Fungal infections in the OPAT setting

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Overview

- Fungal infections that may be suitable for OPAT
  - Duration of therapy
  - *Candida spp, Aspergillus spp* infections
  - Resistance
- Antifungal agents
  - Practical considerations
- Current use of antifungals in OPAT
  - Published literature
What fungal infections?

- **Candida spp.**
  - Non-albicans spp.
  - Prosthetic joint infections/OM
  - Endocarditis

- **Aspergillus spp.**
  - CPA
  - IA (resistance/drug intolerance)

- **Scedosporium spp.**
  - Chronic pulmonary infection
  - Bronchitis

- **Others**
  - Endemic fungi
  - *Cryptococcus spp.*
  - Mucor
  - *Fusarium spp.*

- **Azole intolerance and/or resistance**

**OPAT**
Indications & duration of therapy

- Uncommon infections
  - Hampered by paucity of published data
- Often occur in immunocompromised populations
  - Patients may not be well enough for discharge
  - Treatment of underlying condition
- Need for surgical intervention
  - Delay / consideration in discharge planning
Candidaemia

- Removal of intravascular cathether
- Echinocandins recommended first line
  - Exception *C. parapsilosis*
- Alternatives: Amphotericin B, voriconazole, fluconazole
- Uncomplicated 14 days of therapy
  - Oral switch after 10 days
Candida spp. Infections

- Endocarditis
  - Surgery within 1 week
  - 6-8 weeks of AmphoB or echinocandin +/- flucytosine
- Bone & Joint infection
  - Surgical debridement
  - Fluconazole 6-12 months
  - AmphoB 2-6 weeks, then fluconazole 5-11 months
  - Caspofungin 3 weeks, then fluconazole ≥ 4 weeks
  - Posaconazole or voriconazole x 6-12 weeks

ESCMID guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients
Aspergillus spp. Infections

- Azoles are mainstay of therapy
- Drug intolerance/ resistance issues/ salvage may require use of amphotericinB or echinocandin
- Duration will depend on condition being treated
  - IA
  - CPA
Others

- **Endemic mycoses**
  - Moderate/severe disease therapy often started with amphotericinB

- **Scedosporium spp.**
  - Often resistant to multiple antifungals
  - No clear guidelines for duration of therapy

- **Cryptococcus spp.**
  - Induction phase – amphotericinB

- Mucor
## Resistance

<table>
<thead>
<tr>
<th>Candida species</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Voriconazole&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Flucytosine</th>
<th>Amphotericin B</th>
<th>Candins&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>C. albicans</td>
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<td>C. tropicalis</td>
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<td>C. parapsilosis</td>
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<td>S (to I?)</td>
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<tr>
<td>C. glabrata</td>
<td>S-DD to R&lt;sup&gt;b&lt;/sup&gt;</td>
<td>S-DD to R&lt;sup&gt;c&lt;/sup&gt;</td>
<td>S to I&lt;sup&gt;d&lt;/sup&gt;</td>
<td>S</td>
<td>S to I&lt;sup&gt;e&lt;/sup&gt;</td>
<td>S</td>
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<tr>
<td>C. krusei</td>
<td>R</td>
<td>S-DD to R&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>I to R</td>
<td>S to I&lt;sup&gt;e&lt;/sup&gt;</td>
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<tr>
<td>C. lusitaniae</td>
<td>S</td>
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<td>S to R&lt;sup&gt;f&lt;/sup&gt;</td>
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High rates of echinocandin resistance (>12%)
- Fluconazole-resistant *Candida glabrata* clinical isolates

Epidemiology of *Candida spp* changes with selective pressure.
- Fluconazole-resistant *Candida spp*

Emergence of rare, multidrug-resistant *Candida* species

Resistance

3,249 unselected *Aspergillus section fumigatus* isolates screened from 23 centers.

51 *A. section fumigatus* azole resistant from 12 centers.
Prevalence of resistance: 0 - 4.2% per center.

40 *Aspergillus fumigatus*
11 sibling species:
5 *A. lentulus*
3 *A. sydowii*
3 *Neosartorya* spp.

Courtesy of Paul Verweij & Jan van der Linden

Global increase in drug resistance

Figure 1. Epidemiology of ITZ Resistance in the *A. fumigatus* isolates.
Blue bars represent the number of patients with a positive *A. fumigatus* culture (left y-axis) and the red line represents the percentage of those patients with an ITZ+ isolate (right y-axis). The x-axis is the year.

doi:10.1371/journal.pmed.0050219.g001
What antifungal agents?

- Echinocandins
  - Micafungin
  - Caspofungin
  - Anidulafungin
- Liposomal AmphotericinB
- Posaconazole?
Echinocandins

- Micafungin, Caspofungin, Anidulafungin
- Target fungal cell wall
- Used treatment invasive *Candida spp* infections, *Aspergillus spp* infections
- Activity against *Candida spp* in biofilms
- May require loading dose
- No renal dosing required
Echinocandins- adverse reactions

- Hepatotoxicity
- Infusion related side effects (histamine release)
- Phlebitis
- GI disturbance
- Electrolyte disturbances (<1%*)
Liposomal Amphotericin B

- Polyene antifungal agent
- Disrupts fungal cell wall synthesis
- Active against a large number of fungi in vitro
  - *Candida spp, Aspergillus spp*, Mucorales, black moulds
- Drug elimination bi-phasic, terminal half life 15 days
  - Primary route of elimination unknown
Liposomal Amphotericin B- adverse reactions

- Infusion related reactions
  - Nausea, vomiting, chills, rigors
- Phlebitis
- Nephrotoxicity
- Electrolyte disturbances
- Normocytic normochromic anaemia
- Elevated transaminases
Liposomal Amphotericin B

- Test dose recommended
- Infusion rate 2.5mg/kg
  - Often given over 4-6h
- Premedication
  - Hydrocortisone & chlorphenamine
- Pre-hydration
- Renal function monitoring
  - Daily initially, then twice weekly

Practical considerations

- Reconstitution
  - Performed aseptically
- Stability
  - Echinocandins; 24-48h
  - Liposomal AmphoB; 7 days
- Refrigeration
No items found.
2012 survey of US ID physicians
  - 47% reported having ever used amphotericin in OPAT
  - 14% in similar survey performed in Ireland

Amphotericin use (all formulations) 1997-2002
  - High rate of complications (72%), particularly >65yo
    - Nephrotoxicity, electrolyte disturbances
  - Readmissions 12%, cessation treatment 25%

Fungal infections in OPAT

- Possible to treat a variety of fungal infections
  - Careful patient consideration
  - Practical aspects and services available
    - Particularly with vulnerable patient populations
  - Need for close monitoring
    - Initiation
  - May require initiation of therapy in hospital
- Need for robust data on safety and efficacy of use of antifungals in OPAT setting
Thank You