Table 1. Strength of recommendation and quality of evidence

Strength of Recommendation	**Definition**
Grade A	Strong support of a recommendation for use
Grade B	Moderate support of a recommendation for use
Grade C	Marginal support of a recommendation for use
Grade D	Support of a recommendation against use
Quality of Evidence	**Definition**
Level I	Evidence from at least 1 properly* designed randomized, controlled trial (orientated on the primary endpoint of the trial)
Level II	Evidence from at least 1 well-designed clinical trial (incl. secondary endpoints), 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
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

*poor quality of planning, inconsistency of results, indirectness of evidence etc. would lower the Strength of Recommendation.

Table 2. Neonatal and paediatric dosages of antifungal agents for prophylaxis and treatment of invasive aspergillosis.

Antifungal agent	Indication	Dosages
Amphotericin B deoxycholate	Treatment	1 to 1.5 mg/kg per day intravenously in one dose
Amphotericin B lipid complex	Treatment	5 mg/kg per day intravenously in one dose
Liposomal amphotericin B	Prophylaxis (non-approved indication)	1 mg/kg intravenously every other day or 2·5 mg/kg intravenously twice weekly
Liposomal amphotericin B	Treatment	Not approved in infants < 1 month of age. 3 mg/kg per day intravenously in one dose
Aerosolised liposomal amphotericin B	Prophylaxis (non-approved route of administration)	12·5 mg on 2 consecutive days per week
Itraconazole	Prophylaxis and treatment	5 mg/kg per day of the oral suspension in children aged ≥ 2 years in two divided doses, plus TDM For treatment, 10 mg/kg per day in two divided doses on day 1 (non-approved in EU in patients < 18 years)
Posaconazole	Prophylaxis	Gastro-resistant tablet (preferred formulation): 300 mg per day in one dose (day 1, two doses of 300 mg) in children aged ≥ 13 years Oral suspension: 600 mg per day in three divided doses plus TDM in children aged ≥ 13 years (not approved in EU in patients < 18 years)
	Treatment	Gastro-resistant tablet (preferred formulation): 300 mg per day in one dose (day 1, two doses of 300 mg) in children aged ≥ 13 years Oral suspension: 800 mg per day in two or four divided doses plus TDM in children aged ≥13 years Intravenous solution: 300 mg per day in one dose (day 1, two doses of 300 mg) in children aged ≥13 years (not approved in EU in patients < 18 years)
Voriconazole	Prophylaxis and treatment	Not approved in children < 2 years of age; Children aged 2 – < 12 years or aged 12–14 years and weighing < 50 kg: 8 mg/kg (day 1, 9 mg/kg) twice daily intravenously or 9 mg/kg twice daily orally, plus TDM; Children aged ≥ 15 years or aged 12–14 yrs and weighing ≥ 50 kg: 4 mg/kg (day 1, 6 mg/kg) twice daily intravenously or 200 mg twice daily orally, plus TDM
Caspofungin	Treatment	Children ≥ 1 year of age: 50 mg/m² per day (day 1, 70 mg/m²) intravenously in one dose, max 70 mg per day. Children aged 3 – 12 months: 50 mg/m² per day Infants < 3 months of age: 25 mg/m² per day
Micafungin	Prophylaxis (non-approved indication)	1 mg/kg per day (or in children weighing ≥50 kg, 50 mg) intravenously in one dose
Micafungin	Treatment (non-approved indication)	2–4 mg/kg per day intravenously (children weighing ≥ 50 kg: 100–200 mg) in one dose

TDM, therapeutic drug monitoring

Table 3. Indication for primary antifungal prophylaxis in paediatric patient populations at risk to develop invasive aspergillosis

Population	Intention	Intervention / Method	SoR	QoE	Comments	References
Allo- HSCT, Pre engraftment, granulocytopaenic phase	To prevent invasive aspergillosis (and other relevant IFDs)	Antifungal agents	B	II t	-	Adult data: [37-42] Paed data: [29,31]
Allo-HSCT, post engraftment phase, GvhD and augmented immunosuppression	To prevent invasive aspergillosis (and other relevant IFDs)	Antifungal agents	A	II t	-	Adult data: [37-43] Paed data: [29-31]
High-risk patients with de novo or recurrent leukemia, bone marrow failure syndromes with prolonged & profound granulocytopaenia	To prevent invasive aspergillosis (and other relevant IFDs)	Antifungal agents	A	II t	-	Adult data: [44] Paed data: [29,32-35]
Lung (+/-heart) transplant	To prevent invasive aspergillosis	Antifungal agents	A	III t	Duration: ≥ 12 months	Adult data: [45-47] Paed data: [36,48]
Heart transplant with high risk profile (e.g. acute rejection, re-exploration, hemodialysis)	To prevent invasive aspergillosis	Antifungal agents	B	III t	Only for high-risk heart transplantation	Adult data: [45,47,49] Paed data: [36]
Liver transplant with high-risk profile (e.g. MELD score >30, liver failure, renal failure, re-intervention)	To prevent invasive aspergillosis	Antifungal agents	B	III t	Higher risk for invasive candidiasis than for invasive aspergillosis	Adult data: [45,47,50-52] Paed data: [36,53]
Kidney transplant, liver and heart transplant with low-risk profile	To prevent invasive aspergillosis	Antifungal agents	D	III t	Very low risk for invasive aspergillosis	Adult data: [45] Paed data: [36]
Chronic Granulomatous Disease (CGD) patients	To prevent invasive aspergillosis	Antifungal agents	A	II	Highest life-time incidence of invasive aspergillosis	Clinical trial: [54] Paed data: [20-22]

SoR, Strength of recommendation; QoE, Quality of evidence; IFD, invasive fungal disease; HSCT, haematopoietic stem cell transplantation; GvhD, graft-versus-host disease; MELD, model for end-stage liver disease

Table 4. Antifungal prophylaxis in paediatric patient populations at high risk to develop invasive aspergillosis.

Population	Intention	Intervention	SoR	QoE	Comments	References
Allogeneic HSCT, pre-engraftment phase; Allogeneic HSCT, post-engraftment phase, GvhD and augmented immunosuppression; High-risk patients with de novo or recurrent leukaemia, bone marrow failure syndromes with prolonged and profound granulocytopaenia	Prevention of IA	Itraconazole	A/B*	II t	Approved indication; not approved EU < 18 years TDM recommended	Adult data: [37,38,55,56] TDM; [57] Paed PK/ safety/ supportive efficacy: [58-63]
		Posaconazole	A	II t	Approved indication; not approved EU < 18 years; only supportive paediatric data for ≥ 13 years of age TDM recommended;	Adult data: [40,43,44,64] TDM: [65,66] Paed PK/safety/ supportive efficacy: [67-74]
		Voriconazole	A	II t	Not approved for <2 years; Inference from efficacy from HSCT trials and supportive studies; TDM recommended	Adult data: [39,40,75,76] TDM: [77-79] Paed PK/safety/ supportive efficacy: [71,80-88]
		Liposomal amphotericin B	B	II t /III*	Not approved for prophylaxis; optimal dose of alternate administration unknown; alternative if triazoles are not tolerated / contraindicated	Adult data: [89-92] Paed PK/safety/ supportive efficacy: [93-99]
		Micafungin	B	II t /III*	No definite evidence (trend only) for prophylactic efficacy against *Aspergillus* spp. Alternative if triazoles are not tolerated or contraindicated	Adult data: [100,101] Paed PK/safety/ supportive efficacy: [100,102-110]
		Aerosolized liposomal amphotericin B	C	II t /III*	Non-approved route of administration; paediatric dosages	Adult data: [111]

					unknown; does not provide prevention of *Candida* infections.	
		Caspofungin	C	II /III*	Not approved for prophylaxis. Limited clinical data	Adult data: [112,113] Paed PK/safety/ supportive efficacy: [114-119]
Chronic granulomatous disease (CGD) patients	Prevention of IA	Itraconazole	A	II	Approved indication; not approved in the EU for < 18 years; TDM recommended	Clinical trial: [54] TDM: [57] Paed PK/Safety: [58-60] Safety & Efficacy: [26,129]
		Posaconazole	A	III	Not EU approved for children < 18 years; PK and safety data for children ≥ 4 years TDM recommended;	TDM: [65] Paed PK/Safety: [67-70]
		Interferon-ɣ 50 µg sc 3x/week	B	II t		Clinical trial: [130] Safety & Efficacy: [131-133]

* SoR = B for allogeneic HSCT post-engraftment phase, GvhD (graft-versus-host disease) and augmented immunosuppression

* QoE = III for allogeneic HSCT post-engraftment phase, GvhD and augmented immunosuppression

SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis; PK, pharmacokinetics; TDM, therapeutic drug monitoring; HSCT, haematopoietic stem cell transplantation

Table 5. Diagnostic modalities to detect invasive aspergillosis in paediatric patient populations.

Population	Intention	Intervention	SoR	QoE	Comments	References
Allogeneic HSCT, hematologic malignancies, bone marrow failure syndromes with prolonged & profound granulocytopaenia (considered to be at high-risk to develop IA)	Early diagnostic modality to detect IA in an early phase triggered by persistent febrile neutropenia, clinical findings, or positive serum GM or *Aspergillus* positive sputum	CT of the chest	A	II t	Signs considered typical of IFD/IA in adults (e.g., halo sign, air crescent sign, and cavities) are not seen in the majority of children with pulmonary mold infections. Radiographic findings in immunocompromised children with invasive pulmonary fungal disease are often unspecific.	Paed data: [14,140, 141] Adult data: [142-144]
		X-ray of the chest	C	II		
Allogeneic HSCT, hematologic malignancies, bone marrow failure syndromes with prolonged & profound granulocytopaenia (considered to be at high-risk to develop IA)	Early detection of IA	Screening by serum galactomannan (GM) twice weekly	B	II	Although assay seems to have a sensitivity and specificity profile that is similar to that observed in adults, careful interpretation necessary due to limitations such as wide variations regarding cut-off, definition of positivity etc. Use of systemic mold-active antifungals may decrease the performance of the test. GM-assay not validated in non-neutropenic patients.	[145-156]

		Screening by ß-D-glucan in serum/plasma	D	III	Data limited in children; optimal cut-off in children unknown (mean BG levels higher in immunocompetent uninfected children than adults)	Meta-analysis: [151,157, 158] Paed data: [155,158-163]
Immunocompromised patients including HSCT, haematological malignancies, bone marrow failure syndromes, SOT, CGD patients, patients treated with prolonged courses of immunosuppressive drugs or corticosteroids	Evaluation of suspected IA (e.g. clinical symptoms, imaging abnormalities)	Galactomannan in serum/plasma	B	II	GM-assay not validated in non-neutropenic patients and of low sensitivity in non-neutropenic patients. Use of systemic mold-active antifungals may decrease the performance of the test.	Paed Data: [152,153, 155,164]
		Galactomannan in BAL	B	II t	Although assay seems to have a sensitivity and specificity profile that is similar to that observed in adults, careful interpretation necessary due to limitations such as wide variations regarding cut-off, definition of positivity, use of mold-active antifungals, etc.	Adult data: [165-171] Paed data: [172,173]
		Galactomannan in CSF	B	II	GM-assay not validated for detection of GM in CSF.	Case reports/series (3 kids/8 adults): [174-179]
		ß-D-glucan in serum/plasma	D	III	Data limited in children; optimal cut-off in children unknown (mean BG levels higher in immunocompetent uninfected children than adults)	Meta-analysis: [153,157, 158] Paed data: [159-161, 180,181]

SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis; IFD, invasive fungal disease; HSCT, haematopoietic stem cell transplantation; SOT, solid organ transplant; CGD, chronic granulomatous disease

Table 6. Primary therapy of invasive aspergillosis in paediatric patient populations.

Population	Intention	Intervention	SoR	QoE	Comment	Ref
Paediatric HSCT, cancer, and bone marrow failure syndromes, solid organ transplant patients, chronic granulomatous disease patients	Treatment proven/probable IA	Voriconazole	A	II t	Not approved in patients <2 yrs; TDM recommended	Adult data: [196-201] TDM: [77-79] Paed PK: [80-85] Paed safety & supportive efficacy: [86,88,202-204]
		Liposomal amphotericin	B	II t	Comparison between 2 dosages of L-AmB, no comparison to voriconazole	Adult data: [205] Paed PK: [94,98,206, 207] Paed safety & supportive efficacy: [95,96,208, 209]
		Caspofungin	C	II t	Pivotal study prematurely stopped due to low accrual	Adult data: [210-212] Paed PK: [114,115, 117,119] Paed safety & supportive efficacy: [116,208, 213-220]
		Liposomal AmB + echinocandin	C	II t	Comparison made between high-dose L-AmB and the combination of caspofungin and standard dose L-AmB	Adult data: [221, 222] Paed safety & supportive efficacy: [208,216]
		Voriconazole + echinocandin	C	II t	Randomized comparison of voriconazole plus anidulafungin vs. voriconazole did not meet the primary endpoint of improved survival at 6 weeks	Adult data: [223-225] Paed safety & supportive efficacy: [216]

		AmB lipid complex	C	III	Data derived from large phase II trials in adult and paediatric patients and the CLEAR registry	Adult data: [226-228] Paed PK: [229] Paed safety & supportive efficacy: [230-232]
		Itraconazole IV	C	III	Not approved in subjects <18 years; sparse paediatric PK and safety data concerning intravenous itraconazole. TDM recommended	Adult data: [233,234] TDM: [40] Paed PK: [63] Paed safety & supportive efficacy: [235,236]
		AmB deoxycholate	D	II t	Recommendation based on increased rates of renal adverse events and infusion related reactions	Adult data: [196] Ped PK and safety: [237-241]
		AmB colloidal dispersion	D	II t	Recommendation based on increased rates of infusion related reactions	Adult data: [242,243] Paed PK and safety: [244]

SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis; PK, pharmacokinetics; TDM, therapeutic drug monitoring; HSCT, haematopoietic stem cell transplantation

Table 7. Salvage therapy of invasive aspergillosis in paediatric haemato-oncology patients.

Population	Intention	Intervention	SoR	QoE	Comments	References
HSCT, cancer, and bone marrow failure syndromes	Treatment of refractory proven or probable IA	Voriconazole	A	II t	Recommendation for voriconazole-naïve patients Not approved patients <2 yrs; TDM strongly recommended	Adult data: [196,198,225] TDM: [77-79] Paed PK: [80-85] Paed safety & supportive efficacy: [86,88,202-204,287]
		Liposomal AmB	B	II t	Recommendation for patients failing adequate voriconazole treatment (based on TDM) Comparison between 2 dosages in the pivotal registration trial	Adult data: [205] Paed PK: [94,98,207] Paed safety & supportive efficacy: [95,96,209]
		AmB lipid complex	B	II	Data derived from large phase II trials in adult and paediatric patients and the CLEAR registry	Adult data: [226,228] Paed PK: [230] Paed safety & supportive efficacy: [230-232]
		Caspofungin	B	II t	Open, noncomparative, multicenter clinical trial	Adult data: [219,286] Paed PK: [114,115,117,119] Paed safety & supportive efficacy: [116,216-218,220]
		Posaconazole	B	II t	Not approved in the EU in subjects < 18 yrs; only supportive paediatric data ≥ 13 yrs of age. No paediatric data exist for IV formulation. TDM recommended for the suspension	Adult data: [273] TDM: [65,66,272] Paed PK: [67,68,121] Paed safety & supportive efficacy: [69-73]
		Liposomal AmB + echinocandin	C	II t		Adult data: [208,221,288] Paed safety: [216]

		Micafungin	C	II t	Indication not approved	Adult data: [289,290] Paed PK: [102,103,106,109, 110] Paed safety: [104,107,291]
		Voriconazole + echinocandin	C	II t	Randomized comparison of voriconazole plus anidulafungin vs. voriconazole did not meet the primary endpoint of improved survival at 6 weeks	Adult data: [223] Paed safety & supportive efficacy: [216]
		Itraconazole	C	III	Not approved in subjects <18 years; sparse paediatric PK and safety data concerning intravenous itraconazole. TDM recommended	Adult data: [233,234] TDM: [57] Paed PK: [63] Paed safety & supportive efficacy: [235,236]
		AmB colloidal dispersion	D	II t	Recommendation based on increased rates of infusion related reactions	Adult data: [242,243] Paed PK & safety: [244]
		AmB deoxycholate	D	II t	Recommendation based on increased rates of renal AEs and infusion related reactions	Adult data: [196] Paed PK & safety: [237-241]

SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis; PK, pharmacokinetics; TDM, therapeutic drug monitoring; HSCT, haematopoietic stem cell transplantation; AE, adverse events

Table 8. Empiric and pre-emptive antifungal therapy in paediatric haemato-oncology patients considered to be at high-risk to develop invasive aspergillosis.

Intention	Intervention / Method	SoR	QoE	Comments	References
Management of persistent (>96 hours) febrile neutropaenia without obvious cause and treatment of 'occult' IFD (empiric therapy)	Liposomal amphotericin B	A	I	Randomised clinical trials in paediatrics show similar safety and efficacy in larger adult clinical trials. Both L-AmB as Caspofungin are approved for this indication in children. If patients receive mold-active antifungal prophylaxis, switching to a different class of mold-active antifungal is recommended (no grading due to lack of data). Empirical antifungal treatment should be continued until resolution of fever and neutropenia.	Paed data: [293-295] Adult data: [302,303]
	Caspofungin	A	I		Paed data: [294,295,304] Adult data: [303]
	AmB colloidal dispersion	D	II		Paed data: [244] Adult data: [242]
	AmB deoxycholate	D	II		Paed data: [241] Adult data: [242]
Early treatment of IA based on at least one positive clinical, imaging or microbiological feature suggesting IA (pre-emptive therapy)	Treatment recommendations correspond to those made for targeted therapy	A	II	The performed studies have shown that use and cost of antifungals can be diminished substantially by a pre-emptive approach compared to an empirical approach without an increase in mortality. Pre-emptive treatment strategy only feasible if rapid imaging and mycology results are available. If mold-active prophylaxis is given, a pre-emptive treatment is less useful due to lesser sensitivity of used diagnostic tools.	Paed data: [300,301] Adult data: [296-299]

SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis; IFD, invasive fungal disease;