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)

Meeting: September 8-10th, 2011
Final version: Jan 19th, 2012
Introduction and Background
IFDs in Pediatric Patients with Leukemia or HSCT

- Children and adolescents are similarly vulnerable to IFDs relative to adults, and have similar presentations, distributions and patterns of fungal diseases.

- However, differences exist as to:
  - underlying conditions and epidemiology
  - usefulness of newer diagnostic tools
  - pharmacology of antifungal agents
  - evidence from interventional phase III studies
Pediatric Cancer/HSCT Patients at Risk for IFDs

- Major risk factors are similar as in adults
- Underlying conditions, however, their treatment, prognosis and comorbidities are different

- Evaluation of the natural incidence of IFDs in pediatric patients relies on historical data of limited quality
  - prophylactic / empiric use of antifungals in the majority of contemporary series
  - differences in the use of diagnostic procedures, IFD definitions, population denominators, and fungal pathogens included
## Incidence, probable/proven IFD in children

<table>
<thead>
<tr>
<th>Ref</th>
<th>Patients studied</th>
<th>IFD incidence</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kobayashi et al. (Japan) 2008.</td>
<td>334 Hem. malignancies, HSCT and others</td>
<td>AML 11.7%; alloHSCT 8.1%; ALL 2.0%; sporadic in solid tumors moulds &gt;&gt; yeast</td>
<td>II retrospective</td>
</tr>
<tr>
<td>Kaya et al. (Turkey) 2009</td>
<td>155 AL during intensive chemotherapy</td>
<td>AML 12.4; ALL 8.4 yeast &gt;&gt; moulds</td>
<td>II retrospective</td>
</tr>
<tr>
<td>Castagnola et al. (Italy) 2010</td>
<td>240 AML</td>
<td>10% of all courses; recurrent AML: 15% moulds &gt;&gt; yeast</td>
<td>II retrospective</td>
</tr>
<tr>
<td>Hale et al. (AUS) 2010</td>
<td>Acute leukemia / HSCT patients</td>
<td>Recurrent leukemia 21%; ALL 18.5%; alloHSCT 15.2%; AML 8.8%; yeast &gt;&gt; moulds</td>
<td>II retrospective</td>
</tr>
<tr>
<td>Mor et al. (Israel) 2011</td>
<td>1047 HSCT and heme/onc patients</td>
<td>AML 13.6%; ALL 5.9%; alloHSCT 3.9%; autoHSCT 3.0%; solid tumors 1.6%; lymphoma 0.8% moulds &gt;&gt; yeast</td>
<td>II retrospective</td>
</tr>
</tbody>
</table>
## Mortality, probable/proven IFD in children

<table>
<thead>
<tr>
<th>Ref</th>
<th>Patients studied</th>
<th>Mortality rate (% of infected patients)</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kobayashi et al. (Japan) 2008.</td>
<td>hematologic malignancies, HSCT and others</td>
<td>48.2% overall*</td>
<td>II retrospective</td>
</tr>
<tr>
<td>Kaya et al. (Turkey) 2009</td>
<td>AL during intensive chemotherapy</td>
<td>4.7% overall</td>
<td>II retrospective</td>
</tr>
<tr>
<td>Castagnola et al. (Italy) 2010</td>
<td>AML</td>
<td>20% overall</td>
<td>II retrospective</td>
</tr>
<tr>
<td>Hale et al. (AUS) 2010</td>
<td>Acute leukemia / HSCT patients</td>
<td>22% in yeast, 50% in mould infections</td>
<td>II retrospective</td>
</tr>
<tr>
<td>Mor et al. (Israel) 2011</td>
<td>HSCT and hematology/oncology patients</td>
<td>21.7% overall</td>
<td>II retrospective</td>
</tr>
</tbody>
</table>

*in invasive pulmonary aspergillosis – the mortality was above 70%
## Stratification of Risk of IFDs in Pediatric Cancer / HSCT Patients

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

* consider that low and sporadic risk is not equal to no risk

** depending on the protocol and additional risk factors, risk for IFD may exceed 10 %

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 (investigational)
  - imaging studies as mandated by clinical findings

- Pediatric data on the diagnostic usefulness of chest CT imaging, antigen markers, and the use of empirical and pre-emptive therapy addressed in detail
Diagnostic Considerations: Overriding Principle

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

- However, considering the risks and benefits in each individual patient, appropriate efforts should be made to perform the necessary procedures in order to identify the causative agent and to allow for resistance testing.
Antifungal Drugs: Pediatric Approval Status

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

Cell wall
- Echinocandins
  > Caspofungin
  > Micafungin
  > Anidulafungin *

Nucleic acid synthesis
> Flucytosine

* not approved in pediatric patients
## Pediatric PK: Getting Dosages Right

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage*</th>
<th>Comment</th>
<th>PK References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>8-12 mg/kg/d qd iv/po</td>
<td>Optimal dose uncertain</td>
<td>Lee 1992; Brammer 1994;</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>5 mg/kg/d bid po</td>
<td>Limited data, not licensed</td>
<td>De Repentigny 1998; Groll 2002</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>600-800 mg/d (tid, bid/qid) po</td>
<td>Only &gt;13 yrs, not licensed</td>
<td>Krishna 2007</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>8-14 mg/kg/d bid iv 400 mg/d bid po</td>
<td>Optimal dose uncertain, and age-dependent</td>
<td>Walsh 2004; Karlsson 2009</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>1.5 (d1:3) mg/kg/d iv</td>
<td>Studies under way, not licensed</td>
<td>Benjamin 2006</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>50 (d1:70) mg/m²/d iv</td>
<td>Robust dataset and models</td>
<td>Walsh 2005; Neely 2009</td>
</tr>
<tr>
<td>Micafungin</td>
<td>1-4 mg/kg/d iv</td>
<td>Robust dataset and models</td>
<td>Seibel 2005; Hope 2007</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>3-&gt;5 mg/kg/d iv</td>
<td>Weight-based dosage inferred without robust PK</td>
<td>Hong 2006</td>
</tr>
<tr>
<td>Amphotericin B Lipid Complex</td>
<td>5 mg/kg/d iv</td>
<td>Limited PK data in children</td>
<td>Walsh 1997</td>
</tr>
</tbody>
</table>

*Dosages may vary according to indication*
Dosage / Dosage Interval

Pharmacokinetics
- Absorption
- Distribution
- Metabolization
- Elimination

Concentration at Target Site

Pharmacological Effects
- Efficacy and Toxicity

Disease-related Factors

Growth and Development

Groll 2011
Maturation processes of excretory organs

- Scaling of dosing regimens based on weight or body surface area generally inappropriate
- Separate pharmacokinetic studies required

Changes in body mass and body composition
Clinical studies on pharmacokinetics, safety and tolerance are a prerequisite.

If underlying conditions, cause of targeted disease and expected response to therapy 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.

A note about grading

- Potentially slightly different from adults
- 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
Primary and secondary prophylaxis
Randomized trials on IFD prophylaxis with inclusion of pediatric patients

- One randomized, double-blind study in 882 HSCT patients included 84 children <16 yrs, comparing micafungin vs. fluconazole (separately analyzed) (van Burik 2004); in another study in 600 HSCT recipients, comparing fluconazole vs. voriconazole, 51 children > 2 yrs were enrolled (Wingard; Blood 2010) (children not separately analyzed)

- Other studies included only few children, were observational, or also included superficial infections in the efficacy assessments
## Pediatric Antifungal Prophylaxis: Literature Review

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Population</th>
<th>n</th>
<th>Antifungal</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bochennek CMI 2011</td>
<td>prospective</td>
<td>Hemato-oncology</td>
<td>44 (46)*</td>
<td>L-AmB 2.5 mg/kg 2x/wk</td>
<td>1 possible IFD</td>
</tr>
<tr>
<td>Molina 2011</td>
<td>observational</td>
<td>Allo-HSCT</td>
<td>46</td>
<td>VORI 10-14 mg/kg/d</td>
<td>1 IA (11 emp.)</td>
</tr>
<tr>
<td>Mehta 2010</td>
<td>Prospective Pk-study</td>
<td>HSCT</td>
<td>15</td>
<td>MICA 3 mg/kg/48hrs</td>
<td>n.a.</td>
</tr>
<tr>
<td>Panapogulu 2010</td>
<td>retrospective</td>
<td>Hemato-oncology</td>
<td>69 (236)*</td>
<td>VORI 8 mg/kg/d</td>
<td>2 proven 1 probable 4 suspected</td>
</tr>
<tr>
<td>Kusuki 2009</td>
<td>retrospective</td>
<td>Hemato-onco HSCT</td>
<td>53 (146)*</td>
<td>MICA 3 mg/kg/d</td>
<td>10 suspected 1 IFD</td>
</tr>
<tr>
<td>Roman 2008</td>
<td>prospective</td>
<td>Allo-HSCT</td>
<td>51 (57)*</td>
<td>L-AmB 3 mg/kg/d</td>
<td>No IFD</td>
</tr>
<tr>
<td>Simon 2007</td>
<td>retrospective</td>
<td>oncology</td>
<td>18</td>
<td>L-AmB 2.5 mg/kg 2x/wk</td>
<td>No IFD</td>
</tr>
</tbody>
</table>

* Number of episodes
# Pediatric Antifungal Prophylaxis: Literature Review

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Population</th>
<th>n</th>
<th>Antifungal</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simon 2007</td>
<td>prospective</td>
<td>oncology</td>
<td>39 (44)*</td>
<td>ITRA po 8 mg/kg/d</td>
<td>1 possible IA</td>
</tr>
<tr>
<td>Grigull 2007</td>
<td>retrospect</td>
<td>Allo-HSCT</td>
<td>53</td>
<td>ITRA po/iv 5 mg/kg/d</td>
<td>2 IFD</td>
</tr>
<tr>
<td>Van Burik 2004</td>
<td>Prosp./rand. double-blind</td>
<td>Allo/auto-HSCT</td>
<td>39 45</td>
<td>MICA 1 mg/kg FLU 8 mg/kg</td>
<td>69% / 53% ‘success’</td>
</tr>
<tr>
<td>Uhlenbrock 2001</td>
<td>Prospective **randomized</td>
<td>Hemato-oncology</td>
<td>16</td>
<td>L-AmB 1 mg/kg 3x/wk</td>
<td>5 probable 6 emp ther</td>
</tr>
<tr>
<td>Mehta 2006</td>
<td>prospective</td>
<td>Allo-HSCT</td>
<td>14</td>
<td>L-AmB 10 mg/kg 1x/wk</td>
<td>1 suspected</td>
</tr>
<tr>
<td>Foot 1999</td>
<td>prospective</td>
<td>HSCT</td>
<td>106</td>
<td>ITRA oral 5 mg/kg/d</td>
<td>No IFD 27 emp ther</td>
</tr>
<tr>
<td>Groll 1997</td>
<td>Prospective</td>
<td>chemotherapy</td>
<td>50</td>
<td>FLU 3 mg/kg/d Nystatine</td>
<td>No differences</td>
</tr>
<tr>
<td>Ninane 1994</td>
<td>Prospective</td>
<td>chemotherapy</td>
<td>245 257</td>
<td>FLU 3 mg/kg/d oral AmB</td>
<td>2 IFD 5 IFD</td>
</tr>
</tbody>
</table>

* Number of episodes; ** compared to pre-emptive strategy
Recommendations

Based on

- Efficacy in phase II and III trials in adults, corresponding to updated ECIL-3 recommendation ¹
- Availability / assessment of pediatric
  - quality PK data
  - safety data
  - supportive efficacy data
- regulatory approval also considered

¹ Maertens 2011
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 (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
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 (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
Recommendation for secondary antifungal prophylaxis in children with leukemia or undergoing HSCT

- Estimated incidences of recurrence of IFD 30-50%

- Secondary prophylaxis is recommended, targeted against the previous infecting agent, as long as the patients are neutropenic or immunosuppressed (AII)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Population</th>
<th>n</th>
<th>Antifungal</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allinson 2008</td>
<td>retrospect</td>
<td>HSCT</td>
<td>11 (11-18 y)</td>
<td>L-AmB followed by VORI p.o.</td>
<td>3/11 IA</td>
</tr>
</tbody>
</table>

ECIL-3 Update 2009, Maertens 2011
## Pediatric Dosages / Key References

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage for Prophylaxis</th>
<th>Key References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>8-12 mg/kg/d qd iv/po (max. 400mg/d)</td>
<td>Lee 1992; Brammer 1994; Ninane 1994; Novelli 1999; Goodman 1992; Slavin 1995; Marr 2000; Menichetti 1994; Rotstein 1999</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>5 mg/kg/d bid po +TDM</td>
<td>De Repentigny 1998; Groll 2002; Foot 1999; Menichetti 1999; Harousseau 2000; Marr 2004; Winston 2003</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>600 mg/d tid po +TDM</td>
<td>Krishna 2007; Cornely 2007; Ullmann 2007</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>&lt;13 yrs 14 mg/kg/d bid / &gt;12 yrs 400 mg/d bid iv; 400 mg/d bid po (all) +TDM</td>
<td>Walsh 2004; Karlsson 2009; Molina 2011; Wingard 2010; Marks 2011</td>
</tr>
<tr>
<td>Micafungin</td>
<td>1 mg/kg (&gt;=50kg: 50 mg) qd iv</td>
<td>Seibel 2005; Hope 2007; Arrieta 2011; Van Burik 2006</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>1 mg/kg or 2.5 mg/kg twice weekly iv</td>
<td>Ringden 1997; Hong 2006; Kolve 2009; Bochennek 2011; Tollemar 1993; Kelsey 1999; Penack 2006</td>
</tr>
</tbody>
</table>

Key references include:
*Pediatric PK, safety, and efficacy data, if available
Pivotal adult phase II I clinical trials*
Newer diagnostic tools: antigen markers and imaging
Galactomannan (GM)

Background

- GM is released by *Aspergillus* spp and can be detected by an FDA-approved enzyme immunoassay (Platelia™).
- Causes for false-positivity of GM include concomitant administration of various antibiotic compounds, cross-reactivity with *Penicillium marneffei* or *Cryptococcus neoformans*, and, in the pediatric population, milk-based diet and *Bifidobacterium bifidum*.
- Based on studies in adults, GM positivity in serum, bronchoalveolar lavage fluid and cerebrospinal fluid are included as a mycological criterion in the revised definitions of invasive fungal disease from the EORTC/MSG consensus group.
- To date, no formal recommendations have been made for GM testing for the pediatric populations.

De Pauw 2008
Analysis of GM in serum

- 10 studies evaluating GM in serum in children (7 prospective)
- Most studies assess serial GM testing in children with hematological malignancies and after allogeneic HSCT (“screening”, performed once or twice weekly)
- 20 - 347 patients, 413 - 2376 samples
- Study endpoints mostly rather vague, including parameters such as “performance” or “diagnostic value” of GM testing in immunocompromised children

## Analysis of GM in serum

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of samples</th>
<th>Type of collection</th>
<th>Def of positivity</th>
<th>Cut-off</th>
<th>Definition of IFD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steinbach et al</td>
<td>826</td>
<td>screening 2x/week during immunosppr</td>
<td>per sample</td>
<td>≥ 0.5</td>
<td>EORTC/MSG</td>
</tr>
<tr>
<td>Hayden et al</td>
<td>990</td>
<td>screening 1x/week during neutropenia</td>
<td>per sample</td>
<td>≥ 0.5</td>
<td>EORTC/MSG</td>
</tr>
<tr>
<td>Armenian et al</td>
<td>1086</td>
<td>screening 2x/week during immunosppr</td>
<td>2 consec samples</td>
<td>≥ 0.5</td>
<td>EORTC/MSG</td>
</tr>
<tr>
<td>Castagnola et al</td>
<td>1798</td>
<td>not specified (at least 2/week)</td>
<td>per sample or</td>
<td>≥ 0.7 single test</td>
<td>EORTC/MSG</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 consec samples</td>
<td>0.5-0.7 2 consec tests</td>
<td></td>
</tr>
<tr>
<td>Rohrlich et al</td>
<td>413</td>
<td>screening 2x/week during immunosppr</td>
<td>2 consec samples</td>
<td>≥ 0.93 ng/ml</td>
<td>Guiot CID 1994</td>
</tr>
<tr>
<td>Challier et al</td>
<td>not specified</td>
<td>not specified</td>
<td>not specified</td>
<td>≥ 1 ng/ml</td>
<td>EORTC/MSG</td>
</tr>
<tr>
<td>Sulahian et al</td>
<td>2376</td>
<td>screening 2x/week during immunosppr</td>
<td>2 consec samples</td>
<td>≥ 1.5</td>
<td>internal definition</td>
</tr>
<tr>
<td>Herbrecht et al</td>
<td>not reported</td>
<td>on suspicion on oncol pts</td>
<td>per sample</td>
<td>≥ 1.5</td>
<td>EORTC/MSG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>screening 1x/week during neutropenia in HSCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hovi et al</td>
<td>932</td>
<td>screening 1x/week during neutropenia</td>
<td>not reported</td>
<td>not reported</td>
<td>EORTC/MSG</td>
</tr>
<tr>
<td>El Mahallawy et al</td>
<td>not reported</td>
<td>not reported</td>
<td>not reported</td>
<td>not reported</td>
<td>EORTC/MSG</td>
</tr>
</tbody>
</table>
Analysis of GM in serum

- Number of patients with proven/probable IFD and of controls vary widely [median 9.5 (range, 1-28) and 63 (range 8-338), respectively].
- True-positive results of GM in serum range from 0 to 100% [studies with ≥10 patients with proven/probable IFD (n=4): the true-positive results 28 - 92% (median, 71.5%)]
- True-negative results of GM in serum range 22 to 100% [studies with ≥10 controls (n=7): the true-negative results 49 - 100% (median, 88.5%)]
- Comparison of 5 studies which use EORTC/MSG criteria and give adequate information for individual patients with results of a formal meta-analysis of adult data

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.76 (95%CI 0.62 - 0.87)</td>
<td>0.73 (95%CI 0.46 - 0.61)</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.86 (95%CI 0.68 - 0.95)</td>
<td>0.90 (95%CI 0.88 - 0.92)</td>
</tr>
</tbody>
</table>

Pfeiffer 2006
Analysis of GM in serum

- Most studies do not report on positive and negative predictive values of GM testing
- The results of the studies of GM in children have to be interpreted with caution, since these studies suffer from heterogeneity of cut-off values, of definitions of assay positivity, and of the analyses performed (e.g., analyzing patients, episodes or some single sample results)
Analysis of GM in BAL/CNS

- Retrospective analysis in 59 immunocompromised children (9 with proven/probable invasive pulmonary aspergillosis) suggests that BAL GM is a valuable adjunctive diagnostic tool.

- GM testing in the CNS is supported by small retrospective case reports and case series:
  - GM levels in the CSF in 5 patients with probable CNS aspergillosis were significantly higher than those of 16 control patients indicating the potential diagnostic value of GM in CSF.
Recommendations

- When GM in serum is used for screening for invasive mold infection in children with hematological malignancies/undergoing HSCT, the assay has a sensitivity and specificity profile that is similar to that observed in adults. Despite a number of limitations of the available pediatric data (wide variations amongst the studies regarding cut-off, definition of positivity etc), prospective monitoring of GM in serum every three to four days in children at high risk for IFD is reasonable for early diagnosis of invasive aspergillosis (AII)

- Although the optimal cut-off value of GM in the serum of children is not well defined, published data support the use of a threshold of an optical density index 0.5. (serum specimens) (BIII)
Recommendations

- The very limited published data support the value of GM in the diagnosis of pulmonary aspergillosis (GM in BAL; cut-off 1) and central nervous system aspergillosis (GM in CSF; cut-off 0.5) in children (BIII).

- Systemic mold-active prophylaxis may decrease the performance of the test (BIII).
β-D-Glucan (BG)

Background

➢ BG can be detected in infections due to
  ➢ *Aspergillus* and *Candida* spp, but also in those due to *Fusarium*, *Trichosporum*, *Saccharomyces*, and *Pneumocystis jirovecii*
  ➢ bacteria such as *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*
  ➢ in healthy individuals

➢ BG absent in cryptococcosis and zygomycosis.

➢ Antibiotics such as cefepime, piperacillin/tazobactam or meropenem may cause positive BG levels

➢ Similar to GM, BG is included as mycological criterion in the revised definitions of invasive fungal disease from the EORTC/MSG consensus group.

Karageorgopoulos 2011; Oz 2011; De Pauw 2008
Analysis of BG

BG testing in adults:

- good diagnostic accuracy for early diagnosis of IFD
  - 2979 patients (594 with proven or probable IFD): pooled sensitivity 76.8% (95%CI 67.1% – 84.3%)
  - pooled specificity 85.3% (95%CI, 79.6% – 89.7%)

Very limited data in children:

- elevated levels of BG were reported in four children with IFD (3 patients with candidemia, one patient probable aspergillosis).
- mean BG levels are higher in immunocompetent uninfected children than adults: optimal cut-off in children?

Recommendations

- Although BG testing has been shown to be useful in diagnosing IFD in adult patients, data are too limited to make any recommendations on BG testing in children.
Imaging studies

Background

- In adults, systematic CT scans allow earlier diagnosis of invasive pulmonary aspergillosis which is associated with improved prognosis.
- Pulmonary nodules, in particular nodules with halo sign, air crescent sign and cavitation are typical CT findings for fungal pneumonia in adults and are a clinical criterion in the revised definitions of invasive fungal disease from the EORTC/MSG consensus group.
- Appearance of these findings depend on time of imaging and are not specific for fungal infections.

Caillot 1997; Heussel 1999
Analysis of imaging

- Limited data on imaging studies in children with underlying malignancies and persistent febrile neutropenia
- None of these studies were designed to evaluate the impact of CT imaging on the decision to withhold or to initiate antifungal therapy
- In contrast to adult patients, typical signs of IFD (e.g., halo sign, air crescent sign, and cavities) are not seen in the majority of children
- Radiographic findings in immunocompromised children with invasive pulmonary fungal disease are often unspecific, in particular in the younger age group (e.g., < 5-year of age): multiple nodules or fluffy masses and infiltrates which look like mass lesions were the two basic types of involvement

Taccone 1993; Archibald 2001; Burgos 2008
Recommendations

- In high-risk children with persistent febrile neutropenia that persists 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 invasive 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)
Management of persistently or recurrently febrile neutropenic children:
Empiric / pre-emptive therapy
Analysis

➢ To date, no study compared empirical antifungal therapy with no therapy in children with persistent febrile neutropenia

➢ 3 prospective randomized trials in children

➢ Prentice et al 1997
  ➢ AmB-D (1 mg/kg) vs L-AmB (1 mg/kg) vs L-AmB (3 mg/kg)
  ➢ n=204, >60% children with leukemia

➢ Sanders et al 2000
  ➢ AmB-D (0.8 mg/kg) vs ABCD* 4 mg/kg
  ➢ n=49, >60% children with leukemia/HSCT

➢ Maertens et al 2010
  ➢ L-AmB (3 mg/kg) vs Caspo (50 mg/m^2 after loading day 1)
  ➢ n=82, >70% children with leukemia/HSCT

*not licensed for this indication in children

Prentice 1997; Sanders 2000; Maertens 2010
### Analysis: efficacy

All 3 studies use composite endpoints for the assessment of efficacy

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Treatment 3</th>
<th>Efficacy (n, %)*</th>
<th>Breakthrough IFD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prentice et al</td>
<td>AmB-D</td>
<td>L-AmB 1</td>
<td>L-AmB 3</td>
<td>51%</td>
<td>1 (C.alb.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>64%</td>
<td>3 (2 C.alb., 1 IA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>63% (NS)</td>
<td>1 (IA)</td>
</tr>
<tr>
<td>Sanders et al</td>
<td>AmB-D</td>
<td>ABCD</td>
<td></td>
<td>41%</td>
<td>2 (IA, yeast)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>69% (NS)</td>
<td>1 (Fusarium)</td>
</tr>
<tr>
<td>Maertens et al</td>
<td>L-AmB</td>
<td>Caspo</td>
<td></td>
<td>32%</td>
<td>1 (IA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>46% (NS)</td>
<td>0</td>
</tr>
</tbody>
</table>

Conclusion: L-AmB = Caspo; L-AmB slightly better than AmB-D; AmB-D=ABCD

Data supported by much larger datasets in adults

Prentice 1997; White 1998; Walsh 1999
## Analysis: Safety

<table>
<thead>
<tr>
<th></th>
<th>Prentice et al</th>
<th>Sanders et al</th>
<th>Maertens et al</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AmB-D</td>
<td>L-AmB1</td>
<td>L-AmB 3</td>
</tr>
<tr>
<td>Nephrotoxicity (creatinine)</td>
<td>21%</td>
<td>8 %</td>
<td>11 %</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>26 %</td>
<td>10 %</td>
<td>11 %</td>
</tr>
<tr>
<td></td>
<td>(P=.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrotoxicity (creatinine)</td>
<td>9.1 %</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>55 %</td>
<td>52 %</td>
<td></td>
</tr>
<tr>
<td>Infusion related (e.g, chills)</td>
<td>50 %</td>
<td>78 %</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>11.5%</td>
<td>1.8 %</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>11.5 %</td>
<td>3.6 %</td>
<td></td>
</tr>
<tr>
<td>Discontinued due to AEs</td>
<td>11.5 %</td>
<td>3.6 %</td>
<td></td>
</tr>
</tbody>
</table>

### Conclusion:
- Caspo better tolerated than L-Am-B; L-AmB better tolerated than AmB-D; ABCD with less nephrotoxicity than AmB-D, but with more infusion related side effects.
- Data supported by much larger datasets in adults.

Prentice 1997; White 1998; Walsh 1999
Recommendations

- In neutropenic children with acute leukemia/allogeneic HSCT, empirical antifungal treatment, if chosen as strategy, should be initiated after 96 hours of fever with unclear etiology that is unresponsive to broad-spectrum antibacterial agents (BII)
- Both caspofungin (50 mg/m²/day, day 1 70 mg/m²; max 70 mg/d) and liposomal amphotericin B (1-3 mg/kg/d*), which are approved for this indication in children of all ages, can be recommended for empirical antifungal therapy in children (AI)
  * L-AmB is approved for empirical therapy in some countries at the dosage of 3 mg/kg/d, in others at dosages between 1 and 3 mg/kg/d
- Although there are no adult or pediatric data to recommend a specific empirical antifungal agent for patients already receiving mold-active antifungal prophylaxis, however, switching to a different class of mold-active antifungal agent seems reasonable (no rating due to no data) Patients receiving antifungal prophylaxis without mold activity (e.g. fluconazole) should be given either caspofungin or L-AmB for empirical therapy as described above (no rating due to the lack of data)
- Empirical antifungal treatment should be continued until resolution of neutropenia (BII)
- Although there are no data on pre-emptive antifungal strategies in children, it may be an alternative to the empirical antifungal approach (no rating)
Suggested diagnostic and therapeutic algorithm for children with persistent febrile neutropenia

Diagnostic work-up to include blood cultures, serum GM (>1x), and chest CT (other imaging as indicated)

- Work-up negative:
  Continue mold-active antifungal prophylaxis or start mold-active empirical antifungal therapy

- Positive blood cultures:
  Treat according to species identified and in vitro susceptibility

- GM positive (>1x), chest CT negative:
  Start pre-emptive antifungal therapy (change of class if on mold-active prophylaxis)

- Positive chest CT / positive imaging:
  Start pre-emptive therapy (change of class if on mold-active prophylaxis) and pursue invasive diagnostic procedure

- If proven IFD: treat according to species / in vitro susceptibility
Treatment of Established Invasive Fungal Infections
Infectious Syndromes

• Invasive Aspergillosis
• Candidemia/ Invasive Candidiasis
• Rare molds
  – mucorales
  – infections due to *Scedosporium* spp.
    • *Scedosporium apiospermum* complex
    • *Scedosporium prolificans*
  – infections due to *Fusarium* spp.
Recommendations

Based on

- Efficacy in phase II and III trials in adults, corresponding to updated ECIL-3 recommendation \(^1\)
- Availability / assessment of pediatric
  - quality PK data
  - safety data
  - supportive efficacy data
- regulatory approval also considered

\(^1\) Maertens 2011
Recommendations: 1st line Therapy of Invasive Aspergillosis

**Antifungal therapy:** *

ABLC \hspace{2cm} B II¹
Liposomal AmB \hspace{2cm} B I¹
Voriconazole i.v. \hspace{2cm} A I¹

Combination therapy \hspace{2cm} 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
Recommendations: 2\textsuperscript{nd} line Therapy of Invasive Aspergillosis

\textit{Antifungal therapy: *}

Amphotericin B Lipid Complex 1  \hspace{1cm} B II
Caspofungin  \hspace{1cm} A II
Liposomal Amphotericin B 1  \hspace{1cm} B I
Voriconazole + TDM 2  \hspace{1cm} A I
Combination therapy (salvage)  \hspace{1cm} CII

Further options include itraconazole +TDM, posaconazole +TDM for children >12 yrs, and micafungin 3 (no grading)

1 in amphotericin B naïve patients
2 in voriconazole naïve patients
3 micafungin does not have a license in the EU for aspergillosis

* in alphabetical order
Recommendations: Principles / Adjunctive Therapies

Principal management includes antifungal therapy, control of underlying conditions and surgery (no grading) $^{1,2}$

Adjunctive cytokines (G-CSF, GM-CSF, IFN-$\gamma$) (no grading)
Granulocyte transfusions for patients with profound and persistent neutropenia (no grading) $^3$

$^1$ Control of underlying condition includes hematopoietic growth factor if neutropenia, discontinuation/tapering of steroids, reduction of immunosuppressive therapy.
$^2$ Surgery should be considered on a case by case basis, using a multi-disciplinary approach
$^3$ risk of severe complications (hemoptysis, pneumothorax, worsening respiratory function) for rapid increase of PMN count
Recommendations: Candidemia and Invasive Candidiasis

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

**Antifungal therapy:** *

<table>
<thead>
<tr>
<th>Drug</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B Lipid Complex</td>
<td>C II</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>B II</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>B II</td>
</tr>
<tr>
<td>Liposomal Amphotericin B</td>
<td>B II</td>
</tr>
<tr>
<td>Micafungin 1,2</td>
<td>B II</td>
</tr>
<tr>
<td>Voriconazole 2</td>
<td>B II</td>
</tr>
</tbody>
</table>

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.

* in alphabetical order
Pediatric Mucormycosis

- Systematic literature review of 157 pediatric cases in patients 0-18 years
- Amphotericin B and surgery significantly improved outcome
- Antifungal therapy and particularly surgery reduced risk of death by 92% (OR: 0.07; 95% CI: 0.04–0.25) and 84% (OR: 0.16; 95% CI: 0.09–0.61), respectively

Zaoutis Pediatr Infect Dis J 2007
### Recommendations: 1\textsuperscript{st} line therapy of Mucormycosis

#### Antifungal therapy: *

<table>
<thead>
<tr>
<th>Drug</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABLC</td>
<td>II\textsuperscript{1}</td>
</tr>
<tr>
<td>Liposomal AmB</td>
<td>II\textsuperscript{1}</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>III\textsuperscript{2}</td>
</tr>
</tbody>
</table>

- Combination therapy: CIII

\textsuperscript{1} liposomal amphotericin B should be preferred in CNS infection and/or renal failure

\textsuperscript{2} limited data exist to support use of posaconazole as first line treatment. May be used as an alternative in the 2nd line setting when amphotericin B is contraindicated

---

*in alphabetical order; Skiada et al. ECIL-3 (submitted)*
Recommendations: 2nd line therapy of Mucormycosis

**Antifungal therapy:**

- Posaconazole  
  - B II \(^1\)
- Combination lipid AmB and caspofungin  
  - C III
- Combination lipid AmB and posaconazole  
  - C III

\(^1\) overlap of a few days (at least 5) with first line therapy to obtain appropriate serum levels. Monitoring of serum levels should be considered

*Skiada et al. ECIL-3 (submitted)*
Recommendations: Principles / Adjunctive Therapies

Management includes antifungal therapy, control of underlying conditions and surgery (no grading) $^1,2$

Hyperbaric oxygen, cytokines, granulocytes transfusions (no grading)

$^1$ control of underlying condition includes hematopoietic growth factor if neutropenia, discontinuation/tapering of steroids, reduction of immunosuppressive therapy

$^2$ surgery should be considered on a case by case basis, using a multi-disciplinary approach
Recommendations: Scedosporiosis and Fusariosis

Management includes antifungal therapy, control of underlying conditions and surgery (no grading) ¹,²

Based on limited clinical and preclinical data, voriconazole is the preferred agent for treatment of scedosporiosis and fusariosis (BII).

Lipid formulations of amphotericin B and posaconazole are alternative choices only due to fewer published data (no grading)

¹ control of underlying condition includes hematopoietic growth factor if neutropenia, discontinuation/tapering of steroids, reduction of immunosuppressive therapy
² surgery should be considered on a case by case basis, using a multi-disciplinary approach
# Pediatric Dosages / Key References

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage for Treatment</th>
<th>Key References *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>8-12 mg/kg/d qd iv/po</td>
<td>Lee 1992; Brammer 1994; Novelli 1999; Rex 1994; Anaissie 1996; Rex 2003;</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>5 mg/kg/d bid po +TDM</td>
<td>De Repentigny 1998; Groll 2002; Foot 1999; Denning 1994; Caillot 2001</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>800 mg/d (bid/qid) po +TDM in children &gt; 12 years</td>
<td>Krishna 2007; Lehrnbecher 2010; Cesaro 2011; Walsh 2007</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>&lt;13 yrs 14 mg/kg/d bid / &gt;12 yrs 400 mg/d bid iv; 400 mg/d bid po (all) +TDM</td>
<td>Walsh 2004; Karlsson 2009; Walsh 2002; Herbrecht 2002; Kullberg 2005</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>50 (d1:70) mg/m² qd iv Maximum: 70 mg QD</td>
<td>Walsh 2005; Neely 2009; Zaoutis 2009; Zaoutis 2009; Mora-Duarte 2002; Maertens 2004; Pappas 2007; Betts 2009</td>
</tr>
<tr>
<td>Micafungin</td>
<td>2-4 mg/kg qd iv</td>
<td>Seibel 2005; Hope 2007; Arrieta 2010; Queiroz-Telles 2008; Denning 2006; Kuse 2007; Pappas 2007</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>3 (-&gt;5) mg/kg qd iv</td>
<td>Hong 2006; Queiroz-Telles 2008; Kolve 2009; Cornely 2007; Kuse 2007</td>
</tr>
<tr>
<td>Amphotericin B Lipid Complex</td>
<td>5 mg/kg qd iv</td>
<td>Walsh 1997; Walsh 1999; Wiley 2005; Walsh 1998</td>
</tr>
</tbody>
</table>

* Pediatric PK, safety, and efficacy data, if available

Pivotal adult phase II Iclinical trials