ECIL 4 – Pediatric Group Considerations for Fungal Diseases and Antifungal Treatment in Children

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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

Ref	Patients studied	IFD incidence	Evidence
Kobayashi et al. (Japan) 2008.	334 Hem. malignancies, HSCT and others	AML 11.7%; alloHSCT 8.1%; ALL 2.0%; sporadic in solid tumors moulds >> yeast	II retro- spective
Kaya et al. (Turkey) 2009	155 AL during intensive chemotherapy	AML 12,4; ALL 8,4 yeast >> moulds	II retro- spective
Castagnola et al. (Italy) 2010	240 AML	10% of all courses; recurrent AML: 15% moulds >> yeast	II retro- spective
Hale et al. (AUS) 2010	Acute leukemia / HSCT patients	Recurrent leukemia 21%; ALL 18.5%; alloHSCT 15.2%; AML 8.8%; yeast >> moulds	II retro- spective
Mor et al. (Israel) 2011	1047 HSCT and heme/onc patients	AML 13.6%; ALL 5.9%; alloHSCT 3.9%; autoHSCT 3.0%; solid tumors 1.6%; lymphoma 0.8% moulds >> yeast	II retro- spective

Mortality, probable/proven IFD in children

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

*in invasive pulmonary aspergillosis – the mortality was above 70%

Stratification of Risk of IFDs in Pediatric Cancer / HSCT Patients

Risk stratum	**Patient population**
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

* 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 %

Groll et al. 1999; Hovi et al. 2000; Lin et al. 2001; Benjamin et al. 2002; Zaoutis et al. 2004; Zaoutis et al. 2005; Zaoutis et al. 2006; Rosen et al. 2005; Kobayashi et al. 2008; Kaya et al. 2009; Castagnola et al. 2010; Hale et al. 2010; Mor et al. 2011

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

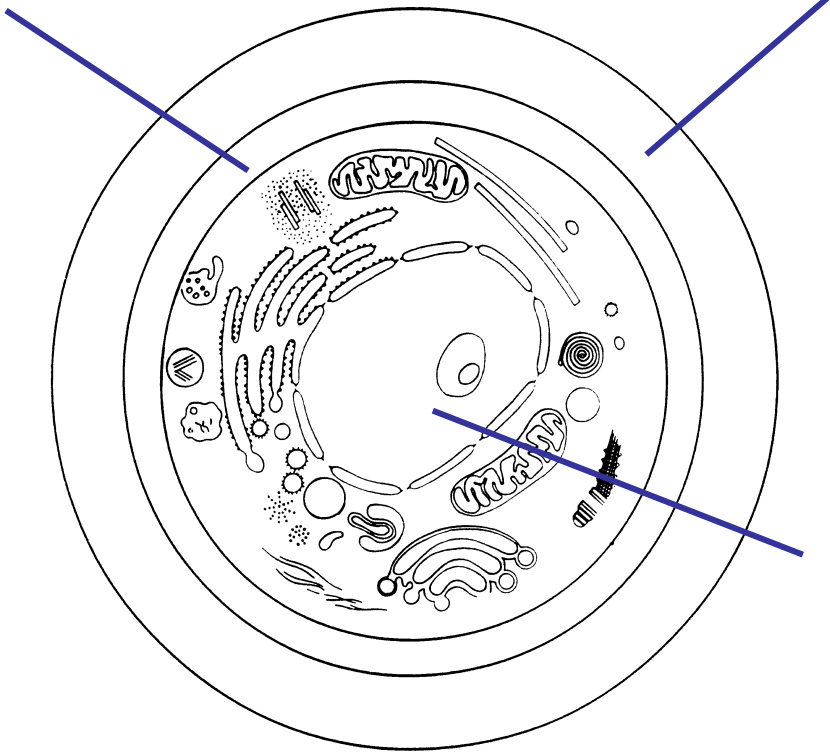
- In practice, treatment often needs to be started pre-emptively on the basis of clinical findings, imaging results and/or antigen markers
- However, considering the risks and benefits in each individual patient, appropriate efforts should be made to perform the necessary procedures in order to identify 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

Agent	Dosage*	Comment	PK References
Fluconazole	8-12 mg/kg/d qd iv/po	Optimal dose uncertain	Lee 1992; Brammer 1994;
Itraconazole	5 mg/kg/d bid po	Limited data, not licensed	De Repentigny 1998; Groll 2002
Posaconazole	600-800 mg/d (tid, bid/qid) po	Only >13 yrs, not licensed	Krishna 2007
Voriconazole	8-14 mg/kg/d bid iv 400 mg/d bid po	Optimal dose uncertain, and age-dependent	Walsh 2004; Karlsson 2009
Anidulafungin	1.5 (d1:3) mg/kg/d iv	Studies under way, not licensed	Benjamin 2006
Caspofungin	50 (d1:70) mg/m^2/d iv	Robust dataset and models	Walsh 2005; Neely 2009
Micafungin	1-4 mg/kg/d iv	Robust dataset and models	Seibel 2005; Hope 2007
Liposomal amphotericin B	3->5 mg/kg/d iv	Weight-based dosage inferred without robust PK	Hong 2006
Amphotericin B Lipid Complex	5 mg/kg/d iv	Limited PK data in children	Walsh 1997

** Dosages may vary according to indication*

Dosage / Dosage Interval

Disease-related Factors

Growth and Development

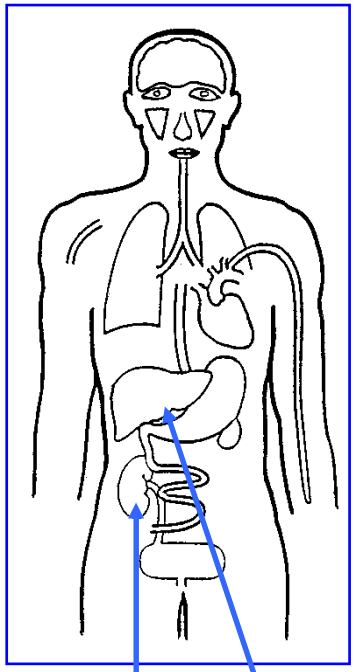
Pharmacokinetics

Absorption
Distribution
Metabolization
Elimination

Concentration at Target Site

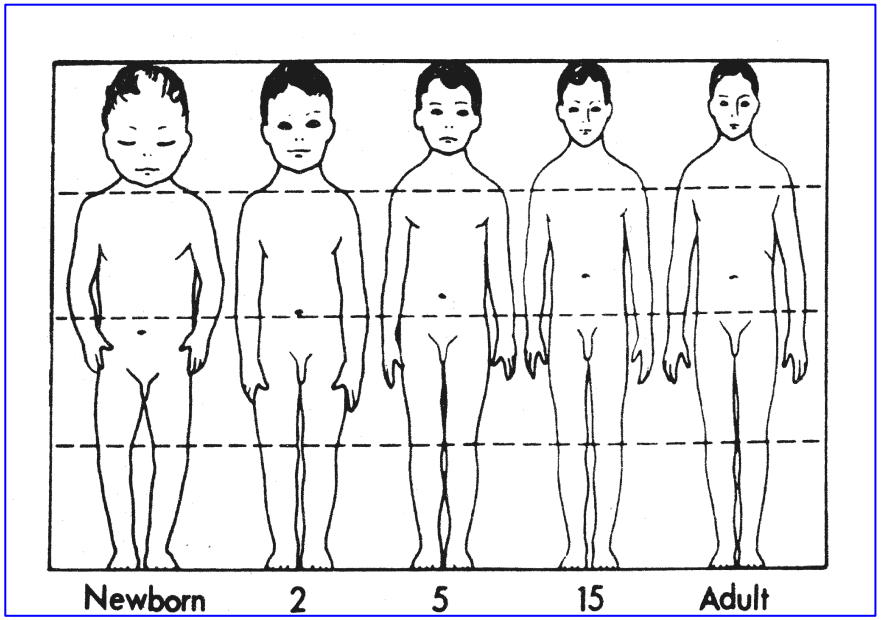
Pharmacological Effects

Efficacy and Toxicity



Maturation processes of excretory organs

Changes in body mass and body composition



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

Groll 2011

Drug Development in Pediatrics - EMA Regulatory Guidance Summary

- 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

European Medicines Agency. ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PAEDIATRIC POPULATION (CPMP/ICH/2711/99). http://www.tga.gov.au/docs/pdf/euguide/ich/271199en.pdf; 2001. Accessed July 26, 2011.

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 enroled (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

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

* *Number of episodes*

Pediatric Antifungal Prophylaxis: Literature Review

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

** 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 <u>allogeneic</u> 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 <u>allogeneic</u> 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

TDM, therapeutic drug monitoring

Recommendation for secondary antifungal prophylaxis in children with leukemia or undergoing HSCT

Reference	Design	Population	n	Antifungal	Outcome
Allinson 2008	retrospect	HSCT	11 (11-18 y)	L-AmB followed by VORI p.o.	3/11 IA

- 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)

ECIL-3 Update 2009, Maertens 2011

Pediatric Dosages / Key References

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

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 populatipon, 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

Rohrlich 1996; Sulahian 1996; Herbrecht 2002; Challier 2004; El-Mahallawy 2006; Hovi 2007; Steinbach 2007; Hayden 2008; Armenian 2009; Castagnola 2010

Analysis of GM in serum

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

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

	Children	Adults
➢Sensitivity	0.76 (95%CI 0.62 - 0.87)	0.73 (95%CI 0.46 - 0.61)
➢Specificity	0.86 (95%CI 0.68 - 0.95)	0.90 (95%CI 0.88 - 0.92)

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

Desai 2009; Roilides 2003

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).

ß-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?

Karageorgopoulos 2011, Mularoni, 2010, Smith 2007

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 (1mg/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* 4mg/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

Prentice et al	**AmB-D**	**L-AmB 1**	**L-AmB 3**	
Efficacy (n, %)*	51%	64%	63%	(NS)
Breakthrough IFD	1 (*C.alb.*)	3 (2 *C.alb.*,1 IA)	1 (IA)	
Sanders et al	**AmB- D**	**ABCD**		
Efficacy	41%	69%		(NS)
Breakthrough IFD	2 (IA, yeast)	1 (Fusarium)		
Maertens et al	**L-AmB**	**Caspo**		
Efficacy	32%	46%		(NS)
Breakthrough IFD	1 (IA)	0		

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

Data supported by much larger datasets in adults

Prentice 1997; White 1998; Walsh 1999

Analysis: safety

Prentice et al	**AmB-D**	**L-AmB1**	**L-AmB 3**	(*P*=.01)
Nephrotoxicity (creatinine)	21%	8 %	11 %	
Hypokalemia	26 %	10 %	11 %	

Sanders et al	**AmB-D**	**ABCD**
Nephrotoxicity (creatinine)	9.1 %	0
Hypokalemia	55 %	52 %
Infusion related (e.g, chills)	50 %	78 %

Maertens et al	**L-AmB**	**Caspo**	(NS)
Tachycardia	11.5%	1.8 %	
Hypokalemia	11.5 %	3.6 %	
Discontinued due to AEs	11.5 %	3.6 %	

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/m^2/day, day 1 70 mg/m^2; 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	B II[1]
Liposomal AmB	B I [1]
Voriconazole i.v.	A I [1]
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*

Recommendations:
2nd line Therapy of Invasive Aspergillosis

Antifungal therapy: *

Amphotericin B Lipid Complex [1]	B II
Caspofungin	A II
Liposomal Amphotericin B [1]	B I
Voriconazole + TDM [2]	A I
Combination therapy (salvage)	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-γ)(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: *

Amphotericin B Lipid Complex	C II
Caspofungin [2]	B II
Fluconazole [2]	B II
Liposomal Amphotericin B	B II
Micafungin [1,2]	B II
Voriconazole [2]	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.

* *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: 1st line therapy of Mucormycosis

Antifungal therapy: *

ABLC	B II[1]
Liposomal AmB	B II[1]
Posaconazole	CIII[2]
Combination therapy	CIII

[1] liposomal amphotericin B should be preferred in CNS infection and/or renal failure

[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

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

** Pediatric PK , safety, and efficacy data, if available Pivotal adult phase II Iclinical trials*