Treatment and Prophylaxis

Andreas H. Groll, M.D.
Infectious Disease Research Program
Center for Bone Marrow Transplantation and
Department of Pediatric Hematology/Oncology
University Children‘s Hospital Münster, Germany
Pediatric Antifungal Armamentarium

**Cell membrane**
- Polyenes
  - DAMB
  - LAMB
  - ABLC
- Triazoles
  - Fluconazole
  - Itraconazole
  - Voriconazole *
  - Posaconazole

**Cell wall**
- Echinocandins
  - Caspofungin
  - Micafungin
  - Anidulafungin

**Nucleic acid synthesis**
- Flucytosine
EMA Guidance for Pediatric Drug Development

- Clinical studies on pharmacokinetics, safety and tolerance are prerequisite
- If underlying conditions, cause of targeted disease and expected response are similar

Data generated in adults can be used to support documentation of efficacy

However, the regulations stress the importance of post-marketing surveillance to increase the pediatric database.
Algorithms of Antifungal Interventions

- Primary prophylaxis
- Empirical therapy
- Pre-emptive therapy
- Treatment of documented infections
- Secondary prophylaxis

Focus on cancer/HSCT patients and recommendations of the ECIL Pediatric Group
Guided by concepts of pediatric drug development

Decisions based on

- efficacy in pediatric patient when available
- if only adult efficacy data are available, then grading in pediatrics depends on availability of:
  - quality PK study
  - safety data
- regulatory approval also considered
Treatment Algorithms for Invasive Fungal Diseases
Overriding Principle

• In practice, treatment often needs to be started pre-emptively on the basis of clinical findings, imaging results and/or antigen markers

• Despite this situation, however, all efforts should be made to perform the necessary procedures to
  • identify the causative agent
  • to allow for resistance testing
### Candidemia: First-line Clinical Trial Data

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Success at EOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-AMB 0.7-0.9 mg/kg/d</td>
<td>62 – 79% ¹⁻⁴</td>
</tr>
<tr>
<td>Fluconazole 400 mg/d</td>
<td>72% ¹</td>
</tr>
<tr>
<td>Flu 800 + D-AMB 0.7 *</td>
<td>68% ⁵</td>
</tr>
<tr>
<td>ABLC 5 mg/kg/d *</td>
<td>65% ⁴</td>
</tr>
<tr>
<td>L-AMB 3 mg/kg/d</td>
<td>89.5% ⁶</td>
</tr>
<tr>
<td>Caspofungin 70/50 mg/d</td>
<td>74% ²</td>
</tr>
<tr>
<td><strong>Voriconazole 12/6 mg/kg/d</strong></td>
<td>70% ³</td>
</tr>
<tr>
<td>Micafungin 100 mg/d</td>
<td>89.6% ⁶</td>
</tr>
<tr>
<td><strong>Anidulafungin 200/100 mg/d</strong> **</td>
<td>75,6% ⁷</td>
</tr>
</tbody>
</table>

¹, Rex 94; 2, Mora 02; 3, Kullberg 04; 4, Anaissie 95; 5, Rex 01; 6, Kuse 07; 7, Pappas 07; 8, Reboli 07
ECIL 4 Recommendations: Candidemia and Invasive Candidiasis

Management includes antifungal therapy, control of underlying condition(s), surgery, removal of central venous line (no grading)

**Antifungal therapy:** *

- Amphotericin B Lipid Complex: C II
- Caspofungin: B II
- Fluconazole: B II
- Liposomal Amphotericin B: B II
- Micafungin: B II
- Voriconazole + TDM: B II

1 note EMA Black Box Warning for micafungin; implications for other echinocandins not clear

2 C.krusei is inherently resistant to fluconazole; C.glabrata has variable susceptibility to fluconazole, and treatment with fluconazole is not advised; echinocandins have higher MICs against C.parapsilosis, however, the clinical implications are unknown.
Initial Treatment Algorithm

**FLU / VORI likely effective**

**yes**

- **Fluconazole**
  - **Azole exposed**
  - **Colonized with or high incidence of glabrata/krusei**
  - **unstable pt**
  - **neutropenic pt**

**no**

- **Extended spectrum, fungicidal AF (ECH / AMB)**
  - **Step-down guided by species and susceptibility**

*modified from Kullberg 05*
General Management Issues

Consider catheter removal

- CSFs in neutropenic patients, discontinuation of steroids in immunosuppressed patients
- Therapy for 14 days after last pos. blood culture and resolution of all clinical symptoms
- Fundoscopy (ultrasound) prior to end of treatment

# Invasive Aspergillosis: First Line Clinical Trial Data

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CR/PR at 3 mo</th>
<th>Surv. at 3 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voriconazole 12/8 mg/kg</td>
<td>52.8 %</td>
<td>70.8 %</td>
</tr>
<tr>
<td>D-AMB 1.0 mg/kg + OLAT</td>
<td>31.6 %</td>
<td>57.9 %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CR/PR at EOT</th>
<th>Surv. at 3 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-AMB 3 mg/kg</td>
<td>50.0 %</td>
<td>72 %</td>
</tr>
<tr>
<td>L-AMB 10 / 3 mg/kg</td>
<td>46.0 %</td>
<td>59 %</td>
</tr>
</tbody>
</table>

*Herbrecht 02; Cornely 05*
ECIL 4 Recommendations:
1st line Therapy of Invasive Aspergillosis

Antifungal therapy: *

ABLC          B II¹
Liposomal AmB  B I¹
Voriconazole i.v. +TDM  A I¹
Combination therapy  C III

¹ voriconazole should be preferred in CNS infection.
² oral voriconazole should be used in presence of renal failure because of potential for accumulation of the cyclodextrin excipient

* in alphabetical order
Initial Treatment Algorithm in Pediatric Patients

Voriconazole susceptible strain likely

no

Voriconazole

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
Voriconazole: Current Dosage Recommendation

**Children 2 to 11 years and adolescents 12-14 years and <50 kg**
- 2x8 mg/kg IV (day 1: 2x9 mg/kg)
- 2x9 mg/kg PO (max: 2x350mg)

**Adolescents ≥12 to 14 years and > 50 kg and those 15 years and beyond:**
- 2x4 mg/kg IV (2x6 mg day 1)
- 2x200 mg PO (2x400 mg day 1) (adult dose)
Is TDM Indicated to Guide VCZ Treatment?

The pharmacology of VCZ makes it a candidate for TDM

- Interpretation of concentrations requires achievement of steady state – achievement of steady state, however, uncertain in a non-linear drug
  - Start monitoring early to avoid subtherapeutic exposure early during therapy

- Current boundaries for the therapeutic use range between 2 to 6 ug/mL at trough
  - Increments/decrement not defined – suggestion: 50 and 100 mg per dose in children and adolescents, respectively
General Management Issues

- **Adjunctive surgery:** skin and soft tissue infections; impeding arrosion of pulmonary arteries; operable CNS or lung lesions

- CSFs in neutropenic patients
- D/c of steroids immunosuppressed pts
- Evaluation for further sites of infection (CNS)
- Duration of therapy determined response and reversal of deficit in host defenses

### Options for Non-Aspergillus Mould Infections

<table>
<thead>
<tr>
<th></th>
<th>AMB</th>
<th>CAS</th>
<th>VCZ</th>
<th>ITC</th>
<th>PCZ</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>A. fumigatus</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><em>A. flavus</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><em>A. niger</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><em>A. terreus</em></td>
<td>I-R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Zygomycetes</td>
<td>S</td>
<td>R</td>
<td>R</td>
<td>S-I</td>
<td>S-I</td>
</tr>
<tr>
<td>Hyalohyphomyc</td>
<td>I-R</td>
<td>R</td>
<td>I-R</td>
<td>I-R</td>
<td>I-R</td>
</tr>
<tr>
<td>Phaeohyphomyc</td>
<td>S-I</td>
<td>I-R</td>
<td>S-I</td>
<td>S-I</td>
<td>S-I</td>
</tr>
</tbody>
</table>

References:
Empirical / Pre-emptive Therapy and Primary Chemoprophylaxis
Antifungal Prevention: Rationale / Strategies

• Difficulties in diagnosis and prognostic impact of early treatment provide rationale for initiation of treatment before a definite microbiological diagnosis
  – Empirical therapy (*fever criterion*)
  – Pre-emptive therapy (*CT, galactomannan*)

• Also available: Primary prophylaxis
ECIL 4 Recommendations:
Empirical and Pre-emptive Therapy

- If chosen as strategy, empirical therapy should be initiated after 96 hours of fever with unclear origin unresponsive to broad-spectrum antibacterial agents (BII)
- Both caspofungin and liposomal amphotericin B (1-3 mg/kg/d) can be recommended for empirical antifungal therapy in children (AI)
- Although there are no data for patients already receiving mold-active antifungal prophylaxis, however, switching to a different class of mold-active antifungal agent seems reasonable (no grading)
- Therapy should be continued until resolution of neutropenia (BII)
- Although there are no data on pre-emptive strategies in children, it may be an alternative to empirical therapy (no grading)
Primary Chemoprophylaxis: Targets and Intention

• **Target:**
  – Populations at high risk (≥ 10%)
    • AML, recurrent leukemia’s, ? high risk ALL
    • Allogeneic HSCT
      – ANC ≤500
      – grade III/IV GVHD

• **Intention:**
  – Reduction of invasive fungal diseases
  – Reduction of overall patient mortality
## Primary Chemoprophylaxis: Strategies in Adults and Impact

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Impact on invasive infections</th>
<th>Impact on overall mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical azoles / polyenes</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Aerosolized DAMB</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Aerosolized LAMB</td>
<td>+ (IA)</td>
<td>0</td>
</tr>
<tr>
<td>Low-dose DAMB / ABLC</td>
<td>?</td>
<td>0</td>
</tr>
<tr>
<td>Low-dose LAMB</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Fluconazole 400mg</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Itraconazole (≥0.5µg/mL)</td>
<td>+ (+IA)</td>
<td>0</td>
</tr>
<tr>
<td>Micafungin</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>+ (+ IA)</td>
<td>+</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

References in Groll & Tragiannidis Sem Hematol 2009; 46: 212
ECIL 4 Recommendations:
Primary Chemoprophylaxis in Leukemia Patients

- Primary antifungal prophylaxis against IFDs should be considered in high risk patients (BII)

- **Options include (alphabetical order):**
  - fluconazole (CI) (active only against yeast)
  - itraconazole (BI), TDM recommended
  - liposomal amphotericin (BII)
  - Posaconazole (BI for children >12 years), TDM recommended
  - other options include voriconazole +TDM, micafungin, and aerosolized liposomal amphotericin B (no grading)
  - note: caution should be used with the concurrent use of itraconazole, posaconazole, voriconazole with vincristin

TDM, therapeutic drug monitoring
ECIL 4 Recommendations:
Primary Chemoprophylaxis in allo HSCT: Neutropenic Phase

- Primary prophylaxis against IFDs is recommended during the neutropenic phase until engraftment (BII)

- Options include (alphabetical order)
  - fluconazole (AI) (active only against yeast)
  - Itraconazole (BI), TDM recommended
  - liposomal amphotericin (CIII)
  - micafungin (CI)
  - Voriconazole (BI), TDM recommended

- other options include aerosolized LAMB and posaconazole + TDM (no grading)

TDM, therapeutic drug monitoring
ECIL 4 Recommendations:
Primary Chemoprophylaxis in allo HSCT: Post Engraftment

- **No GVHD, standard immunosuppression:**
  - continue prophylaxis until immune recovery (no grading)

- **GVHD, augmented immunosuppression:**
  - primary prophylaxis against mould and yeast infections is recommended (AII); options include *(in alph. order)*:
    - itraconazole (CII), TDM recommended
    - posaconazole (BI for children >12 years), TDM recommended
    - voriconazole (BI), TDM recommended

  other options include liposomal amphotericin B and micafungin (no grading)

*TDM, therapeutic drug monitoring*
# Algorithm for Persistently Febrile Neutropenic or for Symptomatic Patients

Diagnostic work up including blood cultures, galactomannan antigen x3, chest CT and other imaging as indicated

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All studies negative:</strong></td>
<td>- Continue prophylaxis or start empirical therapy (change of class)</td>
</tr>
<tr>
<td><strong>Positive blood cultures:</strong></td>
<td>- Treat according to species/in vitro susceptibility (change of class)</td>
</tr>
<tr>
<td><strong>Galactomannan positive, chest CT negative:</strong></td>
<td>- Start pre-emptive antifungal therapy (change of class)</td>
</tr>
<tr>
<td><strong>Positive chest CT / positive imaging:</strong></td>
<td>- Start pre-emptive therapy (change of class) and pursue invasive diagnostic procedures</td>
</tr>
</tbody>
</table>
Conclusions
Invasive Fungal Infections

Continue to be important causes of morbidity and mortality
Further research needed

- Epidemiology and outcome
- Imaging and molecular diagnostics
- Phase IV clinical programs
- Education and procedural auditing
ECIL 4 – Pediatric Group
Considerations for Fungal Diseases and Antifungal Treatment in Children

Elio Castagnola (Italy); Simone Cesaro (Italy); Jean-Hugues Dalle (France); Dan Engelhard (Israel); William Hope (United Kingdom); Thomas Lehrnbecher (Germany); Emmanuel Roilides (Greece); Jan Styczynski (Poland), Adilia Warris (The Netherlands)

Co-ordinator: Andreas H. Groll (Germany)

European Conference on Infections in Leukemia
- a joint initiative of EBMT, ICHS, EORTC and European LeukemiaNet
Current Fungal Infection Reports

Editor-in-Chief: Andreas H. Groll

Current Fungal Infection Reports provides in-depth review articles contributed by international experts on the most significant developments in the field. By presenting clear, insightful, balanced reviews that emphasize recently published papers of major importance, the journal elucidates current and emerging approaches to the diagnosis, treatment, management, and prevention of fungal infection.

On the homepage of Current Fungal Infection Reports at springer.com you can

► Read the most downloaded articles for free
► Sign up for our Table of Contents Alerts
► Get to know the complete Editorial Board
► Find submission information

4 issues/year

Electronic access
► springerlink.com