



From September 19th to 21st 2019

8th

EUROPEAN
CONFERENCE
ON **I**NFECTIONS IN
LEUKAEMIA

The Pediatric Group

FINAL SLIDE SET

Mercure Sophia Antipolis
Sophia Antipolis France



ECIL-8 - The Pediatric Group

Group members:

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Co-ordinators:

Andreas H. Groll and Thomas Lehrnbecher

Guideline Methodology



Population and Search Criteria (1)

- Leukemia-, lymphoma-, and auto / allo HSCT patients
- Literature search
 - English language only
 - PubMed and references from the retrieved studies
 - Fungal infections (update of ECIL 4 in 2012): 2010 – June 2019
 - Bacterial infections (new guideline): 2000 – June 2019
- Conferences: 2017, 2018, 2019; including ECCMID, ID-Week -
! only supportive as data are preliminary

Population and Search Criteria (2)

- Randomized and larger observational pediatric ($\geq 90\% \leq 18$ y) or mixed pediatric/adult studies with separately retrievable **pediatric data** from high- and middle income countries
- **Adult ECIL guidelines plus important adult randomized or observational studies published between the respective conference until 6/2019**
- Deposit of PDFs in Dropbox, organized in folders according to topics (open)
- Each working group *selects and records* their MeSH terms
- Each working group *records the flow of their literature selection* process
- ! Each working group dealing with interventions *selects the critical endpoints* for the recommendations (column: 'intention'; f.e. to impact on overall survival, to prevent infections, to cure)

Grading

ESCMID/ECMM grading system *

Two Independent Evaluations:

1. Strength of Recommendation = SoR
2. Quality of Evidence = QoE

→ Allows strong recommendations in the absence of highest quality of evidence.

Grading – Strength of Recommendation

Grade of Recommendation	Definition
Grade A	The guideline group <u>strongly</u> supports a recommendation for use
Grade B	The guideline group <u>moderately</u> supports a recommendation for use
Grade C	The guideline group <u>marginally</u> supports a recommendation for use
Grade D	The guideline group supports a recommendation <u>against</u> use

Grading – Quality of Evidence

Level of Evidence	Definition
Level I	Evidence from at least 1 properly designed randomized, controlled trial
Level II	Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees



Grading – *Source of Level II Evidence*

Added Index	Source of Level II Evidence
r	Meta-analysis or systematic review of RCT
t	Transferred evidence i.e. results from different patients' cohorts, or similar immune-status situation
h	Comparator group: historical control
u	Uncontrolled trials
a	For published abstract presented at an international symposium or meeting



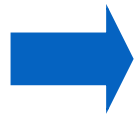
Guiding Principles for Treatment / Prophylaxis



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

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 April 22, 2014

Pediatric Recommendations

➤ Based on

- Efficacy in phase II and III trials in adults, corresponding to adult ECIL recommendation *(if underlying conditions are similar)*
- Availability / assessment of pediatric
 - quality PK data
 - safety data
 - supportive efficacy data
- regulatory approval also being considered and incorporated (Y/N)

Hope et al. CMI 2012; Groll et al. Lancet Oncol. 2014; Warris et al. 2019

Update ECIL-4 Fungal Infections



Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or allogeneic haemopoietic stem-cell transplantation

Andreas H Grall, Elio Castagnola, Simone Cesaro, Jean-Hugues Dalle, Dan Engelhard, William Hope, Emmanuel Roilides, Jan Styczynski, Adilia Warris, Thomas Lehrnbecher, on behalf of the Fourth European Conference on Infections in Leukaemia, a joint venture of the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT-IDWP), the Infectious Diseases Group of the European Organisation for Research and Treatment of Cancer (EORTC-IDG), the International Immunocompromised Host Society (IHS), and the European Leukaemia Net (ELN)

Invasive opportunistic fungal diseases (IFDs) are important causes of morbidity and mortality in paediatric patients with cancer and those who have had an allogeneic haemopoietic stem-cell transplantation (HSCT). Apart from differences in underlying disorders and comorbidities relative to those of adults, IFDs in infants, children, and adolescents are unique with respect to their epidemiology, the usefulness of diagnostic methods, the pharmacology and dosing of antifungal agents, and the absence of interventional phase 3 clinical trials for guidance of evidence-based decisions. To better define the state of knowledge on IFDs in paediatric patients with cancer and allogeneic HSCT and to improve IFD diagnosis, prevention, and management, the Fourth European Conference on Infections in Leukaemia (ECIL-4) in 2011 convened a group that reviewed the scientific literature on IFDs and graded the available quality of evidence according to the Infectious Diseases Society of America grading system. The final considerations and recommendations of the group are summarised in this manuscript.

Risk Factors and Epidemiology



Pediatric Cancer/HSCT Patients at risk for IFDs (ECIL4/ECIL8)

- 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 case series
 - differences in the use of diagnostic procedures, IFD definitions, population denominators, and fungal pathogens included

Pediatric Cancer/HSCT Patients at risk for IFDs (ECIL4/**ECIL8**)

- Prolonged and profound granulocytopenia (ANC of $\leq 500/\mu\text{L}$ for ≥ 10 days)
- Use of glucocorticosteroids (≥ 0.3 mg/kg/day prednisone equivalent)
- Mucosal tissue damage
- Limited to invasive candidiasis: the presence of central venous catheters
- Risk constellations identified by multivariable analyses:
 - acute myeloblastic leukaemia (AML),
 - high risk acute lymphatic leukaemia (ALL)
 - recurrent acute leukaemia
 - intensive care unit (ICU) admission
 - post allogeneic HSCT
 - presence of graft-vs.-host disease (GVHD)
 - *increasing age without threshold (Fisher et al., systematic review, JPIDS 2017)*

Revised Stratification of Risk of IFDs in Pediatric Cancer/HSCT Patients (ECIL-4/**ECIL-8**) **NO CHANGES**

Risk stratum	Patient population
High risk ($\geq 10\%$)	<ul style="list-style-type: none"> -acute myeloblastic leukemia -recurrent acute leukemia's -allogeneic HSCT -acute lymphoblastic leukemia *
Low risk ($\leq 5\%$) **	<ul style="list-style-type: none"> -acute lymphoblastic leukemia * -non-<i>Hodgkin</i> lymphoma's -autologous HSCT
Sporadic occurrence **	<ul style="list-style-type: none"> -pediatric solid tumors -brain tumors -<i>Hodgkin's</i> 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

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 (RELEVANT STUDIES BETWEEN 2011 and 2019 TO BE ADDED)

Diagnosis



Diagnostic considerations

- Standard diagnostic procedures such as cultures, microscopy, and histology not different between children and adults and therefore, not addressed
- Focus on biomarkers and imaging studies
- Candidemia:
The number of blood cultures recommended in a single session is three with a total volume varying according to the age of the patient: *
 - 40–60 mL adults/adolescents
 - 20 mL between 12 and 36 kg
 - 6 mL between 2 and 12 kg
 - 2–4 mL for children under 2 kg

* Ullman et al, Clin Microbiol Infect 2012; 18 (Suppl. 7): 1–8



Biomarkers for Early Detection of IFD (ECIL-8)

Recommendations	Remarks
<p>Serum GM</p> <p>Prospective monitoring twice weekly for early diagnosis of invasive aspergillosis in children at high risk for <i>IFD</i> (A-II for pts not on mold-active prophylaxis; D-II for pts on mold-active prophylaxis).</p> <p>Diagnostic use for children with prolonged FN and/or abnormalities in chest CT (A-II).</p> <p>Threshold for a positive test result in serum is an optical density index of ≥ 0.5 (B-II); administration of systemic mould-active antifungal prophylaxis might decrease the performance of the galactomannan antigen assay in serum (B-III)</p>	<p>Combined sensitivity and specificity of five paediatric studies with adequate data were 0.76 (95% CI 0.62–0.87) and 0.86 (95% CI 0.68–0.95). The performance of the galactomannan assay in serum under non-surveillance conditions (eg, in patients presenting with new pulmonary infiltrates) is unclear and needs future assessment.</p> <p>Performance of GM testing in children similar to adults (Lehrnbecher CID 2016); Careful interpretation necessary due to limitations such as 1) poor positive predictive values means that actions based on test results are often incorrect. 2) high negative predictive values are less useful as GM does not rule out non-Aspergillus molds 3) GM-assay not validated in non-neutropenic patients 4) Causes of false-positive galactomannan test results include cross-reaction from an existing non-Aspergillus fungal infection (eg, <i>Histoplasma</i> spp, <i>Penicillium marneffei</i>), the intravenous administration of fungal-derived products such as betalactam antibiotics, various blood products, or poor post-extraction management of samples in the laboratory. Posaconazole or voriconazole prophylaxis might prevent the circulation of galactomannan antigen</p>



Biomarkers for Early Detection of IFD (ECIL-8)

Recommendations	Remarks
<p>Serum β-D-glucan</p> <p>No specific recommendations and no grading</p> <p>Recommendation against use, moderate-quality evidence (DII)</p>	<p>Although included as a mycological criterion in the EORTC/MSG definitions of IFDs, data from children are very scarce and the optimal threshold for positivity of β-D-glucan testing in children is unknown</p> <p>Poor positive predictive values and limited data in prolonged FN setting (Lehrnbecher CID 2016; Guitard 2016, Calibri 2017, Gupta2017)</p>
<p>Detection of fungal nucleic acids in plasma, serum or whole blood</p> <ul style="list-style-type: none">- screening: no data, no recomm.- diagnosis: B-II	<p>PCR-based methods in blood and serum included in the 2019 revised EORTC/MSG IFD definitions .</p> <p>(Donnelly 2019; Lehrnbecher 2016, Löffler 2017, Gupta 2017)</p>

Biomarkers for Early Detection of IFD (ECIL-8)

Recommendations	Remarks
<p>GM in BAL</p> <p>An optical density index threshold for a positive test (OD) of 1 is an adjunctive method for diagnosis of invasive pulmonary aspergillosis (B-III) (A-III)</p>	<p>Supported by data from adults and retrospective data from 59 immunocompromised children two retrospective pediatric studies (Desai PIDJ 2009, de Mol Pediatr Pulmonol 2013)</p>
<p>GM in CSF</p> <p>An optical density index threshold for a positive test of 1.0 is an adjunctive method for diagnosis of CNS aspergillosis (A-II)</p>	<p>Supported by data from adults and a few pediatric patients with probable CNS aspergillosis (Chong 2016, Lehrnbecher (in press))</p> <p>Assay not validated in CSF</p>
<p>PCR in BAL or tissue / body fluids (A-III) preferentially in a reference laboratory</p>	<p>Supported by well documented cases / cases</p>
<p>BDG in CSF - no grading</p>	<p>Data extremely limited in children and adults (Salvatore 2016)</p>

Imaging to Detect IFD During Prolonged FN (ECIL-8)

Recommendations	Remarks
<p>Perform CT of the lungs</p> <p>Imaging studies (eg, CT scan of the lung or adequate imaging of the symptomatic region) should be done in high-risk patients with febrile granulocytopenia that persists beyond 96 h or with focal clinical findings (B-II A-II); typical and non-typical pulmonary infiltrates might be indicative of pulmonary IFD and should prompt further diagnostic work-up and initiation of mould-active antifungal treatment (B-II) (AII)</p>	<p>Signs regarded as typical of IFDs in adults (eg, halo sign, air crescent sign, and cavities) are not seen in most children with pulmonary mould infections. Radiographic findings in immunocompromised children with invasive pulmonary fungal disease are often unspecific, particularly in children younger than 5 years</p> <p>Optimal timing of initial and repeated imaging in children not known (Han 15, Zalseka 17, Qiu 2019)</p>
<p><i>Perform CT of the paranasal sinuses only in patients with localizing signs or symptoms (B-III)</i></p> <p>Perform appropriate cranial imaging in patients with pulmonary <i><u>infiltrates due to probable/proven pulmonary mold infection even when neurologically asymptomatic (B-II)</u></i></p>	<p>It is a weak recommendation because studies directly addressing the utility of routine sinus CTs are limited (Lehrnbecher JCO 2017)</p> <p>Retrospective analysis of 29 children with CNS mold infection demonstrated that one third did not have neurological symptoms (Lauten 2019; Broenen 14)</p>



Prophylaxis



Primary and Secondary Prophylaxis (ECIL-4/ECIL-8)

- May be indicated in pediatric patients who are at high risk for developing IFDs
- While the term 'high-risk' is not properly defined, a natural incidence rate of IFDs of $> 10\%$ is usually considered as high-risk
 - However, although the patient population at high risk is defined, *the local epidemiology* is an important additional consideration for designing an appropriate institutional prophylaxis strategy
 - Furthermore, low or sporadic risk is not equal to no risk and a *personalised assessment* may be indicated for individual patients based on specific individual risk factors

Recommendation on Antifungal Prophylaxis (1) (ECIL-8)

Primary antifungal prophylaxis is strongly recommended in pediatric patients at high risk (>10% estimated natural incidence) to develop IFDs (A-IIt); this includes patients with AML, recurrent leukemia, high risk ALL, and those undergoing allo HSCT in the pre-engraftment phase and in the post engraftment phase until immunoreconstitution or in situations of augmented immunosuppression in the context of GVHD

For mold-active triazoles, drug-drug interactions need to be carefully considered; the concurrent use of vincristine is strictly contraindicated due to potential aggravation of polyneuropathies

Intervention	SoR	QoE	Comments	Reference ECIL-4 + new
Fluconazole 8-12 mg/kg/d IV/PO in one single dose (max. 400mg/d)	A	II-t	Leukemia and allo-HSCT pre-engraftment: Fluconazole is active only against yeasts and should only be used if the institutional incidence of invasive mould infections is low, or if there are active diagnostic and therapeutic algorithms for mould infections (Tethier 2012) Allo-HSCT post engraftment:: Fluconazole is not recommended due to predominant role of mold infections in this setting	Clinical trials in adults: Goodman 1992; Slavin 1995; Marr 2000; Menichetti 1994; Rotstein 1999 PK studies in paediatric patients: Lee 1992; Brammer 1994; Van der Elst 2014 Safety and efficacy in paediatric patients: Novelli 1999; Egunsola 2013 ;
Posaconazole Patients ≥13 yrs: Delayed release tablets, 300 mg in one single daily dose (day 1: 300 mg twice daily) Patients from 1 month to 12 years: Oral suspension, starting dose 6 mg/kg three times daily	A	II-t	Spectrum includes both yeasts and molds; approved indication in adults. A novel delayed release oral suspension is under evaluation (Groll 2019); no dosing recommendations exist for the IV formulation Until approval of the delayed release suspension, in pediatric patients ≥13 yrs , adult doses of the delayed release tablets (Tragiannidis 2019) may be used; the use of the approved oral solution is discouraged in this age group (Arrieta 2019) For pediatric patients from 1 month to 12 years , a starting dose of the approved oral suspension of 6 mg/kg TID may be used (Arrieta 2019) TDM is suggested; dosing target: trough concentration of ≥ 0.7mg/L	Clinical trials in adults: Cornely 2007; Ullmann 2007 PK studies in pediatric patients: Krishna 2007; Welzen 2011; Arrieta 2019; Groll 19 Dosing target: Jang 2010; Lewis 2015 Safety and efficacy in pediatric patients: Lehrnbecher 2010; Cesaro 2011; Döring 2012; Heinz 2016; Arrieta 2019; Groll 2019



Recommendation on Antifungal Prophylaxis (2) (ECIL-8)

Intervention	SoR	QoE	Comments	Reference ECIL-4 + new
Itraconazole 5 mg/kg/d PO (≥ 2 years of age) in two divided doses	B	II-t	Spectrum includes both yeasts and moulds; approved indication; not approved in subjects <18 years TDM is suggested; dosing target: trough concentration of ≥ 0.5 mg/L	Clinical trials in adults: Marr 2004; Winston 2003; Menichetti 1999; Harousseau 2000; TDM dosing target: Lewis 2015 PK studies in pediatric patients: De Repentigny 1998; Groll 2002; Kim 2015 Safety and efficacy in pediatric patients: Foot 1999; Kim 2015 ; Allegra 2017
Voriconazole 2- <12 yrs /12-14 yrs and <50kg: 8 mg/kg BID (day 1: 9) IV and 9 mg/kg BID PO; / ≥ 15 yrs and 12-14 yrs and ≥ 50 kg: 4 mg/kg BID (day 1: 6) IV; 200 mg BID PO	B	II-t	Spectrum includes both yeasts and moulds; approved indication for subjects <2 years; TDM is suggested; target: trough concentration of 1.0 to 5.0 mg/L	<i>Clinical trials in adults: Wingard 2010; Marks 2011</i> <i>TDM dosing target: Troke 2011; Park 2012; Lewis 2015</i> <i>PK studies in paediatric patients: Walsh 2004; Walsh 2010; Karlsson 2009; Michael 2010; Driscoll 2011; Driscoll 2011; Friberg 2012</i> <i>Safety and efficacy in paediatric patients: Molina 2011; Pieper 2012; Martin 2017;</i>
Liposomal amphotericin B 1 mg/kg IV every other day / 2.5 mg/kg IV twice weekly	B	II-t / II	Spectrum includes both yeasts and moulds; not approved for prophylaxis. Alternative option for patients who do not tolerate triazoles or have contraindications to triazoles	Clinical trials in adults: Tollemar 1993; Kelsey 1999; Penack 2006; Cornely PK studies in pediatric patients: Hong 2006; Lestner 2016 ; Seibel 2017 Safety and efficacy in pediatric patients: Ringden 1997; Queiroz-Telles 2008; Maertens 2010; Kolve 2009; Bochennek 11



Recommendation on Antifungal Prophylaxis (3) (ECIL-8)

Intervention	SoR	QoE	Comments	Reference ECIL-4 + new
Micafungin 1 mg/kg/d (≥ 50 kg: 50 mg) IV in one single dose / 4 mg/kg twice weekly	C	I / II	Spectrum includes Candida and Aspergillus; approved for prophylaxis of invasive Candida infections in granulocytopenic patients.	Clinical trials in adults: van Burik 2006 PK studies in pediatric patients: Seibel 2005; Hope 2007 Safety and efficacy in pediatric patients: Arrieta 2011; van Burik 2006; Mehta 2010; Bochenek 15
Aerosolised liposomal amphotericin B 12,5 mg on 2 consecutive days per week (no grading)	-	-	Targeted against pulmonary mould infections; non-approved route of administration, appropriate doses and dosage schedule unknown in subjects < 18 year	Clinical trials in adults: Rijnders 2008
Isavuconazole 10 mg/kg IV with a max. dose of 372 mg isavuconazonium sulfate once daily (d 1 and 2: every 8 hours)	-	-	No approved indication, not approved in pediatric patients. Suggested dose corresponds to that under investigation in a pediatric phase II trial conducted as part of the Pediatric Investigation Plan (PIP)	Clinical trials in adults: No controlled studies PK study in pediatric patients: Arrieta 2019;



Empiric and Pre-emptive Therapy



Empirical antifungal therapy: Recommendations (ECIL-8)

Recommendation and grading	Comments
<p>If chosen as a strategy, it should be initiated in high-risk granulocytopenic paediatric patients after 96 h of fever of unclear cause that is unresponsive to broad-spectrum antibacterial agents (B-II), and be continued until resolution of neutropenia in the absence of suspected or documented invasive fungal disease (B-II). Both caspofungin (50 mg/m² per day; day 1, 70 mg/m²; maximum 70 mg per day) and liposomal amphotericin B (1–3 mg/kg per day) can be recommended (A-I). A similar approach can be chosen in granulocytopenic patients who develop recurrent fever after defervescence on initiation of broad-spectrum antibacterial agents (no grading). In patients already receiving mould-active antifungal prophylaxis, switching to a different class of mould-active antifungal agents seems reasonable (no grading)</p> <p>As most data are transferred from adult studies and 2) the compounds are not approved for children (itraconazole) or not approved for this indication (itraconazole, voriconazole, micafungin), itraconazole, voriconazole, and micafungin should not be used for empirical antifungal therapy in children (DII)</p> <p>Amphotericin B deoxycholate and ABCD should not be used for empirical antifungal therapy (D-I)</p>	<p>Randomised clinical trials with both caspofungin and liposomal amphotericin B done in paediatric patients show similar safety and efficacy relative to much larger trials in adults with similar study design. Both compounds are approved for empirical antifungal therapy in both children and adults.</p> <p>Empirical antifungal therapy might also be considered in individual persistently febrile patients with low-risk disorders and profound and persistent granulocytopenia and severe mucosal damage (no grading)</p> <p>FOR REFERENCES SEE APPENDIX</p>



Pre-emptive Antifungal Therapy: Recommendations (ECIL-8)

Recommendation and grading	Comments
<i>Pre-emptive (diagnostic-driven) therapy might be an alternative to the empirical antifungal approach (no grading) (B-II)</i>	<p>No data in children; feasibility shown in adults and accepted as an alternative to the empirical approach in high-risk adult granulocytopenic patients. Rapid availability of pulmonary CT and galactomannan results are a prerequisite; capability of undertaking bronchoscopies with bronchoalveolar lavage is desirable.</p> <p>(Santolaya JAC 2018)</p>



Targeted Therapy



Targeted Treatment of Established Fungal Infections (ECIL-8)

Fungal Infectious Syndromes in Children with Leukemia/HSCT

- Invasive Aspergillosis (IA)
- Candidemia/Invasive Candidiasis (IC)
- Rare molds
 - Mucorales
 - Infections due to *Scedosporium* spp.
 - Infections due to *Fusarium* spp.
- NEW: RARE YEAST

NEW: REFERENCE TO ECMM/ESCMID GL's !

ECIL-8 Recommendations for Targeted Treatment: Invasive Aspergillosis, First-Line

Intervention	SoR	QoE	Comments	Reference ECIL-4 + new
Voriconazole 2- <12 yrs /12-14 yrs and <50kg: 8 mg/kg BID (day 1: 9) IV and 9 mg/kg BID PO; / ≥15 yrs and 12-14 yrs and ≥50kg: 4 mg/kg BID (day 1: 6) IV; 200 mg BID PO +TDM (all)	A	II-t	Approved in subjects <2 years; TDM suggested; target: trough concentration of between 1.0 and 5.0 mg/L Current treatment of choice for infections involving the CNS. A switch in class is to be considered in patients with breakthrough aspergillosis on mold-active azole prophylaxis	Clinical trials in adults: Herbrecht 2002; Maertens 2016 TDM dosing target: Troke 2011; Park 2012; Lewis 2015 PK studies in paediatric patients: Walsh 2004; Walsh 2010; Karlsson 2009; Michael 2010; Driscoll 2011; Driscoll 2011; Friberg 2012 Safety and efficacy in paediatric patients: Pieper 2012; Molina 2011; Martin 2017 ;
Liposomal amphotericin B 3 mg/kg/d IV in one single dose	B	II-t	Pivotal phase III trial was comparison between two different dosage strategies but no head-to-head comparison to the reference agent at the time of its conduct (i.e., voriconazole) First option if azole-resistance is suspected or confirmed	Clinical trials in adults: Cornely 2007 PK studies in paediatric patients: Hong 2006; Lestner 2016; Seibel 2017 Safety and efficacy in paediatric patients: Prentice 1997; Kolve 2009; Queiroz-Telles 2008; Maertens 2010
Amphotericin B lipid complex 5 mg/kg/d IV in one single dose	C	II	No controlled first-line data but solid second line experience in treatment-naïve patients receiving the compound on the basis of its improved safety profile relative to amphotericin B deoxycholate	Clinical trials in adults: Walsh 1998 PK studies in pediatric patients: Walsh 1997; Safety and efficacy in pediatric patients: Walsh 1999; Wiley 2005;
Combination therapy (voriconazole or liposomal amphotericin B plus echinocandin)	C	II-t	Randomized clinical trial of voriconazole plus anidulafungin vs. voriconazole in adults showed no differences in the primary endpoint. Randomized trial of liposomal amphotericin B plus caspofungin underpowered	Marr 2015 ; Caillot 2007
Isavuconazole 10 mg/kg IV with a max. dose of 372 mg isavuconazonium sulfate once daily (d 1 and 2: every 8 hours)	-	-	Equivalent to voriconazole in randomized phase III clinical trial in adults; pediatric development on going in phase II	Clinical trials in adults: Maertens 2016 PK study in pediatric patients: Arrieta 2019



ECIL-8 Recommendations for Targeted Treatment: Invasive Aspergillosis, Second-Line

Intervention	SoR	QoE	Comments	Reference ECIL-4 + new
Voriconazole 2- <12 yrs /12-14 yrs and <50kg: 8 mg/kg BID (day 1: 9) IV and 9 mg/kg BID PO; / ≥15 yrs and 12-14 yrs and ≥50kg: 4 mg/kg BID (day 1: 6) IV; 200 mg BID PO +TDM (all)	A	II-t	Second line option for azole-naïve patients. Inference for efficacy from two pivotal first-line phase III trials and a second line phase II trial. Approved in subjects <2 years; TDM suggested; target: trough concentration of between 1.0 and 5.0 mg/L	Clinical trials in adults: Herbrecht 2002; Maertens 2016; Denning 2006 TDM dosing target: Troke 2011; Park 2012; Lewis 2015 PK studies in paediatric patients: Walsh 2004; Walsh 2010; Karlsson 2009; Michael 2010; Driscoll 2011; Driscoll 2011; Friberg 2012 Safety and efficacy in paediatric patients: Pieper 2012; Molina 2011; Martin 2017;
Liposomal amphotericin B 3 mg/kg/d IV in one single dose	A	II-t	Second-line option for patients not responding to or being intolerant of voriconazole; inference for efficacy from the pivotal first-line phase III trial	Clinical trials in adults: Cornely 2007 PK studies in paediatric patients: Hong 2006; Lestner 2016; Seibel 2017 Safety and efficacy in paediatric patients: Prentice 1997; Kolve 2009; Queiroz-Telles 2008; Maertens 2010
Amphotericin B lipid complex 5 mg/kg/d IV in one single dose	B	II	Solid second line experience based on data obtained through phase II and IV clinical studies	Clinical trials in adults: Walsh 1998 PK studies in pediatric patients: Walsh 1997; Safety and efficacy in pediatric patients: Walsh 1999; Wiley 2005;
Caspofungin 50 (d1:70) mg/m ² /d IV in one single dose	B	II-t	Efficacy demonstrated in pivotal phase II trial; approved for second line therapy in both children and adults.	Clinical trials in adults: Maertens 2004 PK studies in pediatric patients: Walsh 05; Neely 09; Li 11 Safety and efficacy in pediatric patients: Zaoutis 09; Zaoutis 09; Maertens 2010
Combination therapy (voriconazole or lipos. amphotericin B plus echinocandin)	C	II-t	Assessment of efficacy based on small phase II and retrospective cohort studies (both combinations) and inference from first-line studies	Maar 2004; Maertens 2006; Singh 2006; Caillot 2007; Marr 2015; Raad 2015



ECIL-8 Recommendations for Targeted Treatment: Invasive Candidiasis

Intervention	SoR	QoE	Comments	Reference ECIL-4 + new
Caspofungin 50 (d1:70) mg/m ² /d IV in one single dose	A	II-t	Fungicidal activity, consider for granulocytopaenic and haemodynamically unstable patients; higher MICs against <i>C.parapsilosis</i> group; not associated with diminished efficacy	Clinical trials in adults: Mora-Duarte 2002; Pappas 2007; Betts 2009 PK studies in paediatric patients: Walsh 2005; Neely 2009; Li 2011 Safety and efficacy in paediatric patients: Zaoutis 2009; Zaoutis 2009 ; Maertens 2010
Liposomal amphotericin B 3 mg/kg/d IV in one single dose	A	II-t	Fungicidal activity, consider for granulocytopaenic and haemodynamically unstable patients	Clinical trials in adults: Pappas 2007 PK studies in paediatric patients: Hong 2006; Lestner 2016; Seibel 2017 Safety and efficacy in paediatric patients: Prentice 1997; Kolve 2009; Queiroz-Telles 2008; Maertens 2010
Micafungin 2-4 mg/kg/d IV (≥ 50kg: 100 - 200 mg) in one single dose	A	II-t	Fungicidal activity, consider for granulocytopaenic and haemodynamically unstable patients; higher MICs against <i>C.parapsilosis</i> group; not associated with diminished efficacy	Clinical trials in adults: Pappas 2007; Kuse 2007 PK studies in paediatric patients: Seibel 2005; Hope 2007 Safety and efficacy in paediatric patients: Queiroz-Telles 2008; Arrieta 2011
Voriconazole 2- <12 yrs /12-14 yrs and <50kg: 8 mg/kg BID (day 1: 9) IV and 9 mg/kg BID PO; / ≥15 yrs and 12-14 yrs and ≥50kg: 4 mg/kg BID (day 1: 6) IV; 200 mg BID PO +TDM (all)	A	II-t	Fungistatic activity; relative to fluconazole, spectrum extends to <i>C.glabrata</i> and <i>C.krusei</i> . Not approved in subjects <2 years; TDM suggested; target: trough concentration of between 1.0 and 5.0 mg/L	Clinical trials in adults: Kullberg 2011 TDM dosing target: Troke 2011; Park 2012; Lewis 2015 PK studies in paediatric patients: Walsh 2004; Walsh 2010; Karlsson 2009; Michael 2010; Driscoll 2011; Driscoll 2011; Friberg 2012 Safety and efficacy in paediatric patients: Pieper 2012; Molina 2011; Mori 2015; Martin 2017;



ECIL-8 Recommendations for Targeted Treatment: Invasive Candidiasis

Intervention	SoR	QoE	Comments	Reference ECIL-4 + new
Fluconazole 12 mg/kg/d IV in one single dose (max. 800mg/d)	B	II-t	Non- granulocytopaenic and haemodynamically stable patients; Fungistatic activity; not recommended for infections by <i>C. krusei</i> and <i>C.glabrata</i> . Option for step down	Clinical trials in adults: Rex 1994; Anaissie 1996; Rex 2003 ; Reboli 2007; Reboli 2011 PK studies in paediatric patients: Lee 1992; Brammer 1994; Van der Elst 2014 Safety and efficacy in paediatric patients: Novelli 1999; Egunsola 2013 ; Step-down: Kullberg 2005; Reboli 2007; Vazquez 2014
	D	II-t	Not recommended for granulocytopaenic and haemodynamically unstable patients;	Kett 2011; Andes 2012
Amphotericin B lipid complex 5 mg/kg/d IV in one single dose	C	II	Fungicidal activity; lower grading because of absence of completely published first-line phase III data and limited paediatric PK studies	Clinical trials in adults: Anaissie 2005; Walsh 1998 PK studies in pediatric patients: Walsh 1997; Safety and efficacy in pediatric patients: Walsh 1999; Wiley 2005;
Anidulafungin 1.5 mg/kg/d IV (d1: 3 mg/kg) in one single dose	-	-	Fungicidal activity, consider for granulocytopaenic and haemodynamically unstable patients; higher MICs against <i>C.parapsilosis</i> group; not associated with diminished efficacy Provisional A-II-t recommendation, depending upon regulatory approval for pediatric patients by the EMA	Clinical trials in adults: Reboli 2007 PK-studies in pediatric patients: Benjamin 2006 Safety and efficacy in pediatric patients: Benjamin 2006; Roilides 2019



Recommendation for Targeted Treatment: Mucormycosis

General consideration

Management includes:

- early antifungal therapy
- control of underlying conditions¹
- surgery (for cutaneous and rhinoorbitocerebral forms, to be discussed on case basis for other locations)

A thorough evaluation for disseminated disease, in particular the CNS is required

Hyperbaric oxygen, granulocytes transfusions (no grading)

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

ECIL-8 Recommendations for Targeted Treatment: Mucormycosis, First-Line

Intervention	SoR	QoE	Comments	Reference ECIL-4 + new
Liposomal amphotericin B 5-10 mg/kg/d IV in one single dose	A	II-t	Preferred first-line therapy, particularly for infections involving the CNS (Groll 2000) or in patients with renal failure (Wingard 2000)	Clinical trials in adults: Walsh 2001; Rüping 2010; Shoham 2010; Skiada 2011; Wattier 2015; Lanternier 2015 PK studies in paediatric patients: Hong 2006; Lestner 2016; Seibel 2017 Safety and efficacy in paediatric patients: Queiroz-Telles 2008; Kolve 2009; Dehority 2009; Muggeo 2018
Amphotericin B lipid complex 5 mg/kg/d IV in one single dose	B	II	Recommendations similar as for adults (Tissot 2017) Solid experience in treatment-naïve patients receiving the compound on the basis of its improved safety profile relative to amphotericin B deoxycholate	Clinical trials in adults: Walsh 98; Larkin 2003 PK studies in pediatric patients: Walsh 1997; Safety and efficacy in pediatric patients: Walsh 1999; Wiley 2005
Combination therapy (lipid amphotericin B plus caspofungin or posaconazole)	C	III	Recommendations similar as for adults (Tissot 2017)	Clinical data in adults: Reed 2008; Pagano 2013 Preclinical data: Ibrahim AAC 2008; Ibrahim AAC 2009; Rodriguez AAC 2008
Posaconazole Patients ≥13 yrs: Delayed release tablets, 300 mg in one single daily dose (day 1: 300 mg twice daily) Patients from 1 month to 12 years: Oral suspension, starting dose 6 mg/kg three times daily	-	-	Non-approved indication; no data in adults that would support use as first-line treatment (Tissot 2017). Pediatric development ongoing, no recommendation	PK studies in pediatric patients: Groll 2019 Safety and efficacy in pediatric patients: Lehnbecher 2010; Cesaro 2011; Döring 2012; Heinz 2016; Arrieta 2019; Groll 2019
Isavuconazole 10 mg/kg IV with a max. dose of 372 mg isavuconazole-zonium sulfate once daily (d 1 and 2: every 8 hours)	-	-	Approved in adults as first line therapy if amphotericin B treatment is not appropriate. Pediatric development ongoing, no pediatric efficacy data, no recommendation.	Clinical trials in adults: Marty 2016 PK study in pediatric patients: Arrieta 2019;



ECIL-8 Recommendations for Targeted Treatment: Mucormycosis, Second-Line

Intervention	SoR	QoE	Comments	Reference ECIL-4 + new
Isavuconazole 10 mg/kg IV with a max. dose of 372 mg isavuconazonium sulfate once daily (d 1 and 2: every 8 hours)	B	II-t	<p>Approved in adults as first line therapy if amphotericin B treatment is not appropriate. Pediatric development ongoing, no pediatric efficacy data.</p> <p>Recommended dose corresponds to that currently investigated in a pediatric phase II trial conducted as part of the Pediatric Investigation Plan (PIP) agreed upon by the EMA</p> <p>In pediatric patients ≥ 13 yrs, adult doses of the IV solution and the tablet formulation may be used (B-II-t);</p>	Clinical trials in adults: Marty 2016 PK study in pediatric patients: Arrieta 2019 ;
Posaconazole Patients ≥ 13 yrs: Delayed release tablets, 300 mg in one single daily dose (day 1: 300 mg twice daily) Patients from 1 month to 12 years: Oral suspension, starting dose 6 mg/kg three times daily	B	II-t	<p>Non-approved indication; recommendations similar as for adults (Tissot 2017). Pediatric development ongoing.</p> <p>A novel delayed release oral suspension is under evaluation (Groll 2019); no dosing recommendations exist for the IV formulation</p> <p>For pediatric patients ≥ 13 yrs, adult doses of the delayed release tablets may be used (B-II-t); the use of the approved oral solution is discouraged in this age group (D-II; Arrieta 2019)</p> <p>For pediatric patients from 1 month to 12 years, for the approved oral suspension, a starting dose of 6 mg/kg TID may be used (Arrieta 2019) coupled with TDM</p>	Clinical trials in adults: Greenberg 2006 ; van Burik 2006 PK studies in pediatric patients: Groll 2019 Safety and efficacy in pediatric patients: Lehrnbecher 2010 ; Cesaro 2011 ; Döring 2012 ; Heinz 2016 ; Arrieta 2019 ; Groll 2019
Combination therapy (lipid amphotericin B plus caspofungin or posaconazole)	B	III	Recommendations similar as for adults (Tissot 2017)	Clinical data in adults: Reed 2008 ; Pagano 2013 Preclinical data: Ibrahim AAC 2008 ; Ibrahim AAC 2009 ; Rodriguez AAC 2008

