ONLINE APPENDIX: ADDITIONAL SOURCE DATA CITATIONS

1. Risk factors and epidemiology of invasive fungal diseases


2. Pharmacology of antifungal agents in pediatric patients

*Amphotericin B lipid formulations and flucytosine:*

Walsh TJ, Shad A, Bekersky I et al. Safety, tolerability and pharmacokinetics of liposomal amphotericin B in immunocompromised pediatric patients. In 48th Interscience Conference on Antimicrobial Agents and Chemotherapy; American Society for Microbiology, Washington, DC, 2008; abstract A-005


Fluconazole and itraconazole:


Foot AB, Veys PA, Gibson BE. Itraconazole oral solution as antifungal prophylaxis in children undergoing stem cell transplantation or intensive chemotherapy for haematological disorders. Bone Marrow Transplant 1999; 24: 1089–93.

Posaconazole and voriconazole:


**Anidulafungin, caspofungin and micafungin:**


**3. Diagnosis of invasive fungal diseases**

**Galactomannan:**
• Fisher BT, Zaoutis TE, Park JR et al. Galactomannan antigen testing for diagnosis of invasive aspergillosis in pediatric hematology patients. *J Ped Infect Dis* 2012; 1: 103–11

**Fungal nucleic acids:**


4. Prophylaxis of invasive fungal diseases

**Primary prophylaxis:**


**Secondary prophylaxis:**

• Cordonnier C, Maury S, Pautas C et al. Secondary antifungal prophylaxis with voriconazole to adhere to scheduled treatment in leukemic patients and stem cell transplant recipients. *Bone Marrow Transplant* 2004; **33**: 943–8.

5. **Empirical and pre-emptive (diagnostic driven) therapy**


6. **Targeted treatment of invasive fungal diseases**

**Invasive Candida infections:**

Infections by Mucorales:


• van Burik JA, Hare RS, Solomon HF, Corrado ML, Kontoyiannis DP. Posaconazole is effective as salvage therapy in zygomyosis: a retrospective summary of 91 cases. *Clin Infect Dis* 2006; **42**: e61–5.
Table 2 (Appendix): Suggested diagnostic and therapeutic algorithm for high-risk granulocytopenic paediatric patients with cancer or haematopoietic stem cell transplantation and persistent or recurrent fever

<table>
<thead>
<tr>
<th>Diagnostic work up including blood cultures, serum galactomannan (&gt;1x), high resolution chest CT (other imaging as indicated)</th>
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</thead>
<tbody>
<tr>
<td><strong>All studies negative:</strong></td>
</tr>
<tr>
<td>- Continue mould-active antifungal prophylaxis or start mould-active empirical antifungal therapy (consider change of class if on mould-active prophylaxis)</td>
</tr>
<tr>
<td><strong>Positive blood cultures:</strong></td>
</tr>
<tr>
<td>- Treat according to fungal species and in vitro susceptibility (change of class if on prophylaxis)</td>
</tr>
<tr>
<td><strong>Galactomannan positive (&gt;1x), chest CT negative:</strong></td>
</tr>
<tr>
<td>- Start pre-emptive antifungal therapy (change of class if on mould-active prophylaxis); consider the possibility of false-positive test results and non-pulmonary sites of disease and further imaging</td>
</tr>
<tr>
<td><strong>Positive chest CT (typical or non-typical infiltrates) / positive imaging: with/without positive galactomannan:</strong></td>
</tr>
<tr>
<td>- Start pre-emptive therapy (change of class if on mould-active prophylaxis) and pursue invasive diagnostic procedures</td>
</tr>
<tr>
<td><strong>If proven invasive fungal disease:</strong></td>
</tr>
<tr>
<td>- Treat according to species / in vitro susceptibility, considering prior antifungal therapy</td>
</tr>
</tbody>
</table>

* Most pediatric cancer/HSCT patients have an indwelling central venous catheter; obtaining a blood culture of adequate volume from all lumens of the catheter is important; the utility of additional peripheral blood cultures is controversial. 22, 24
Table 3 (Appendix): Stratification of risk of invasive fungal diseases in paediatric patients with cancer or haematopoietic stem cell transplantation

<table>
<thead>
<tr>
<th>Risk stratum *</th>
<th>Patient population</th>
</tr>
</thead>
</table>
| High risk (close to and ≥ 10 %) | - acute myeloblastic leukaemia  
- recurrent acute leukaemia’s  
- allogeneic haematopoietic stem cell transplantation **  
- high risk acute lymphoblastic leukaemia *** |
| Low risk (close to and < 5 %) | - acute lymphoblastic leukaemia  
- non-Hodgkin lymphoma’s  
- autologous haematopoietic stem cell transplantation |
| Sporadic | - paediatric solid tumours  
- brain tumours  
- Hodgkin’s lymphoma |

* for source data, please refer to the appendix, section 1, risk factors and epidemiology of invasive fungal diseases

** cumulative risk that includes the phase until engraftment and phases of GVHD and augmented immunosuppression post engraftment

*** depending on protocol and risk profile (in particular profound and prolonged granulocytopenia while on steroid treatment), the risk for IFD may be close to or exceed 10 %
<table>
<thead>
<tr>
<th>Antifungal Agent</th>
<th>Summary of Approved Indications *</th>
<th>Paediatric Dosage Range</th>
<th>Specific Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>Treatment of IFDs</td>
<td>0.7-1.0 mg/kg/d IV in one single dose</td>
<td>PK not different relative to adults; infusion-related reactions and nephrotoxicity curtail clinical usefulness</td>
</tr>
<tr>
<td>Amphotericin B colloidal dispersion</td>
<td>2nd line treatment of invasive Aspergillus infections</td>
<td>3-4 mg/kg/d IV in one single dose</td>
<td>PK not different relative to adults, but limited; infusion-related reactions more frequent relative to DAMB; manufacturing discontinued in Europe</td>
</tr>
<tr>
<td>Amphotericin B lipid complex</td>
<td>2nd line treatment of invasive Candida or Aspergillus infections</td>
<td>5 mg/kg/d IV in one single dose</td>
<td>PK not different relative to adults, but limited; infusion-related reactions similarly frequent relative to DAMB;</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>Treatment of IFDs and empirical therapy in granulocytopenic patients</td>
<td>1-&gt;5 mg/kg/d IV in one single dose</td>
<td>PK not different relative to adults, but limited; infusion-related reactions less frequent relative to DAMB;</td>
</tr>
<tr>
<td>Fluorocytosine</td>
<td>Treatment of invasive candidiasis and crypto-coccosis in combination with amphotericin B</td>
<td>100-150 mg/kg/d IV in 3-4 divided doses + TDM</td>
<td>No published PK and safety data for infants and children; robust efficacy data for cryptococcal meningocencephalitis</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Treatment and prevention of superficial and invasive Candida infections; treatment of cryptococcosis and coccidioidomycosis</td>
<td>6-12 mg/kg/d IV/PO in one single dose</td>
<td>Increased weight-normalized plasma clearance relative to adults; optimal dose uncertain beyond the neonatal period. Potential for drug-drug interactions.</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Treatment of superficial Candida infections; 2nd line treatment of invasive candidiasis, aspergillosis and cryptococcosis; antifungal prophylaxis in granulocytopenic patients</td>
<td>5 mg/kg/d PO in two divided doses +TDM</td>
<td>Limited paediatric PK data in 2 to 17 year old subjects, no principal differences relative to adults. Similar problems with absorption. High potential for relevant drug-drug interactions. Not licensed in the EU in subjects &lt;18 years, no PK data for children &lt;2 years</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>2nd line treatment of aspergillosis, fusariosis, chromo-blastomycosis, and coccidioidomycosis; treatment of oropharyngeal candidi-asis; antifungal prophylaxis in AML/MDS and allo-</td>
<td>600-800 mg/d PO in 2 to 4 divided doses + TDM</td>
<td>Limited paediatric PK data; no principal differences relative to adults. Similar problems with absorption. High potential for relevant drug-drug interactions. Not licensed in subjects &lt;18 years in the EU but licensed in adolescents ≥ 13 years of age in the US for prophylaxis</td>
</tr>
</tbody>
</table>
**Voriconazole**  
Treatment of invasive aspergillosis, fusariosis, scedosporiosis; treatment of candidaemia in non-granulocytopenic patients  

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dosing Schedule</th>
<th>Optimal Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-&lt;12 yrs/12-14 yrs and &lt;50kg:</td>
<td>8 mg/kg BID (day 1: 9 mg/kg BID) IV and 9 mg/kg BID PO; ≥15 yrs and 12-14 yrs and ≥50kg:</td>
<td>4 mg/kg BID (day 1: 6 mg/kg BID) IV; 200 mg BID PO +TDM (all)</td>
<td>Optimal dose uncertain, and age-dependent; high PK variability requires TDM, at least in the setting of treatment. High potential for relevant drug-drug interactions. Not licensed in subjects &lt; 2 years of age, and not yet licensed for prophylaxis.</td>
</tr>
<tr>
<td>≥15 yrs and 12-14 yrs and ≥50kg:</td>
<td>4 mg/kg BID (day 1: 6 mg/kg BID) IV; 200 mg BID PO +TDM (all)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Anidulafungin**  
Treatment of invasive candidiasis in non-granulocytopenic patients  

<table>
<thead>
<tr>
<th>Dosing Schedule</th>
<th>PK</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 mg/kg/d (day 1: 3mg/kg) IV in one single dose</td>
<td>PK not different relative to adults; paediatric development well under way. To date, not licensed in subjects &lt;18 years of age.</td>
<td></td>
</tr>
</tbody>
</table>

**Caspofungin**  
Treatment of invasive candidiasis, invasive aspergillosis (2nd line), and for empirical antifungal therapy in granulocytopenic patients  

<table>
<thead>
<tr>
<th>Dosing Schedule</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 (d1:70) mg/m²/d IV in one single dose; max. dose 70 mg/day</td>
<td>Robust paediatric PK datasets / models and safety data</td>
</tr>
</tbody>
</table>

**Micafungin**  
Treatment of oesophageal and invasive candidiasis, prophylaxis of invasive Candida infections in granulocytopenic patients  

<table>
<thead>
<tr>
<th>Dosing Schedule</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4 mg/kg/d IV (≥ 50kg: 50 - 200 mg) in one single dose</td>
<td>Robust paediatric PK dataset / models and safety data; black box warning in the SPC, clinical relevance uncertain</td>
</tr>
</tbody>
</table>

*Summarised tabulation; for specific wording, please refer to the respective summary of product characterisations (SPCs)*

IV, intravenously; PO, orally; DAMB, amphotericin B deoxycholate; TDM, therapeutic drug monitoring; PK, pharmacokinetics

For source data (references), please refer to the appendix, section 2, pharmacology of antifungal agents in pediatric patients