ONLINE APPENDIX: ADDITIONAL SOURCE DATA CITATIONS

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ONLINE APPENDIX: TABLES 2, 3, AND 4

Table 2 (Appendix): Suggested diagnostic and therapeutic algorithm for high-risk granulocytopaenic paediatric patients with cancer or haematopoietic stem cell transplantation and persistent or recurrent fever

• **Diagnostic work up including blood cultures, serum galactomannan (>1x), high resolution chest CT (other imaging as indicated) ***
○ **All studies negative:** • Continue mould-active antifungal prophylaxis or start mould-active empirical antifungal therapy (consider change of class if on mould-active prophylaxis)
○ **Positive blood cultures:** • Treat according to fungal species and *in vitro* susceptibility (change of class if on prophylaxis)
○ **Galactomanan positive (>1x), chest CT negative:** • 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
○ **Positive chest CT (typical or non-typical infiltrates) / positive imaging; with/without positive galactomannan:** • Start pre-emptive therapy (change of class if on mould-active prophylaxis) and pursue invasive diagnostic procedures
○ **If proven invasive fungal disease:** • Treat according to species / in vitro susceptibility, considering prior antifungal therapy

* 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

Risk stratum *	Patient population
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 profund and prolonged granulocytopaenia while on steroid treatment), the risk for IFD may be close to or exceed 10 %*

Table 4 (Appendix): Summary of dosing, pharmacokinetics and regulatory approval of antifungal agents used for management of invasive fungal diseases in paediatric patients

Antifungal Agent	Summary of Approved Indications *	Paediatric Dosage Range	Specific Comments
Amphotericin B deoxycholate	Treatment of IFDs	0.7-1.0 mg/kg/d IV in one single dose	PK not different relative to adults; infusion-related reactions and nephrotoxicity curtail clinical usefulness
Amphotericin B colloidal dispersion	2nd line treatment of invasive *Aspergillus* infections	3-4 mg/kg/d IV in one single dose	PK not different relative to adults, but limited; infusion-related reactions more frequent relative to DAMB; manufacturing discontinued in Europe
Amphotericin B lipid complex	2nd line treatment of invasive *Candida* or *Aspergillus* infections	5 mg/kg/d IV in one single dose	PK not different relative to adults, but limited; infusion-related reactions similarly frequent relative to DAMB;
Liposomal amphotericin B	Treatment of IFDs and empirical therapy in granulocytopaenic patients	1->5 mg/kg/d IV in one single dose	PK not different relative to adults, but limited; infusion-related reactions less frequent relative to DAMB
Fluorocytosine	Treatment of invasive candidiasis and crypto-coccosis in combination with amphotericin B	100-150 mg/kg/d IV in 3-4 divided doses + TDM	No published PK and safety data for infants and children; robust efficacy data for cryptococcal meningoencephalitis
Fluconazole	Treatment and prevention of superficial and invasive *Candida* infections; treatment of cryptococcosis and coccidioidomycosis	6-12 mg/kg/d IV/PO in one single dose	Increased weight-normalized plasma clearance relative to adults; optimal dose uncertain beyond the neonatal period. Potential for drug-drug interactions.
Itraconazole	Treatment of superficial *Candida* infections; 2nd line treatment of invasive candidiasis, aspergillosis and cryptococcosis; antifungal prophylaxis in granulocytopaenic patients	5 mg/kg/d PO in two divided doses +TDM	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 <18 years, no PK data for children <2 years
Posaconazole	2nd line treatment of asper-gillosis, fusariosis, chromo-blastomycosis, and cocci-dioido-mycosis; treatment of oropharyngeal candidi-asis; antifungal prophylaxis in AML/MDS and allo-	600-800 mg/d PO in 2 to 4 divided doses + TDM	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 <18 years in the EU but licensed in adolescents ≥ 13 years of age in the US for prophylaxis

	geneic HSCT patients.		
Voriconazole	Treatment of invasive aspergillosis, fusariosis, scedosporiosis; treatment of candidaemia in non-granulocytopaenic patients	2- <12 yrs /12-14 yrs and <50kg: 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: 4 mg/kg BID (day 1: 6 mg/kg BID) IV; 200 mg BID PO +TDM (all)	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 < 2 years of age, and not yet licensed for prophylaxis
Anidulafungin	Treatment of invasive candidiasis in non-granulocytopaenic patients	1.5 mg/kg/d (day 1: 3mg/kg) IV in one single dose	PK not different relative to adults; paediatric development well under way. To date, not licensed in subjects <18 years of age.
Caspofungin	Treatment of invasive candidiasis, invasive aspergillosis (2nd line), and for empirical antifungal therapy in granulocyto-paenic patients	50 (d1:70) mg/m^2/d IV in one single dose; max. dose 70 mg/day	Robust paediatric PK datasets / models and safety data
Micafungin	Treatment of oesophageal and invasive candidiasis, prophylaxis of invasive *Candida* infections in granulocytopaenic patients	1-4 mg/kg/d IV (≥ 50kg: 50 - 200 mg) in one single dose	Robust paediatric PK dataset / models and safety data; black box warning in the SPC, clinical relevance uncertain

* 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