sup>b</sup> In unique clinical situations in which primary recommendations are not available, consideration of alternative regimens may be made – but not encouraged – as substitutes.

<sup>c</sup> With successful introduction of HAART, a CD4 cell count ≥ 100 cells/µL, and low or nondetectable viral load for ≥ 3 months with minimum of 1 year of antifungal therapy.

<sup>d</sup> Inferior to the primary recommendation.
How to best use drugs?

- Identify the fungus (yeasts or mold or...)
- Local epidemiology (IBK versus ....)
- Previous therapy (azoles or polyenes or...)
- Risk factors
- Severity of clinical presentation
- Underlying diseases
- PK/PD
- Toxicity
Thank you very much for your attention!