Considerations for Antifungal Management in Pediatric Cancer Patients

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Invasive Fungal Diseases

• Frequent cause of infectious morbidity in immunocompromised patients
• Display constant epidemiological shifts
• Remain difficult to diagnose and to manage
• Associated with high case fatality rates
Populations at Risk and Epidemiology
**Invasive Fungal Diseases: Clinical Risk Factors**

**Prolonged neutropenia**
**Corticosteroids**
**Acute/chronic GVHD**
**Tissue damage**

→ **Aspergillus** and other invasive mould infections

→ **Candida** infections

← **Broad spectrum antibiotics**
**Mucosal colonization**
**Central venous catheters**
**Parenteral lipids**
Pediatric Cancer/HSCT Patients at Risk for Invasive Fungal Diseases

- Major risk factors are similar as in adults
- Underlying conditions, however, their treatment, prognosis and comorbidities are different
- Evaluation of the natural incidence in pediatric patients greatly limited by
  - prophylactic / empiric use of antifungals in the majority of contemporary series
  - differences in the use of diagnostic procedures, disease definitions, population denominators
Stratification of Risk of IFDs in Pediatric Cancer / HSCT Patients

<table>
<thead>
<tr>
<th>Risk stratum</th>
<th>Patient population</th>
</tr>
</thead>
</table>
| High risk (≥ 10 %)     | - acute myeloblastic leukemia  
- recurrent acute leukemia’s  
- allogeneic HSCT          |
| Low risk (≤ 5 %) *     | - acute lymphoblastic leukemia **  
- non- *Hodgkin* lymphoma’s  
- autologous HSCT          |
| Sporadic occurrence *  | - pediatric solid tumors  
- brain tumors  
- *Hodgkin’s* lymphoma     |

* depending on the protocol and additional risk factors  
** consider that low and sporadic risk is not equal to no risk

Case fatality rates (crude mortality) between 20 and 70 % for all patients

Usefulness of Newer Diagnostic Tools
Diagnostic Considerations: Standard and Newer Procedures

- Standard diagnostic procedures not different in pediatric patients and therefore, *not addressed*
  - Blood cultures for yeast and certain molds
  - Cultures, microscopy and, if available, PCR from appropriate liquid and solid diagnostic specimens
  - Identification at species level, resistance testing
  - Imaging studies as mandated by clinical findings

- Pediatric data on the diagnostic usefulness of chest CT imaging and antigen markers for diagnosing invasive aspergillosis *addressed in more detail*
## Diagnostic Considerations: Chest CT Imaging and Antigen Markers

<table>
<thead>
<tr>
<th>Pulmonary Findings</th>
<th>59%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nodules</strong></td>
<td>21%</td>
</tr>
<tr>
<td><strong>Cavity</strong></td>
<td>14%</td>
</tr>
<tr>
<td><strong>Halo Sign</strong></td>
<td>6.4%</td>
</tr>
<tr>
<td><strong>Air Crescent sign</strong></td>
<td>1.6%</td>
</tr>
<tr>
<td><strong>Other infiltrates</strong></td>
<td>20.7%</td>
</tr>
<tr>
<td>Sinus</td>
<td>10%</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>10%</td>
</tr>
</tbody>
</table>

### Galactomannan monitoring

**In serum:**

Comparison of 5 pediatric studies with adequate data

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.76 (0.62 - 0.87)</td>
<td>0.73 (0.46 - 0.61)</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.86 (90.68 - 0.95)</td>
<td>0.90 (0.88 - 0.92)</td>
</tr>
</tbody>
</table>

Useful also for diagnostics in BAL/CSF

### Beta-D-Glucan monitoring

In serum: No adequate data

---

ECIL 4 Recommendations

- ...prospective monitoring of GM in serum every three to four days in children at high risk for IFD is reasonable for early diagnosis of IA (AII)

- ...data support a threshold of an optical density index 0.5 for serum (BIII)

- ...data support the value of GM in the diagnosis of pulmonary aspergillosis (GM in BAL; cut-off 1) and CNS aspergillosis (GM in CSF; cut-off 0.5) in children (BIII)

- Mold-active prophylaxis may decrease performance of the test (BIII)

- Data too limited to make any recommendations on BG testing in children
Serum-Galactomannan: Monitoring of Treatment Response
ECIL 4 Recommendations

- In high-risk children with persistent febrile neutropenia beyond 96 hours or with focal clinical findings, imaging studies (e.g., CT-scan of the lung or adequate imaging of the symptomatic region) should be performed (BII)

- In chest X ray and/or CT scan, typical signs of pulmonary fungal disease are often missing, in particular in the younger age group. In contrast, even atypical pulmonary infiltrates (e.g., fluffy masses) may support the diagnosis of invasive pulmonary fungal disease in a patient at high risk

→ further diagnostic work-up (e.g., BAL, biopsy) should be considered and mold-active antifungal treatment should be initiated (BII)
Drugs available for Management of Invasive Fungal Diseases
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.
Treatment Algorithms for Invasive Candidiasis
Inv. Candidiasis: Spectrum of the Disease

Candidemia

- catheter-associated candidemia
- acute dissemin. candidiasis
- candidiasis of deep compartments
- chronic dissemin. candidiasis

Tissue infection

Rex 2000
# 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%</td>
</tr>
<tr>
<td>Fluconazole 400 mg/d</td>
<td>72%</td>
</tr>
<tr>
<td>Flu 800 + D-AMB 0.7 *</td>
<td>68%</td>
</tr>
<tr>
<td>ABLC 5 mg/kg/d *</td>
<td>65%</td>
</tr>
<tr>
<td>L-AMB 3 mg/kg/d</td>
<td>89.5%</td>
</tr>
<tr>
<td>Caspofungin 70/50 mg/d</td>
<td>74%</td>
</tr>
<tr>
<td>Voriconazole 12/6 mg/kg/d</td>
<td>70%</td>
</tr>
<tr>
<td>Micafungin 100 mg/d</td>
<td>89.6%</td>
</tr>
<tr>
<td>Anidulafungin 200/100 mg/d **</td>
<td>75.6%</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  
Caspofungin ²  
Fluconazole ²  
Liposomal Amphotericin B  
Micafungin ¹,²  
Voriconazole ²  

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

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

modified from Kullberg 05
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

Impact of early Catheter Removal (<48h after start of therapy)

• Post-hoc analysis from two phase III trials
• 842 patients with candidemia and baseline CVC

• Multivariate analysis
  – Removal of baseline CVC by 24 or 48h after treatment initiation not associated with overall treatment success, 28-day and 42 day survival
  – High APACHE II scores and persistent neutropenia consistently associated with treatment failure and mortality

• Data suggest catheter removal on case-by-case basis considering risks and difficulties in replacing a CVC and the likelihood that the CVC is source of candidemia

NUCCI et al, CID 2010
Treatment Algorithms for Invasive Aspergillosis
Invasive Aspergillosis: Spectrum of the Disease

- Invasive pulmonary aspergillosis
  - airway invasive
  - angioinvasive
- Paranasal sinus aspergillosis
- Primary cutaneous aspergillosis
- Alimentary tract aspergillosis
- Disseminated aspergillosis
  - CNS
  - various sites
Spectrum of Invasive Mold Infections

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

≥ 80%

≤ 20%

- Other hyalohyphomycetes
- Phaeohyphomycetes
- Zygomycetes
## 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>

- No controlled data on outcome following first-line therapy with CAS and other triazoles

Herbrecht 02; Cornely 05
ECIL 4 Recommendations: 1\textsuperscript{st} line Therapy of Invasive Aspergillosis

**Antifungal therapy:** *

- **ABLC**
  - B II\textsuperscript{1}

- **Liposomal AmB**
  - B I \textsuperscript{1}

- **Voriconazole i.v. + TDM**
  - A I \textsuperscript{1}

- **Combination therapy**
  - C III

\textsuperscript{1} voriconazole should be preferred in CNS infection.

\textsuperscript{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**
  - yes
  - Voriconazole

- no
  - Liposomal Amphotericin
  - VCZ exposed?
  - ? PCZ exposed?
  - high incidence of zygomycosis
  - or
  - no TDM available
  - age < 2 years
  - contraindications

- 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)
Voriconazole: Pediatric Safety and Tolerance

- 107 patients (0.2-18 years; mean: 10.1 years) who received 252 courses IV (10) and (37)/or (205) PO at recommended dosages
- VCZ was administered at median maintenance dosage of 5.9 mg/kg BID (range, 2.2-22.0) for a median of 65 days (range, 1-1002)
- Increases in hepatic transaminases (53.5%), serum bilirubin (23.6%) and alk. phosphatase (10.9%), skin eruptions (5.6%) and neurological adverse events (AEs) (4.8%) mostly mild to moderate
- AEs necessitating discontinuation occurred in 18 courses (7.1%)
- While mean alk. phosphatase, AST and serum bilirubin values were slightly elevated at end of treatment (EOT) (p<0.01), mean ALT and serum creatinine values were not different from baseline.
VCZ TDM in Immunocompromised Pediatric Patients

74 pts (0.2-18y; mean: 10.2y) / 101 courses of VCZ IV (4) and (15)/or (82) PO at median of 4.8 mg/kg BID (r, 2.2-17.4) for a median of 40 days (r, 6-1002)

<table>
<thead>
<tr>
<th>Voriconazole trough [mg/L]</th>
<th>No. (%) of samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.2</td>
<td>56 (22.3)</td>
</tr>
<tr>
<td>0.2 – 0.5</td>
<td>50 (19.9)</td>
</tr>
<tr>
<td>&gt; 0.5 – 1.0</td>
<td>39 (15.5)</td>
</tr>
<tr>
<td>&gt; 1.0 – 2.0</td>
<td>36 (14.3)</td>
</tr>
<tr>
<td>&gt; 2.0 – 5.0</td>
<td>50 (19.9)</td>
</tr>
<tr>
<td>&gt; 5.0</td>
<td>20 ( 8.0)</td>
</tr>
</tbody>
</table>

- some patients have no or low VCZ concentrations
- also: high inter-individual variability in exposure
VCZ TDM – Correlation with Outcome in Patients with IFIs

- trough levels ≤1mg/L associated with treatment failure
- trough levels ≥5.5 mg/L assoc. with neurological toxicity

- Blood levels >1 mg/L reached after increasing the dosage with complete resolution of infection in all 6 cases

Pascual et al. CID 2008
Non-linear relationship with response (p<0.003) with the probability lower at both extremes

Higher free ratios associated with progressively higher probability of response
VCZ for CNS Aspergillosis: A Case

<table>
<thead>
<tr>
<th>Dosage [mg]</th>
<th>Mean VCZ ±SD [ug/mL]</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 BID</td>
<td>0.21 ±0.06</td>
<td>-0.55-0.97</td>
</tr>
<tr>
<td>400 BID</td>
<td>0.73 ±0.14</td>
<td>0.39-1.08</td>
</tr>
<tr>
<td>500 BID</td>
<td>4.53 ±0.69 *</td>
<td>2.30-6.75</td>
</tr>
</tbody>
</table>

* p=0.0012 bei KW ANOVA

- Ratio CSF/plasma: 0.48 (95% C.I.: 33-62) / 7 paired samples
A Rationale for Combination Therapy?

Pharmacokinetic interactions
- Indirect or direct interactions affecting drug concentrations at the target site:
  - amount of drug
  - rate of accumulation
  - ratio of concentrations

Pharmacodynamic interactions
- spectrum
- synergism or antagonism
- resistance
- toxicity

Lewis & Kontoyiannis 01
Voriconazole plus Anidulafungin vs. Voriconazole for Primary Treatment of Inv. Aspergillosis

- Prospective, randomized double-blind clinical trial in allo-HSCT recipients and pat. with HM with proven/probable IA
- Pat. randomized 1:1 mono vs. Combo
- Primary therapy with open-label VOR (d1 = 2x 6mg/kg/d i.v. from d2= 2x 4mg/kg/d) plus blinded AND (200mg/100mg/d) or blinded placebo
- Combo therapy for 2-4 wks; switch to VOR after 2 wks optional (total TX 6 wks)
- Switch to oral VOR after at least 7 d iv. (2x300mg/d)

- Primary endpoint: overall survival at 6wks (MITT)
Voriconazole plus Anidulafungin vs. Voriconazole for Primary Treatment of Inv. Aspergillosis

Marr et al. ECCMID 2012 Poster LB2812
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

- Consolidation with PO triazoles (VCZ, PCZ, ITZ) following stabilization

Granulocyte Transfusions: Outcomes and Complications

Figure 1. Cumulative incidence curves of IA-related deaths for prolonged neutropenic hematologic malignancy (HM) patients with aspergillosis who received GTXs and those who did not (non-GTX) by a competing risk analysis, using death due to other causes as a competing event ($P = 0.018$) ($n = 128$).

Table 3. Multivariate competing risk model for aspergillosis-related mortality, using death due to other causes as a competing event ($n = 128$)

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent neutropenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>71</td>
<td>2.6</td>
<td>1.5, 4.7</td>
<td>0.001</td>
</tr>
<tr>
<td>No</td>
<td>57</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shortness of breath at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>55</td>
<td>2.2</td>
<td>1.3, 3.8</td>
<td>0.003</td>
</tr>
<tr>
<td>No</td>
<td>73</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive care unit (ICU) stay</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>57</td>
<td>3.0</td>
<td>1.8, 5.1</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>71</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azole-containing regimen in primary or salvage antifungal therapy</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>61</td>
<td>0.3</td>
<td>0.2, 0.5</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>67</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Received GTX</td>
<td></td>
<td></td>
<td></td>
<td>0.011</td>
</tr>
<tr>
<td>Yes</td>
<td>53</td>
<td>2.0</td>
<td>1.2, 3.3</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>75</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Antifungal Prevention
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
Empirical Therapy for F+N: Rationale / Indications

• Targeted prevention in high risk situations
• Early treatment of still occult infections

• Longstanding ‘standard of care’ in pts with
  – ANC ≤500/µl ≥ 10 days
  – Persistent fever >3 days
  – Recurrent fever despite ABX

• Given until resolution of neutropenia / breakthrough infection / limiting adverse events

➢ Approved in children: LAMB and CAS
Empirical vs. pre-emptive Antifungal Therapy

- Multicenter, open, randomized noninferiority trial in 293 patients
  - Survival was 97.3% with empirical treatment and 95.1% with preemptive treatment, meeting non-inferiority criteria
  - Probable or proven IFI more common among patients who received preemptive treatment than among patients who received empirical treatment (13 of 143 vs. 4 of 150; P<0.05)
  - Preemptive treatment did not decrease nephrotoxic but decreased costs of antifungal therapy by 35%.

Cordonnier et al. 09
Empirical vs. Pre-emptive Antifungal Therapy


Gray test, p<0.0001

Gray test, p<0.02
Galactomannan and PCR versus culture and histology

- significant reduction in empirical therapy
- no differences toxicity and overall mortality at week 26
- no information on overall antifungal usage or days in hospital

<table>
<thead>
<tr>
<th></th>
<th>Standard diagnosis group (n=122)</th>
<th>Biomarker diagnosis group (n=118)</th>
<th>% difference between groups (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received empirical treatment with antifungal drugs</td>
<td>39 (32%)</td>
<td>18 (15%)</td>
<td>17% (4 to 26)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause</td>
<td>18 (15%)</td>
<td>12 (10%)</td>
<td>5% (-4 to 14)</td>
<td>0.31</td>
</tr>
<tr>
<td>Invasive aspergillosis-related</td>
<td>6 (5%)</td>
<td>3 (3%)</td>
<td>2% (-2.5 to 7.3)</td>
<td>0.5</td>
</tr>
<tr>
<td>Other invasive fungal disease-related</td>
<td>0</td>
<td>2 (2%)</td>
<td>--</td>
<td>0.24</td>
</tr>
<tr>
<td>Incidence of invasive aspergillosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proven</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>--</td>
<td>1.0</td>
</tr>
<tr>
<td>Probable</td>
<td>0</td>
<td>16 (14%)</td>
<td>-14% (-20 to -7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Possible</td>
<td>0</td>
<td>6 (5%)</td>
<td>-5% (-9 to -1)</td>
<td>0.013</td>
</tr>
<tr>
<td>Incidence of other invasive fungal disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proven</td>
<td>4 (3%)</td>
<td>5 (4%)</td>
<td>--</td>
<td>0.75</td>
</tr>
<tr>
<td>Probable</td>
<td>0</td>
<td>1 (1%)</td>
<td>--</td>
<td>0.49</td>
</tr>
</tbody>
</table>
# Primary Chemoprophylaxis: Strategies in Adults and Impact

## Table

<table>
<thead>
<tr>
<th>Strategy</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
Azol-based Prophylaxis, S.O.P. Münster

• AML, recurrent leukemia’s
  – prophylaxis during granulocytopenia
    • VCZ 2x9 mg/kg PO in pts. <13 years old *
    • PCZ 3x200 mg PO in pts. ≥ 13 years old *
  – careful consideration of contraindications / interactions

Alternatives:
• IV MICA 1 mg/kg x7/week; 3 mg/kg QOD
• IV LAMB 1 mg/kg QOD / QD; 2.5mg x2 / x3/week *

*not approved by EMA for prophylaxis in children
References in Tragiannidis et al. Drugs 2012
Azole-based Prophylaxis: Prophylactic Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Patients (36) n (%)</th>
<th>Episodes (130) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>**Empirical Tx ***</td>
<td>7 (19)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>**Pre-emptive Tx **</td>
<td>5 (14)</td>
<td>6 (5)</td>
</tr>
<tr>
<td><strong>Prob./proven IFI</strong></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Discontinuation</strong></td>
<td>3 (8.5)</td>
<td>3 (2)***</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Success</strong></td>
<td>21 (58.5)</td>
<td>111 (85)</td>
</tr>
</tbody>
</table>

* fever criteriom; 11.8 days (1-23) AFs
** pulm. infiltrates in tCT; 26 days (12-33) AFs
*** exanthema post PCZ; continuation with VCZ
Primary Chemoprophylaxis: Practical Approach post allo HSCT

During granulocytopenia until engraftment:

– fluconazole / voriconazole (TDM)

– chest CT for persistent fever / suggestive symptoms
  • if negative – continuation of prophylaxis / empirical therapy
  • if positive – AG testing/invasive diagnostics and treatment as appropriate

During augmented immunosuppression (steroids):

– Voriconazole <13 yrs (TDM); Posaconazole ≥ 13 yrs (TDM);

Alternatives: LAMB 1 mg/kg QOD / LAMB or ABLC 2.5-4.0 mg x2 or x3/wk; Micafungin 1 mg/kg QD or 3mg/kg QOD

References in Tragiannidis et al. Drugs 2012
Local epidemiology
Availability / value of diagnostic tests
Availability of antifungal compounds

Population at risk (e.g. clinical, genetics)

Antifungal strategy

<table>
<thead>
<tr>
<th>Tx Strategy</th>
<th>Prophylaxis</th>
<th>Empiric Tx</th>
<th>Pre-emptive Tx</th>
<th>Specific Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs or symptoms</td>
<td>Fever refractory to antibiotics</td>
<td>Fever refractory to antibiotics</td>
<td>Antigen positive Pulm. infiltrates</td>
<td>Positive culture and/or histology</td>
</tr>
<tr>
<td>Invasive mycosis*</td>
<td>No</td>
<td>Possible</td>
<td>Probable</td>
<td>Proven</td>
</tr>
</tbody>
</table>

* in clinical practice, not EORTC/MSG criteria!
Algorithm for Persistently Febrile Neutropenic or for Symptomatic Patients

<table>
<thead>
<tr>
<th>Diagnostic work up including blood cultures, galactomannan antigen x3, chest CT and other imaging as indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>o All studies negative:</strong></td>
</tr>
<tr>
<td>● <em>Continue prophylaxis or start empirical therapy (change of class)</em></td>
</tr>
<tr>
<td><strong>o Positive blood cultures:</strong></td>
</tr>
<tr>
<td>● <em>Treat according to species/in vitro susceptibility (change of class)</em></td>
</tr>
<tr>
<td><strong>o Galactomannan positive, chest CT negative:</strong></td>
</tr>
<tr>
<td>● <em>Start pre-emptive antifungal therapy (change of class)</em></td>
</tr>
<tr>
<td><strong>o Positive chest CT / positive imaging:</strong></td>
</tr>
<tr>
<td>● <em>Start pre-emptive therapy (change of class) and pursue invasive diagnostic procedures</em></td>
</tr>
</tbody>
</table>
Conclusion
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
# Azole-based Prophylaxis: ALL and Lymphoma’s

<table>
<thead>
<tr>
<th></th>
<th>ALL</th>
<th>Mature B</th>
<th>LB</th>
<th>ALCL</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n (%)</strong></td>
<td>101 (78)</td>
<td>15 (11)</td>
<td>10 (8)</td>
<td>4 (3)</td>
<td>130 (100)</td>
</tr>
<tr>
<td><strong>Prophylaxis ≥1x</strong></td>
<td>24 (24)</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>35 (27)</td>
</tr>
<tr>
<td>**Empir. Tx *</td>
<td>11 (11)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>12 (9)</td>
</tr>
<tr>
<td>**Pre-empt. Tx **</td>
<td>8 (8)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>9 (7)</td>
</tr>
<tr>
<td>**Prob./prov.IFI ***</td>
<td>4 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4 (3)</td>
</tr>
</tbody>
</table>

* Fever criterion; ** pulmon. infiltrates; *** rev. EORTC/MSG
Recommendation for primary antifungal chemoprophylaxis in children undergoing allogeneic HSCT: Neutropenic Phase

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

- **Options include (alphabetical order)**
  - *fluconazole (Al)* (active only against yeast)
  - *Itraconazole (Bl)*, TDM recommended
  - *liposomal amphotericin (CIII)*
  - *micafungin (Cl)*
  - *Voriconazole (Bl)*, TDM recommended
  - *other options include aerosolized LAMB and posaconazole +TDM (no grading)*

*TDM, therapeutic drug monitoring*
Recommendation for primary antifungal chemoprophylaxis in children undergoing allogeneic HSCT: Post engraftment phase

• No GVHD, standard immunosuppression:
  – continue antifungal prophylaxis until immune recovery (no grading)

• GVHD, augmented immunosuppression
  – primary prophylaxis against mold and yeast infections is recommended (AII); options include
    - 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
Recommendation for primary antifungal chemoprophylaxis in pediatric leukemia patients

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

- Options include
  - fluconazole (Cl) (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*
Voriconazole
Voriconazole

- Non-linear pharmacokinetics
- Complex hepatic metabolism
  - Substrate/inhibitor of CYP2C9, 3A4, 2C19
  - Genetic polymorphisms of CYP2C19
- Number of relevant pharmacokinetic interactions
- Toxicity issues with link to exposure
Voriconazole: Pediatric Development

- Two phase II studies investigating the PK of IV VCZ in children 2-12 years at dosages of 2x3 and 2x4 mg/kg
- 355 plasma samples in 35 patients

High interindividual variability
faster clearance / linear pharmacokinetics
Voriconazole: Dosage in children 2 to 11 yrs (1)

<table>
<thead>
<tr>
<th></th>
<th>3mg/kg</th>
<th>4mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>Paed.</em></td>
<td><strong>Adults</strong></td>
</tr>
<tr>
<td>$C_{\text{ave}}$ (ng/ml)</td>
<td>889</td>
<td>1155</td>
</tr>
<tr>
<td>$AUC_\tau$ (ng·h /ml)</td>
<td>10, 670</td>
<td>13, 855</td>
</tr>
</tbody>
</table>

* 35 subjects from SD and MD PK studies
** 236 healthy volunteers from SD and MD PK studies

1.3 -fold dosage

1.3 -fold

2.8 -fold

Walsh et al. AAC 04
VCZ in children 2-11 yrs: A 1501037

Cohort I
(n=18)
6(iv)- 4(iv)- 6(iv)- 4(po)

Interim analysis
(first 12 subjects)

AUC < 40,000 no safety concerns

AUC > 40,000 or safety concerns

Cohort II A
(n = 18)
6(iv)- 6(iv)- 8(iv)- 6(po)

Cohort II B
(n = 18)
6(iv)- 5(iv)- 4(po)- 5(po)
VCZ in children 2-11 yrs: A 1501037 Pop-PK Analysis

Percent deviations from the reference adult population AUC distribution (4 mg/kg BID IV; 200 mg BID PO)
Voriconazole: Initial Pediatric Dose

Dose recommendation for pediatric patients 2 to 11 yrs
- 2x7 mg/kg IV without loading
- 2x200 mg PO without loading

Dosage for adolescents ≥12 yrs
- 2x4 mg/kg IV (2x6 mg day 1)
- 2x200 mg PO (2x400 mg day 1)

Dosage validation (exposure and safety) in two subsequent pediatric PK trials
Voriconazole: Pediatric Dose Finding

40 immunocompromised children 2 to <12, 7 mg/kg IV BID, switched to 200 mg PO BID

IV doses higher than 7 mg/kg are needed to closely match adult exposures, and a weight-based oral dose may be more appropriate

Driscoll et al. AAC 2011
Voriconazole: Pediatric Dose Finding

26 immunocompromised adolescents 12 to <17 years, IV to PO switch, 6 mg/kg IV BID (d1), then 4 mg/kg IV BID, then 300 mg PO

Exposures in adolescents overall comparable to those in adults. Young adolescents 12-14 with low body weight may need higher doses

Driscoll et al. AAC 2011
VCZ in pediatric patients 2-17 years: Population PK Analysis

- Pooled data from 112 immunocompr. children (2 to <12 yrs), 26 immunocompr. adolescents (12 to <17 yrs), and 35 healthy adults
  - Different maintenance doses (i.e., 3, 4, 6, 7, and 8 mg/kg BID IV; 4 mg/kg, 6 mg/kg, and 200 mg BID PO) evaluated in the children
  - The adult dosing regimens (6 mg/kg i.v. BID on day 1, followed by 4 mg/kg BID, and 300 mg orally BID) evaluated in the adolescents

- Two-compartment model with first-order absorption and mixed linear and nonlinear (Michaelis-Menten) elimination developed

- Deterministic simulations based on individual parameter estimates from the final model to derive dosage

Friberg et al. AAC 2012
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)