Invasive Pilzinfektionen:
Von der Epidemiologie zur Therapie

Infektionskolloquium CIDiC
Tübingen
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Roadmap

Epidemiology
Pathomechanism
Diagnosis
Treatment
Trends in fungal diseases

Increasing cases of invasive fungal infections (immunocompromised pts)

Clinical signs are non specific: a continuum of presentations

Poor diagnostic tools

Replacement of sensitive species by resistant ones

Increasing use of prophylaxis and empirical therapy

Increasing drug and hospitalization costs

New hosts – ageing population

No regular surveillance – incidence varies on underlying diseases

Lass-Flörl, CMI 2016
Multi-country burden of fungal diseases

The medically most important opportunistic mycoses in Europe are caused by *Aspergillus spp.* and *Candida spp.*

http://www.life-worldwide.org/
• Resistance to voriconazole uncommon (< 0.5 % resistant) with exception of C. glabrata (10.5 %)
• Echinocandin-resistant C. glabrata were found to be fluconazol resistant (38 %)
Invasive aspergillosis

- *Aspergillus* sp. is major mold pathogen\(^1\)
- importance of early diagnosis\(^2\)
- shift to other patients\(^3\) (ICU and COPD)
- emerging of azole resistance in *Aspergillus* sp.\(^4\)
- decrease of infections due to early diagnosis and prophylaxis\(^5\)
- rare species: hot spot - distributions (eg *A. terreus*)\(^6\)

\(^{1}\) Baddley et al, BMC Infectious Diseases 2013; 13:29
\(^{2}\) Taccone et al, Critical Care 2015; 19:7
\(^{3}\) Muñoz Pet al, Mycoses 2015;58 Suppl 2:1
\(^{5}\) Nachbaur et al, Eur J Haematol 2015;94:258
Occurrence of resistance depends on...

- within the clinical setting
- type of fungal disease
- class of antifungal agent
- treatment duration
- varies between center to center.
Spectrum of opportunistic fungal pathogens is increasing!

Primary antifungal prophylaxis with micafungin in patients with haematological malignancies: real-life data from a retrospective single-centre observational study

Nachbaur D, Lackner M, Auberger J, Lass-Flörl C
Eur J Haematology, 2014

Invasive fungal breakthrough infections, fungal colonization and emergence of resistant strains in high-risk patients receiving antifungal prophylaxis with posaconazole: real-life data from a single centre institutional retrospective observational study

Auberger J, Lass-Flörl C, Aigner M, Clausen J, Gastl G and Nachbaur D
J Antimicrob Chemother, 2012
Mortality in invasive fungal infections is high!

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Mortality</th>
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<tbody>
<tr>
<td>Candida spp</td>
<td>40%</td>
</tr>
<tr>
<td>Aspergillus spp (2001/2009)</td>
<td>62%/31%</td>
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<tr>
<td>Andere invasive Pilze (Fusarium spp., Zygomyzeten)</td>
<td>~80%</td>
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<tr>
<td>Scedosporium spp</td>
<td>100%</td>
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1. Fungal environment

2. Innate and adaptive immunity

3. Time of exposure, route of transmission

4. Selective antifungal pressure

- Immunocompetent pts
  - Trauma pts

- Immunosuppressed pts
  - Cancer
  - Transplantation

- ICU pts
  - Severely ill
1. Humans: new at risk populations

2. Humans and their environment

3. Novel treatment strategies

4. Aging population
Define your individual needs of the three cornerstones.....

Diagnosis

Conventional tests

Antigen tests

Molecular based tests

The patient
Which test when? Which test is bests?
Diagnosis of Mycotic Infections

Diagnosis and identification require microscopic viewing of stained specimens, culturing in selective and enriched media and specific biochemical and serological tests.
Epidemiology
Pathomechanism
Diagnosis
Treatment
Which drug when to use?

- Fungus (spectrum)
- Previous therapy
- Risk factors
- Local epidemiology
- Severity of clinical presentation
- Underlying diseases
- Safety
- PK/PD
The echinocandin classes

- 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)
The azoles

- Fluconazole
  - Small spectrum
  - IV and PO: forms are interchangeable
- Voriconazole
  - Aspergillus
  - IV uses cyclodextrin carrier that is cleared by kidneys. Avoid in renal failure
- Posaconazole (oral, iv)
  - Prophylaxis
  - Broadest azole
- Isavuconazole (oral, iv)
  - Aspergillus & Mucorales
- Safety issues: Are quite good
  - Hepatic injury is main risk
- Drug interactions
  - Have typical range of P450/cytochrome azole problems
The amphotericines

- 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 ampho B” does not describe anything at all!
  - Broadest antifungal activity

Some patients tolerate one but not another
Four unresolved problems

We lack robust, rapid, simple, and cheap tools for sensitive diagnosis - to allow adequate antifungal treatment.

We need safer and more effective antifungal drugs.

What is best prophylaxis?

Currently there are no approved human vaccines for any invasive fungal pathogen.
Thank you very much for your attention!