Pilzinfektionen – welche Diagnostik, welche Therapie?

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Disclosures

• Grants
  – Gilead, Merck, Sharp & Dohme, Pfizer

• Consultant
  – Amplyx, Astellas, Basilea, F2G, Gilead, Merck, Sharp & Dohme, Pfizer, Schering-Plough, Scynexis

• Speakers’ bureau
  – Astellas, Basilea, F2G, Gilead, Merck, Sharp & Dohme, Pfizer, Schering-Plough and Zeneus/Cephalon
6 yo Neutropenic Girl with Recurrent Acute Lymphoblastic Leukemia

- 6-year old profoundly neutropenic girl with recurrent lymphoblastic leukemia
- accidental fall into her sister, laceration on the scalp requiring surgical suture

- admitted with new fever on the next day
  - persistent fever despite broadspectrum ABX, development of severe headaches, increasing swelling and liquid discharge from the wound
  - surgical debridement and biopsies on day 12
Histology revealed invasive hyphal growth, and cultures white/cream-colored colonies with aerial mycelium identified as *Coprinopsis cinerea* by gene sequence analysis (ITS1/ITS2).

Antifungal susceptibility by E-Test (µg/ml):

- **Amphotericin B** 0.006
- **Flucytosine** >32
- **Caspofungin** >32
- **Voriconazole** 0.125
- **Posaconazole**: 0.5

Complete recovery with L-AMB (3 mg/kg/d x6 until neutrophil recovery on HD 18), then POS (100/200 mg QD alternating) + TDM for 66 days.
6 yo Neutropenic Girl with Recurrent Lymphoblastic Leukemia (3)

- General points to be made:
  - Importance of a microbiological diagnosis
  - Invasive, potentially life-threatening infection by a rare environmental filamentous basidiomycete of uncertain behavior reported in only few human beings
  - Antifungal therapy largely empiric
    - MIC-testing not standardized
    - no *in vitro / in vivo* correlations
    - no meaningful clinical data
Risk Factors and Epidemiology
Immunological Risk Factors for IFDs in Pediatric Patients

Deficits of Phagocytic cells

Invasive infections by
- *Cr. neoformans*
- dimorphic moulds

Mucocut. candidiasis

Deficits of T-Lymphocytes

Invasive infections by
- *Candida* spp.
- *Aspergillus* spp.
- rare opport. moulds and yeast
Pediatric Populations at Risk to Develop IFDs

- AML and ALL if neutropenic and on steroids
- Recurrent leukemias
- Hematopoietic stem cell transplantation
  - During granulocytopenia until engraftment
  - During augmented immunosuppression for GVHD

- Very low and extremely low birth weight infants
- Children with life-threatening problems in the ICU

... chronic granulomatous disease; chronic lung disease/CF; lung and heart/lung, liver, small bowel/pancreas transplantation; metabolic diseases

references in Groll AH, Lancet Oncology 2014 (ECIL guideline); Hope et al., CMI 2013 (ESCMID guideline)
Pediatric Populations at Risk to Develop IFDs

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A Preterm Infant…

- Preterm infant, GA 26 w, BW 620gr
- Ventilator
- Multiple perinatal problems
- Day 3-7 CONS sepsis
- Day 16 *Pseudomonas* sepsis
- Day 35 suspected necrotizing enterocolitis
- Day 36-39 *Candida albicans* bloodstream infection
  - CSF sterile, WBC-75, Glucose-N, Protein-115
  - Brain US (-)
Congenital Cutaneous Candidiasis: Prompt Systemic Treatment Is Associated With Improved Outcomes in Neonates

David A. Kaufman,1 Sarah A. Coggins,2 Santina A. Zanelli,1 and Jörn-Hendrik Weitkamp1
Pediatric Populations at Risk to Develop IFDs

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references in Groll AH, Lancet Oncology 2014 (ECIL guideline); Hope et al., CMI 2013 (ESCMID guideline)
18 mo Previously Healthy Girl

- New palpable left lumbosacral mass
- Malaise, refusal to walk
- Elevated temperatures

...  
- MRI shows large paravertebral mass, suggestive of neuroblastoma
- CRP 5.6 mg/dL, laboratory values otherwise ‘normal’

...  
- Catecholamines negative
18 mo Previously Healthy Girl

- Surgical biopsy for tissue diagnosis
  - Liquid collection
  - Multiple cultures: *A.fumigatus*
  - Histopathology: Branching hyphae

- CT shows intrapulmonary lesion
- BAL performed
  - *A. fumigatus* by culture
  - Positive Antigen test

... diagnosis of *Chronic Granulomatous Disease* by functional tests and sequencing

Courtesy of M. Klein
CARD9 Deficiency: Clinical Spectrum

- Presentation with superficial but also invasive mycoses:

<table>
<thead>
<tr>
<th>Fungal diseases</th>
<th>Number of cases (%)</th>
<th>Median age at onset (years)</th>
<th>Mean age at onset (years)</th>
<th>Range of age at onset (years)</th>
<th>Outcome (alive/dead)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMC</td>
<td>22 (37.9%)</td>
<td>8.0</td>
<td>12.9</td>
<td>[Birth–42]</td>
<td>17/5#</td>
</tr>
<tr>
<td>Superficial dermatophytosis</td>
<td>8 (13.8%)</td>
<td>8.0</td>
<td>17.7</td>
<td>[3–42]</td>
<td>7/1#</td>
</tr>
<tr>
<td>Invasive <em>Candida</em> infections</td>
<td>21 (36.2%)</td>
<td>17.5</td>
<td>21.9</td>
<td>[3.5–58*]</td>
<td>17/4</td>
</tr>
<tr>
<td>Extensive/deep dermatophytosis</td>
<td>21 (36.2%)</td>
<td>19.0</td>
<td>24.1</td>
<td>[12–52]</td>
<td>16/5é</td>
</tr>
<tr>
<td>Phaeohyphomycosis</td>
<td>10 (17.2%)</td>
<td>19.0</td>
<td>24.6</td>
<td>[5–48]</td>
<td>9/1</td>
</tr>
<tr>
<td>Invasive extrapulmonary aspergillosis</td>
<td>2 (3.4%)</td>
<td>13.0</td>
<td>13.0</td>
<td>[8–18]</td>
<td>1/1</td>
</tr>
</tbody>
</table>

Corvilain E et al, J Clin Immunol 2018
CARD9-Deficiency: Focus on Superficial / Deep Dermatophytoses

<table>
<thead>
<tr>
<th>Male</th>
<th>12 (70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at first symptoms [years]</td>
<td>8 [2-21]</td>
</tr>
<tr>
<td>First symptoms</td>
<td></td>
</tr>
<tr>
<td>Severe or recurrent tinea capitis</td>
<td>14</td>
</tr>
<tr>
<td>Severe or recurrent tinea corporis</td>
<td>10</td>
</tr>
<tr>
<td>Onychomycosis</td>
<td>6</td>
</tr>
<tr>
<td>Presentations in adulthood</td>
<td></td>
</tr>
<tr>
<td>Lymph node involvement</td>
<td>10</td>
</tr>
<tr>
<td>Central nervous system invasion</td>
<td>1</td>
</tr>
<tr>
<td>Local organ invasion (bone, GI)</td>
<td>2</td>
</tr>
<tr>
<td>Associated infection: thrush</td>
<td>6</td>
</tr>
<tr>
<td>Death</td>
<td>5</td>
</tr>
<tr>
<td>Median age at death [years]</td>
<td>34 [28-91]</td>
</tr>
</tbody>
</table>

STAT 1 GOF Mutation and Fungal Infections

- Chronic mucocutaneous candidiasis (98%)
  - median age first symptoms 1 year
- Superficial dermatophytosis (16%)
- 10% IFI
  - 10 invasive candidiasis
  - 6 *P. jirovecii* pneumonia
  - 5 *Aspergillus* sp. pneumonia
  - 4 cryptococcosis
  - Dimorphic fungal infection: 2 *Histoplasma* sp. pneumonia, 2 disseminated coccidioidomycosis
  - 1 disseminated mucormycosis
- 12% death (30 ans) (38% severe infections (2 fungal))

*Toubiana et al. Blood 2016*
Diagnostic Considerations for Invasive Fungal Diseases
Diagnostic Considerations: Standard Procedures

- Standard diagnostic procedures
  - Comprehensive clinical assessment
  - Blood cultures for yeast and certain molds
  - Cultures, microscopy and, if available, PCR from appropriate liquid and solid diagnostic specimens
  - Imaging studies as mandated by clinical findings

  - Also: Antigen markers (galactomannan, glucan, glucuronoxylomannan) in serum, BAL and CSF for screening and diagnostics
In practice, treatment often needs to be started pre-emptively on the basis of clinical findings, imaging results and/or antigen markers.

Despite these circumstances, however, all efforts should be made to perform the necessary procedures to identify the causative agent and to allow for resistance testing:

- Bronchoscopy and BAL
- Aspirates / tissue biopsies

Always an interdisciplinary approach
“Yeast in blood culture”

50/50

\( \text{Candida albicans} \)
\( \text{Non-alb. Candida spp} \)
\( \text{glabrata} \)
\( \text{parapsilosis} \)
\( \text{tropicalis} \)

Rare opportunistic yeast

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1 Hovi et al. BMT 2000; 2 Kaya et al., PBC 2009; 3 Kobayashi et al., JPHO 2008; 4 Benjamin et al, PIDJ 2002; 5 Rosen et al., JPHO 2005; 6 Hale et al., Br J Haematol 2010; 7 Castagnola et al., 2010; 8 Mor et al., PBC 2011; 9 Trifilio et al., BMT 2007; 10 Pongas et al. CMI 2008;
Non-albicans *Candida* Isolates: New Kid on the Block

Since 2009, *Candida auris* has emerged as a global concern due to multidrug resistance and efficient nosocomial spread in healthcare settings:

- Among clinical isolates, resistance to FLU, AMB occurs in > 90, and 40–50 % of isolates, respectively

Schwartz & Patterson Current Infectious Disease Reports 2018; Chowdhary et al. PloS Pathog 2017;
“Lesions suggestive of IFD”

- Aspergillus fumigatus
- Aspergillus flavus
- Aspergillus niger
- Aspergillus terreus

≥ 80%

- Other hyalohyphomycetes
- Phaeohyphomycetes
- Mucorales

≤ 20%

1 Hovi et al. BMT 2000; 2 Kaya et al., PBC 2009; 3 Kobayashi et al., JPHO 2008; 4 Benjamin et al, PIDJ 2002; 5 Rosen et al., JPHO 2005; 6 Hale et al., Br J Haematol 2010; 7 Castagnola et al., 2010; 8 Mor et al., PBC 2011; 9 Trifilio et al., BMT 2007; 10 Pongas et al. CMI 2008;
Emergence of Azole Resistance in *Aspergillus fumigatus*

- ITZ-resistant isolates found in 32 / 1,219 patients
  - All cases were observed after 1999

Snelders et al. PLOS One 2008; Cover, The Lancet Infectious Diseases 9, 2012
Logistic regression analyses to determine if influenza was independently associated with invasive pulmonary aspergillosis in non-immunocompromised (i.e., no EORTC/MSG host factor) influenza-poss. pts compared with non-immunocompr. pts with severe community-acquired pneumonia who had a negative airway influenza PCR test (control)

- Overall incidence of IPA of 19% (83/432) in the influenza vs. 5% (16/315) in CAP cohort
- Influenza independently associated with IPA (adjusted OR 5·19; p<0·001)
- 51% 90-day mortality in influenza patients with IPA and 28% in those without IPA (p=0·001).
Antifungal Drugs and Management Principles
PK Challenges in Pediatric Patients

- Distribution: larger Vd
- Metabolism/elimination: greater Cl
- Oral Bioavailability/Absorption:
  - may be different
  - development of a palatable oral solution may be a major challenge to providing oral delivery
- Particular challenge: NICU and PICU patients
- Also a challenge: transition to adulthood
Antifungal Agents: Approval in Pediatric Patients

Cell membrane
- Polyenes
  > D-AmB
  > L-AmB
  > ABLC

- Triazoles
  > Fluconazole
  > Itraconazole
  > Voriconazole
  > Posaconazole
  > Isavuconazole

Cell wall
- Echinocandins
  > Caspofungin
  > Micafungin
  > Anidulafungin

Nucleic acid synthesis
  > Flucytosine
Treatment Algorithms for Invasive Candidiasis
Initial Treatment Algorithm for Invasive Candidiasis

FLU / VORI likely effective

no

Extended spectrum, fungicidal AF (ECH / AMB)

Azole exposed
Colonized with or high incidence of glabrata/krusei

unstable pt
neutropenic pt

Step-down guided by species and susceptibility

yes

Fluconazole
Voriconazole

modified from Kullberg 05
Candidemia and Invasive Candidiasis: Recommended Pediatric Dosages

- Fluconazole 12 mg/kg
- Liposomal amphotericin B 3 mg/kg
- Caspofungin 50 (25) mg/m² (d1:70mg/m²) (max.70mg)
- Micafungin 2-4 (4-10) mg/kg (>40 kg: 100 – 200 mg)

- Other options:
  - Voriconazole (IV) 2-11, 12-14 yrs, <50kg: 2x8 (d1: 2x9)
    12-14 yrs >50kg and ≥15: adult dose
  - ABLC 5 mg/kg
  - D-AMB B 0.7-1.0 mg/kg +/- 5-FC 100mg/kg

references in Groll AH, Lancet Oncology 2014 (ECIL guideline); Hope et al., CMI 2013 (ESCMID guideline)
Inv. Candidiasis: Predictors of Outcome

- Patient-level quantitative review of 7 randomized trials for treatment of IC including a total of 1915 patients
- Logistic regression analysis
  - Increasing APACHE II score, immunosuppressive therapy
    - Predictors of mortality
  - removal of a central venous catheter, and
  - treatment with an echinocandin
    - associated with decreased mortality
General Management Issues

• Therapy for 14 days after last pos. BC and resolution of all clinical symptoms
• Change from ECHs/LAMB to FLU
• CSF’s in granulocytopenic patients
• Reduction/ disc. of steroids in immunosuppressed pts
• Fundoscopy to r/o endophthalmitis

Hope et al., CMI 2013 (ESCMID guideline)
Treatment Algorithms for Invasive Aspergillosis
Initial Treatment Algorithm for Invasive Aspergillosis

Voriconazole susceptible strain likely

yes

Voriconazole

Isavuconazole

no

VCZ exposed? PCZ exposed?

High incidence of zygomycosis or

no TDM available age < 2 years contraindications

Liposomal Amphotericin

Modification guided by species, response and tolerance

references in Groll AH, EHD 2011
Invasive Aspergillosis: Current Dosage Recommendations

- **Voriconazole**  
  - 2-11 and 12-14 yrs <50kg: 2x8 (d1: 2x9)  
  - 12-14 yrs >50kg and ≥15: adult dose +TDM

- **L-AMB**  
  - 3 (-5) mg/kg

- ‘Second line’:  
  - ABLC 5 mg/kg / L-AMB 3-5 mg/kg  
  - CAS 50 mg/m² (d1:70 mg/m²) (max. 70 mg)  
  - IV / PO ITZ 200 mg (d1/2: 2x200)/ 2.5mg/kg BID *  
  - IV / PO POS 1x300 mg (d1: 2x300)*  
  - IV / PO Isavuconazole 1x200 mg (d1-2: 3x200mg) *

references in Groll AH, Lancet Oncology 2014
Serum-Galactomannan: Monitoring of Treatment Response

Monitoring Responses to Treatment

- risk assessment
- clinical evaluation
- CT monitoring at d 7 and d 14
- ... biomarkers

... treatment duration: months - years
Treatment of Rare Molds / Prophylaxis
Non-Aspergillus Mold Infections: Treatment Recommendations

• Mucormycosis: > LAMB* 5 -10 mg/kg and day
  > ISAVU* 200 mg/day (d1-2: 3x200)
  > ABLC* 5-7.5 mg/kg and day
  > POSA 300mg/day (d1: 2x300)

• Hyalohyphomycetes (*Fusarium, Scedosporium ...*):
  ➢ Triazoles (VORI*, POSA*, ISA) > AMB

• Phaeohyphomycetes (*Alternaria, Bipolaris ...*):
  ➢ Triazoles (ITRA, VORI, POSA*, ISA) > AMB

Skiada ECIL3 Haematologica 2013; Cornely ESCMID/ECMM CMI 2014; Tissot ECIL6 Haematologica 2017; Chowdhary ESCMID/ECMM CMI 2014; Tortorano ESCMID/ECMM CMI 2014
Primary Chemoprophylaxis

• Allogeneic HSCT
  – *granulocytopenic phase: until engraftment (B II; B II*)
  – *GVHD and augmented immunosuppression (A II; A II*)

• AML and recurrent acute leukemia (*B II; A II*)
• High-risk ALL (*B II; A II*)

• **ESCMID:**
  • VSAA and MDS (*A II*)
  • Chronic granulomatous disease (*A II*)
  • Lung transplant patients (*A III*)
  • Liver (*B-III*), heart transplant pts (*B-III*) with high risk profiles
Why are Fungi Medically Important?
## Estimated Burden of Fungal Infections, Germany 2015

### Table 1: Burden of fungal diseases in Germany according to the selected underlying diseases.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Unknown</th>
<th>HIV/AIDS</th>
<th>Respiratory</th>
<th>Cancer/Tx</th>
<th>ICU</th>
<th>Total burden</th>
<th>Rate/100K²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungal skin diseases</td>
<td>6,721,000</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>6,721,000</td>
<td>8,347</td>
</tr>
<tr>
<td>Oral candidosis</td>
<td>n.a.</td>
<td>15,600</td>
<td>n.a.</td>
<td>97,965</td>
<td>n.a.</td>
<td>113,565</td>
<td>141</td>
</tr>
<tr>
<td>Oesophageal candidosis</td>
<td>3,685</td>
<td>100⁴</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>3,785</td>
<td>4.7</td>
</tr>
<tr>
<td>Candidaemia</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>3,712</td>
<td>n.a.</td>
<td>3,712</td>
<td>4.6</td>
</tr>
<tr>
<td>Candida peritonitis</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>3,700</td>
<td>n.a.</td>
<td>3,700</td>
<td>4.6</td>
</tr>
<tr>
<td>Recurrent vaginal candidosis (4 × year⁻¹ or more)</td>
<td>2,470,200</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>2,470,200</td>
<td>30,685⁵</td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
<td>n.a.</td>
<td>n.a.</td>
<td>123,960</td>
<td>n.a.</td>
<td>n.a.</td>
<td>123,960</td>
<td>154</td>
</tr>
<tr>
<td>Severe asthma with fungal sensitisation</td>
<td>n.a.</td>
<td>n.a.</td>
<td>163,131</td>
<td>n.a.</td>
<td>n.a.</td>
<td>163,131</td>
<td>203</td>
</tr>
<tr>
<td>Chronic pulmonary aspergillosis</td>
<td>n.a.</td>
<td>n.a.</td>
<td>2320</td>
<td>n.a.</td>
<td>n.a.</td>
<td>2320</td>
<td>2.9</td>
</tr>
<tr>
<td>Invasive aspergillosis</td>
<td>n.a.</td>
<td>n.a.</td>
<td>2,569</td>
<td>1711</td>
<td>n.a.</td>
<td>4,280</td>
<td>5.1</td>
</tr>
<tr>
<td>Mucormycosis</td>
<td>19</td>
<td>n.a.</td>
<td>n.a.</td>
<td>57</td>
<td>n.a.</td>
<td>57</td>
<td>0.07</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>42</td>
<td>15</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>15</td>
<td>0.02</td>
</tr>
<tr>
<td>Pneumocystis pneumonia</td>
<td>860</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>1013</td>
<td>1.3</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>5</td>
<td>10</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>15</td>
<td>0.02</td>
</tr>
<tr>
<td>Fungal keratitis</td>
<td>32</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>32</td>
<td>0.04</td>
</tr>
<tr>
<td>Total burden estimated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9,610,789</td>
<td></td>
</tr>
</tbody>
</table>

1. n.a. = not applicable or unknown.
2. Rate/100K = rate per 100,000 individuals from the total population in Germany.
3. According ICD10 code 37.8 (mostly EC).
4. New AIDS-defining disease per year with about 280 AIDS per year in Germany (~20% have oesophageal candidosis). Source: www.gbe-bund.de.
5. According to survey by Foxman et al. 2012, 9% of women in Germany have VVC, we have used a 6% rate to account for some misdiagnosis. Rate per 100,000 is for all females.

Ruhnke M, Groll AH, Mayser P et al; Mycoses 2015