

Fungal infections in the OPAT setting

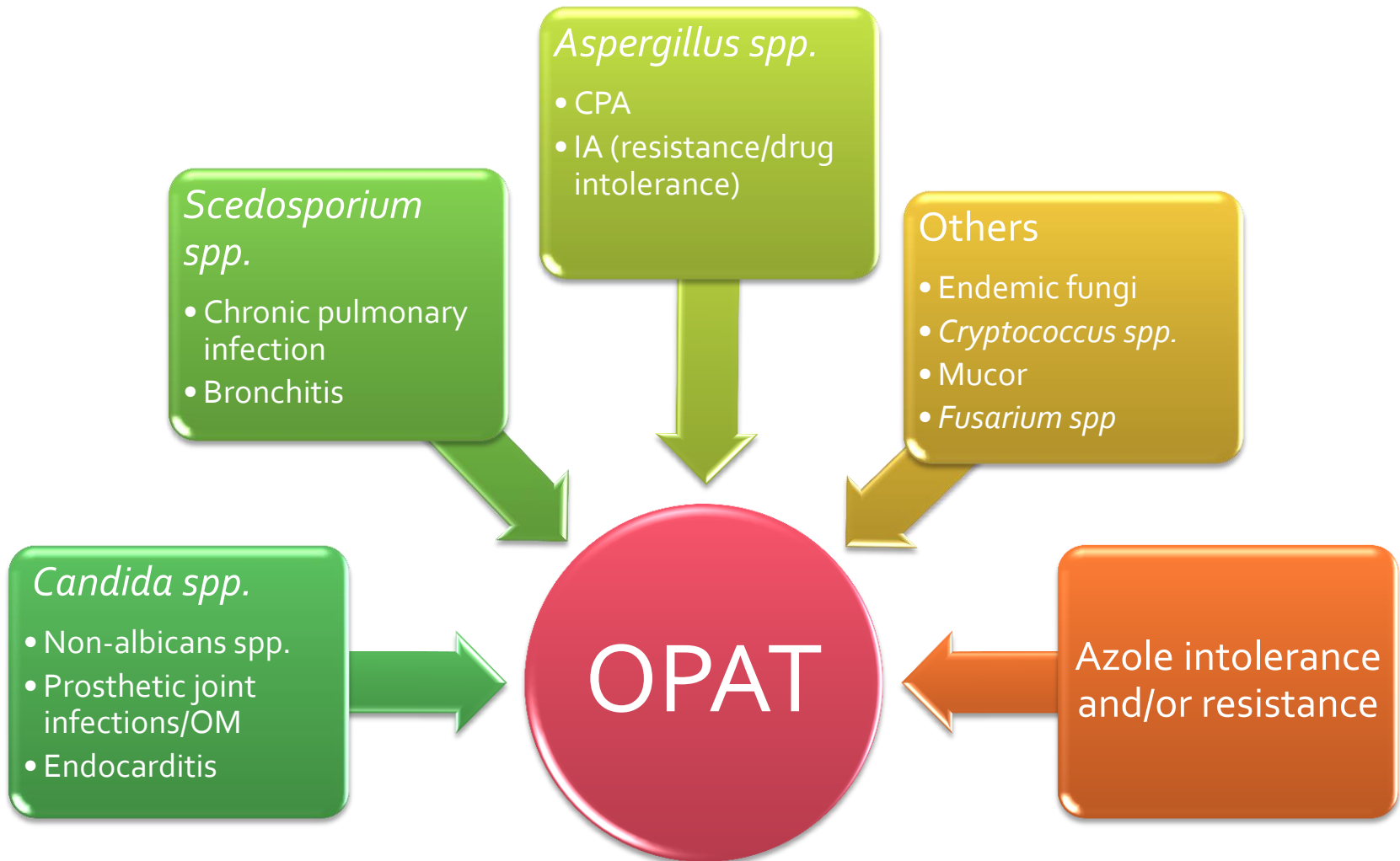
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Overview

- 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?



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

Candida spp. Infections

- Candidaemia
 - Removal of intravascular catheter
 - 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

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

<i>Candida</i> species	Fluconazole	Itraconazole	Voriconazole ^d	Flucytosine	Amphotericin B	Candins ^a
<i>C. albicans</i>	S	S	S	S	S	S
<i>C. tropicalis</i>	S	S	S	S	S	S
<i>C. parapsilosis</i>	S	S	S	S	S	S (to I?)
<i>C. glabrata</i>	S-DD to R ^b	S-DD to R ^c	S to I ^d	S	S to I ^e	S
<i>C. krusei</i>	R	S-DD to R ^c	S to I ^d	I to R	S to I ^e	S
<i>C. lusitanae</i>	S	S	S	S	S to R ^f	S

Resistance

- 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

Alexander et al. Clin Infect Dis 2013; 56:1724–32.

Chow et al. Clin Infect Dis 2008; 46:1206–13

Chowdhary et al. Eur J Clin Microbiol Infect Dis. 2014 Jun;33(6):919-26. doi:

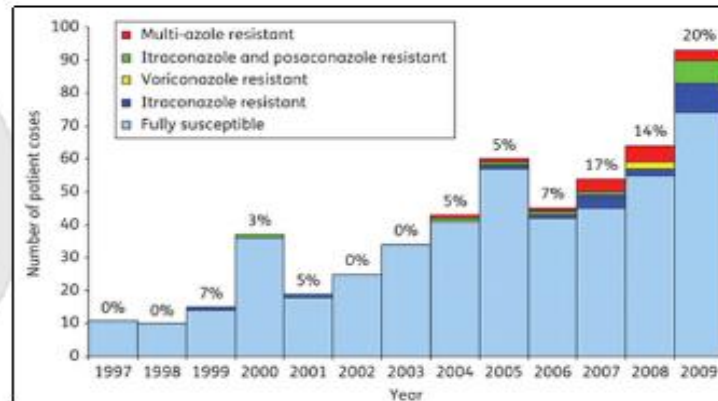
Resistance

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

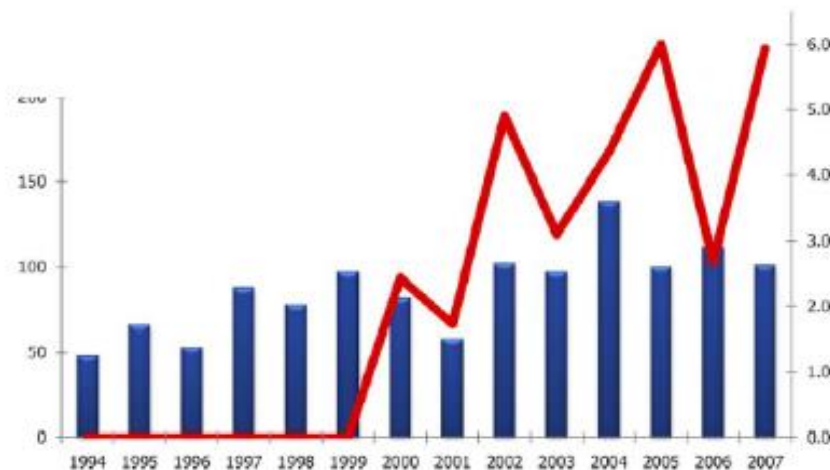


Figure 1. Epidemiology of ITZ Resistance in the *A. fumigatus* Isolates

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

Global increase in drug resistance

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 15days
 - 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 Amphotericin B; 7 days
- Refrigeration

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Published literature

- 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%

Muldoon *et al.* Infect Dis (Lond). 2015 Jan;47(1):39-45

Muldoon *et al.* Eur J Clin Microbiol Infect Dis. 2013 Nov;32(11):1465-70

Malani *et al.* Pharmacotherapy 2005;25(5):690-697

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

A microscopic image showing several branching hyphae of a fungus, likely Aspergillus. The hyphae are filled with numerous small, spherical, light-colored spores. The background is a light, slightly textured surface.

Thank You