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Guidelines

ESCMID-ECMM guideline: diagnosis and management of invasive aspergillosis in neonates and children

A. Warris [1, 7, 8, *], T. Lehrnbecher [2, 7, 8], E. Roilides [3, 7, 8], E. Castagnola [4, 7], R.J.M. Brüggemann [5, 7], A.H. Groll [6, 7, 8]

[1] MRC Centre for Medical Mycology, Institute of Medical Sciences, University of Aberdeen, Aberdeen, United Kingdom
[2] Division of Paediatric Haematology and Oncology, Hospital for Children and Adolescents, Johann Wolfgang Goethe-University, Frankfurt, Germany
[3] Infectious Diseases Unit, 3rd Department of Paediatrics, Faculty of Medicine, Aristotle University 96 School of Health Sciences, Thessaloniki, Greece
[4] Infectious Diseases Unit, IRCCS Istituto Giannina Gaslini Children's Hospital, Genoa, Italy
[5] Radboud Center for Infectious Diseases, Radboud University Medical Centre, Center of Expertise in Mycology Radboudumc/CWZ, European Confederation of Medical Mycology (ECMM) Excellence Center of Medical Mycology, Nijmegen, the Netherlands
[6] Infectious Disease Research Program, Center for Bone Marrow Transplantation and Department of Paediatric Hematology/Oncology, University Children's Hospital Münster, Münster, Germany
[7] European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group (EFISG)
[8] European Confederation of Medical Mycology, the Netherlands

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ABSTRACT

Scope: Presenting symptoms, distributions and patterns of diseases and vulnerability to invasive aspergillosis (IA) are similar between children and adults. However, differences exist in the epidemiology and underlying conditions, the usefulness of newer diagnostic tools, the pharmacology of antifungal agents and in the evidence from interventional phase 3 clinical trials. Therefore, the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and the European Confederation of Medical Mycology (ECMM) have developed a paediatric-specific guideline for the diagnosis and management of IA in neonates and children.
Methods: Review and discussion of the scientific literature and grading of the available quality of evidence was performed by the paediatric subgroup of the ESCMID-ECMM-European Respiratory Society (ERS) *Aspergillus* disease guideline working group, which was assigned the mandate for the development of neonatal- and paediatric-specific recommendations.
Questions: Questions addressed by the guideline included the epidemiology of IA in neonates and children; which paediatric patients may benefit from antifungal prophylaxis; how to diagnose IA in neonates and children; which antifungal agents are available for use in neonates and children; which antifungal agents are suitable for prophylaxis and treatment of IA in neonates and children; what is the role of therapeutic drug monitoring of azole antifungals; and which management strategies are suitable to be used in paediatric patients. This guideline provides recommendations for the diagnosis, prevention and treatment of IA in the paediatric population, including neonates. The aim of this guideline is to facilitate optimal management of neonates and children at risk for or diagnosed with IA. **A. Warris, Clin Microbiol Infect 2019;25:1096**

Introduction

Epidemiology of invasive aspergillosis in neonatal and paediatric patients

Invasive aspergillosis (IA) is a serious infectious complication observed in neonates and in children with primary or acquired immunodeficiencies. Quantitative or qualitative deficiencies of

* Corresponding author. MRC Center for Medical Mycology, University of Aberdeen, Institute of Medical Sciences, Rm 4.23, Foresterhill, AB25 2ZD Aberdeen, UK.
E-mail address: a.warris@abdn.ac.uk (A. Warris).

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neutrophil granulocytes are the major risk factors to develop IA. Consequently, paediatric patient groups vulnerable to IA include children with haematologic malignancies and primary immunodeficiencies, children undergoing haematopoietic stem-cell or solid organ transplantation, those with graft-versus-host disease (GvHD) and children receiving chemotherapy or immune-modulating treatment. In addition, neonates and children admitted to intensive care units are at an increased risk to develop IA [1–6].

The incidence of IA in the various paediatric patient groups is ill defined and varies depending on the intensity of treatment protocols for malignancies and organ transplants, the use of antifungal prophylaxis, the challenges in diagnosing IA and the inconsistencies in diagnostic criteria used [7]. Because neonates and children at risk for IA are in general also at risk for other invasive fungal infections caused by either yeasts or moulds and a proven diagnosis of an invasive mould infection is rarely obtained, epidemiologic studies have focused on the incidence of invasive fungal disease (IFD) using the European Organization for Research and Treatment of Cancer consensus criteria [8] or a modification of those. A retrospective cohort study using the US 2000 Kids' Inpatient Database has provided the most robust estimate of the incidence of paediatric IA so far [6]. The incidence rate of IA among immunocompromised children (including those with malignancies, nonmalignant haematologic or immunologic disorders and transplant patients) was 0.4%, with incidences ranging from 0.1% to 30% [6]. Highest incidences were reported among allogeneic haematopoietic stem-cell transplant (HSCT) recipients, lung transplant recipients, primary immunodeficiencies and acute myeloid leukaemia (AML). Similar incidence rates have been reported among paediatric HSCT patients by other studies [9–13]. The overall case-fatality rates of IA in children with cancer and those receiving a transplant ranges between 20% and 50% but is highly determined by the extent of invasive disease and the severity of immunosuppression [4,14,15]. Incidences of IA range from 26% to 45% in children with chronic granulomatous disease (CGD), and IA is the single most common infectious cause of death [16]. Neonatal IA is an occasional finding with a favourable outcome in 73% of patients [17].

Similar to adults, most children with IA present with pulmonary disease with dissemination to the central nervous system (CNS) in up to 15% [18]. Exceptions are neonates, who more often experience invasive cutaneous aspergillosis [17,19]. *Aspergillus fumigatus* and *A. flavus* are the most common species causing IA in neonates and children [14,15]. IA in children with CGD is predominantly caused by *A. fumigatus* and *A. nidulans,* with the latter species only sporadically encountered in other patient groups [16,20–22].

Motivation for guideline development

International professional organizations have noticed that the development of paediatric-specific guidelines for the management of IFDs has been an unmet need and have therefore initiated an effort to develop such guidelines. The European Society for Clinical Microbiology and Infectious Diseases (ESCMID)-Fungal Infections Study Group (EFISG) was the first to develop a specific guideline for the management of invasive candidiasis in neonates and children [23]. Next to this fungal disease–specific guideline, a guideline for the management of invasive fungal infections in paediatric patients with leukaemia and haematopoietic stem-cell transplantation has been elaborated [24]. This guideline has been developed within the European Conference on Infections in Leukaemia (ECIL) addressing a specific patient population at risk for developing IFD. In the document presented here, the ESCMID-European Confederation of Medical Mycology (ECMM) guideline for the management of IA in neonates and children is presented, the third paediatric-specific guideline for management of IFDs. It is related to the 2017 ESCMID-ECMM-European Respiratory Society (ERS) guideline covering the diagnosis and management of aspergillosis in all patient populations at high risk to develop either invasive or chronic aspergillosis, the executive summary of which was recently published [25].

Aim of guideline

The recommendations presented in this guideline are intended to facilitate optimal management of neonates and children, aged 0 to 18 years of age, at risk for IA and those diagnosed with IA. They are not necessarily exhaustive. Contraindications, drug–drug interactions and specific warnings for each antifungal compound have to be considered by the physician responsible for an individual patient's care.

This paediatric-specific guideline extends the summarized guidance about the prophylaxis and treatment of IA in children as found in the executive summary [25]. In the present guideline, paediatric-specific guidance with respect to diagnostic modalities, secondary prophylaxis, management strategies, breakthrough infection and salvage treatment, as well as specific recommendations for (TDM) of azole antifungals can be found. An extensive overview of the available literature supporting the recommendations is also presented.

For specific recommendations regarding preparation of diagnostic samples, microscopic examinations, cultures, species identification, susceptibility testing and recommendations for infection prevention in the hospital environment, the reader is referred to the executive summary [25].

Guideline development

The paediatric subgroup (AW, TL, ER, EC, RB, AG) of the ESCMID-ECMM-ERS *Aspergillus* disease guideline working group was assigned the mandate for the development of neonatal- and paediatric-specific recommendations as summarized in the executive summary [25]. During 2012–14, documents and discussions were shared by e-mail, teleconferences and face-to-face meetings. Once a first consensus was reached among the paediatric group, the preliminary recommendations were presented to the whole group, discussed, developed further, finalized by group consensus and presented in part at the 2014 European Congress of Clinical Microbiology and Infectious Diseases (ECCMID). This summary was reviewed and approved by all authors and was sent to the ESCMID guideline director for public review. An executive summary was prepared and submitted to *Clinical Microbiology and Infection* in 2017 and published in 2018 after peer review [25]. The methods to evaluate the quality of evidence and to reach group consensus recommendations have been previously described [26]. A modified United States Preventive Service Task Force (USPSFT) grading system https://www.uspreventiveservicestaskforce.org/Page/Name/grade-definitions was adopted for assessing quality of evidence and assigning strength of recommendation. Definitions of the strength of recommendation and quality of the published evidence are provided in Table 1. The quality of the evidence was indexed with a 't' (transferred evidence) if the evidence resulted from studies in different patient populations, e.g. adult patients.

Because the period between the development of the guideline and the publication of the executive summary was long, the paediatric group conducted a review of the literature published between 2014 until the end of 2017 and discussed the findings in a face-to-face meeting at the beginning of 2018. Relevant new literature was included in the text of the guideline, but no changes were made in the consented recommendations as published in the executive summary [25]. All authors fulfill the criteria set forth by the International Committee of Medical Journal Editors (ICMJE). For the purpose of this guideline, further requirements reflecting sufficient

Table 1
Strength of recommendation and quality of evidence

Characteristic	Definition
Strength of recommendation	
Grade A	Strong support of recommendation for use
Grade B	Moderate support of recommendation for use
Grade C	Marginal support of recommendation for use
Grade D	Support of recommendation against use
Quality of evidence	
Level I	Evidence from at least one properly[a] designed randomized controlled trial (orientated on primary end point of trial)
Level II	Evidence from at least one well-designed clinical trial (including secondary end points), without randomization; from cohort or case–control 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[b]	
r	Meta-analysis or systematic review of randomized controlled trial
t	Transferred evidence, i.e. results from different patient cohorts or similar immune-status situation
h	Comparator group: historical control
u	Uncontrolled trials
a	For published abstract presented at international symposium or meeting

[a] Poor quality of planning, inconsistency of results, indirectness of evidence and so on would lower strength of recommendation.
[b] Source of level II evidence.

author contribution were responsiveness throughout the guideline process and disclosure of conflicts of interests.

In the process of defining therapeutic recommendations for neonates and children, we have taken into account the paediatric development regulations and guidelines from the European Medicines Agency (EMA) [27,28]. The EMA accepts the requirement for extrapolation of evidence for efficacy from studies in adults to paediatric patients or from older to younger paediatric patients when the following criteria are met: (a) underlying condition and cause of targeted disease and expected response to therapy are similar; (b) data from clinical studies on pharmacokinetics, safety and tolerance are available for paediatric patients; and (c) supportive paediatric efficacy data exists.

Which paediatric patients may benefit from antifungal prophylaxis?

Primary antifungal chemoprophylaxis may be indicated in patients who are at high risk for developing IA. Although not defined in a rigorous scientific manner, an incidence rate of the disease in a given population of 10% and higher is usually considered as high risk. Following this definition, paediatric populations at high risk to develop IA include children with *de novo* or recurrent acute leukaemia (e.g. AML, recurrent AML and acute lymphoblastic leukaemia (ALL); *de novo* ALL depending on treatment protocol and additional risk factors, including prolonged and profound granulocytopaenia and treatment with glucocorticosteroids); those with bone marrow failure syndromes (e.g. myelodysplastic syndrome and very severe aplastic anaemia) with profound granulocytopaenia; allo-HSCT recipients; patients with CGD; and those undergoing lung or heart/lung transplantation or high-risk liver transplantation [20–22,29–36]. Of note, low or sporadic risk is not equal to no risk, and a personalized assessment may be warranted for individual patients not belonging to the listed entities based on the presence of specific individual risk factors. Most importantly, local epidemiology is an important consideration for designing an appropriate prophylaxis strategy in a given institution. Because IA in neonates is reported only occasionally, specific antifungal prophylaxis against IA in this patient group is not recommended (no grading).

What antifungal agents are available for management of IA in neonates and children?

Unfortunately, not all licensed antifungal agents are approved for use in neonates and children. In addition, for those antifungals with a paediatric label, it often does not cover all paediatric age groups and indications. Paediatric studies to define appropriate doses in specific age groups and in children with specific underlying diseases are still scarce. Table 2 provides an overview of antifungal agents which can be used in neonates and children for the prophylaxis and treatment of IA, the recommended dosages and the status of regulatory approval.

What antifungal agents are recommended for prophylaxis of IA in children?

Considering the patient populations at high risk for IA, the following recommendations are made with specific comments, systematic references and dosages provided in Tables 2–4.

Children undergoing allogeneic HSCT

Antifungal prophylaxis against IA and other relevant IFDs (i.e. invasive candidiasis) should be considered during the granulocytopaenic phase until engraftment (B-IIt). Options include itraconazole (A-IIt); posaconazole for patients ≥13 years of age (A-IIt); and voriconazole for patients >2 years of age (A-IIt). Secondary alternatives include liposomal amphotericin B (B-IIt); micafungin (B-IIt); and, with less strength of evidence, aerosolized liposomal amphotericin B (C-IIt) and caspofungin (C-II). In the absence of GvHD, antifungal prophylaxis may be continued after engraftment until discontinuation of immunosuppression and signs of immune recovery (no grading).

In the presence of GvHD requiring augmented immunosuppression (including but not limited to the use of glucocorticosteroids in therapeutic dosages (≥0.3 mg/kg per day prednisone equivalent) or use of anti-inflammatory antibodies), prophylaxis against IA and other relevant IFDs is recommended (A-IIt). Options include posaconazole for patients ≥13 years of age (A-IIt); and voriconazole for patients >2 years of age (A-IIt). Secondary alternatives are itraconazole (B-IIt); liposomal amphotericin B (B-III); micafungin (B-III); and, with less strength of evidence, aerosolized liposomal amphotericin B (C-III) and caspofungin (C-III). If itraconazole, posaconazole and voriconazole are selected, TDM is recommended with target concentrations similar to those recommended for adults. Special caution must be exerted with the concomitant use of itraconazole, posaconazole and voriconazole with immunosuppressants such as cyclosporine, tacrolimus and sirolimus [120,121].

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

Antifungal agent	Indication	Dose
Amphotericin B deoxycholate	Treatment	1 to 1.5 mg/kg per day intravenously in 1 dose
Amphotericin B lipid complex	Treatment	5 mg/kg per day intravenously in 1 dose
Liposomal amphotericin B	Prophylaxis (nonapproved 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 1 dose
Aerosolized liposomal amphotericin B	Prophylaxis (nonapproved route of administration)	12.5 mg on 2 consecutive days per week
Itraconazole	Prophylaxis and treatment	5 mg/kg per day of oral suspension in children ≥2 years in two divided doses, plus TDM. For treatment, 10 mg/kg per day in two divided doses on day 1 (nonapproved in EU in patients <18 years)
Posaconazole	Prophylaxis	Gastro-resistant tablet (preferred formulation): 300 mg per day in 1 dose (day 1, two doses of 300 mg) in children ≥13 years; oral suspension: 600 mg per day in three divided doses plus TDM in children ≥13 years (not approved in EU in patients <18 years)
	Treatment	Gastro-resistant tablet (preferred formulation): 300 mg per day in 1 dose (day 1, two doses of 300 mg) in children ≥13 years; oral suspension: 800 mg per day in two or four divided doses plus TDM in children ≥13 years; intravenous solution: 300 mg per day in 1 dose (day 1, two doses of 300 mg) in children ≥13 years (not approved in EU in patients <18 years)
Voriconazole	Prophylaxis and treatment	Not approved in children <2 years of age; children 2 to <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 ≥15 years or aged 12–14 years 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/m^2 per day (day 1, 70 mg/m^2) intravenously in 1 dose, max 70 mg per day; children 3–12 months: 50 mg/m^2 per day; infants <3 months of age: 25 mg/m^2 per day
Micafungin	Prophylaxis (nonapproved indication)	1 mg/kg per day (or in children weighing ≥50 kg, 50 mg) intravenously in 1 dose
Micafungin	Treatment (nonapproved indication)	2–4 mg/kg per day intravenously (children weighing ≥50 kg: 100–200 mg) in 1 dose

EU, European Union; TDM, therapeutic drug monitoring.

Table 3
Indication for primary antifungal prophylaxis in paediatric patient populations at risk of developing IA

Population	Intention	Intervention/method	SoR	QoE	Comments	References
Allogeneic HSCT, preengraftment, granulocytopaenic phase	To prevent IA (and other relevant IFDs)	Antifungal agents	B	II t	—	Adult data: [37–42] Paediatric data: [29,31]
Allogeneic HSCT, postengraftment phase, GvHD and augmented immunosuppression	To prevent IA (and other relevant IFDs)	Antifungal agents	A	II t	—	Adult data: [37–43] Paediatric data: [29–31]
High-risk patients with *de novo* or recurrent leukaemia, bone marrow failure syndromes with prolonged and profound granulocytopaenia	To prevent IA (and other relevant IFDs)	Antifungal agents	A	II t	—	Adult data: [44] Paediatric data: [29,32–35]
Lung (with or without heart) transplant	To prevent IA	Antifungal agents	A	III t	Duration: ≥12 months	Adult data: [45–47] Paediatric data: [36,48]
Heart transplant with high-risk profile (e.g. acute rejection, reexploration, haemodialysis)	To prevent IA	Antifungal agents	B	III t	Only for high-risk heart transplantation	Adult data: [45,47,49] Paediatric data: [36]
Liver transplant with high-risk profile (e.g. MELD score >30, liver failure, renal failure, reintervention)	To prevent IA	Antifungal agents	B	III t	Higher risk for invasive candidiasis than for IA	Adult data: [45,47,50–52] Paediatric data: [36,53]
Kidney transplantation, liver and heart transplant with low-risk profile	To prevent IA	Antifungal agents	D	III t	Very low risk for IA	Adult data: [45] Paediatric data: [36]
Chronic granulomatous disease patients	To prevent IA	Antifungal agents	A	II	Highest lifetime incidence of IA	Clinical trial: [54] Paediatric data: [20–22]

GvHD, graft-versus-host disease; HSCT, haematopoietic stem-cell transplantation; IA, invasive aspergillosis; IFD, invasive fungal disease; MELD, Model for End Stage Liver Disease; QoE, quality of evidence; SoR, strength of recommendation.

Children with de novo or recurrent acute leukaemia

Antifungal prophylaxis is recommended for patients with AML, recurrent AML and recurrent ALL (A-IIt); the recommendation for prophylaxis in *de novo* ALL depends on the treatment protocol and additional risk factors including prolonged and profound (≥10 days with an absolute neutrophil count <500/μL) granulocytopaenia and treatment with glucocorticosteroids. Options include itraconazole (A-IIt); posaconazole for patients ≥13 years of age (A-IIt); and voriconazole for patients >2 years of age (A-IIt). Secondary alternatives include liposomal amphotericin B (B-IIt); micafungin (B-IIt); and, with less strength of evidence, aerosolized liposomal amphotericin B (C-IIt) and caspofungin (C-II). If itraconazole, posaconazole and voriconazole are selected, TDM is recommended

Table 4
Antifungal prophylaxis in paediatric patient populations at high risk of developing IA

Population	Intention	Intervention	SoR	QoE	Comments	References
Allogeneic HSCT, preengraftment phase; allogeneic HSCT, postengraftment 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[a]	II t	Approved indication; not approved EU < 18 years; TDM recommended	• Adult data: [37,38,55,56] • TDM: [57] • Paediatric 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] • Paediatric 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] • Paediatric PK/safety/supportive efficacy: [71,80–88]
		Liposomal amphotericin B	B	II t/III[b]	Not approved for prophylaxis; optimal dose of alternate administration unknown; alternative if triazoles are not tolerated/contraindicated	• Adult data: [89–92] Paediatric PK/safety/supportive efficacy: [93–99]
		Micafungin	B	II t/III[b]	No definite evidence (trend only) for prophylactic efficacy against *Aspergillus* spp. Alternative if triazoles are not tolerated or contraindicated	• Adult data: [100,101] • Paediatric PK/safety/supportive efficacy: [100,102–110]
		Aerosolized liposomal amphotericin B	C	II t/III[b]	Nonapproved route of administration; paediatric dosages unknown; does not provide prevention of *Candida* infections.	• Adult data: [111]
		Caspofungin	C	II/III[b]	Not approved for prophylaxis. Limited clinical data	• Adult data: [112,113] • Paediatric PK/safety/supportive efficacy: [114–119]
CGD	Prevention of IA	Itraconazole	A	II	Approved indication; not approved in EU for <18 years; TDM recommended	• Clinical trial: [54] • TDM: [57] • Paediatric PK/safety: • [58–60] • Safety and 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] • Paediatric PK/Safety: [67–70]
		Interferon-γ 50 μg subcutaneously 3 times a week	B	II t		• Clinical trial: [130] • Safety and efficacy: [131–133]

CGD, chronic granulomatous disease; GvHD, graft-versus-host disease; HSCT, haematopoietic stem-cell transplantation; IA, invasive aspergillosis; PK, pharmacokinetics; QoE, quality of evidence; SoR, strength of recommendation; TDM, therapeutic drug monitoring.
[a] SoR indicates B for allogeneic HSCT postengraftment phase, GvHD and augmented immunosuppression.
[b] QoE indicates III for allogeneic HSCT postengraftment phase, GvHD and augmented immunosuppression.

with target concentrations similar to those recommended for adults. Special caution must be exerted with the concomitant use of itraconazole, posaconazole and voriconazole with vincristine and other anticancer agents [122–124].

Children with bone marrow failure syndromes

Antifungal prophylaxis is recommended for patients with profound and prolonged granulocytopaenia (A-IIt). In the absence of separate data, recommendations are similar to those made for patients with acute leukaemia.

Children undergoing lung and/or heart transplantation

Prevention of IA in children with solid organ transplantation depends on the type of transplant. In children undergoing lung (with or without heart) transplantation, anti-*Aspergillus* prophylaxis is strongly recommended for those aged ≥12 months (A-IIIt). In heart transplantation alone, the risk for IA is low, and there is no need of prophylaxis (D-IIIt). However, heart transplantation with a high-risk profile (e.g. acute rejection, reexploration, haemodialysis) is an indication for antifungal prophylaxis (B-IIIt).

Nebulized lipid formulations of amphotericin B or systemic azoles with antimould activity may be used for IA prevention [125] (no grading). The effectiveness and safety of voriconazole prophylaxis has been studied in lung transplant recipients [126]; the overall incidence of IA was 1.5% in the universal prophylaxis voriconazole group compared to 23.5% in the guided prophylaxis group.

Children undergoing liver transplantation

Antifungal prophylaxis is only recommended in those children exhibiting a high-risk profile (e.g. Model for End Stage Liver Disease score >30, liver failure, renal failure, reintervention) (B-IIIt). Duration of prophylaxis is unclear, but a 3- to 4-week treatment or treatment until resolution of risk factors seems appropriate [45]. The drug of choice remains controversial (no grading). Lipid amphotericin B has shown a significant reduction of invasive fungal infections without a mortality reduction [127] but is limited by its potential for nephrotoxicity. Echinocandins are not nephrotoxic, and promising results have been published in preventive studies focusing on high-risk liver transplant recipients [51,128].

Children undergoing kidney transplantation

In paediatric kidney transplant recipients, antifungal prophylaxis to prevent IA is not recommended (D-IIIt).

Children with CGD

Prevention of IA plays a central role in the clinical management of children with CGD and consists of reducing environmental exposure to moulds and the prophylactic use of antifungals. Itraconazole prophylaxis has shown to significantly reduce IFD in CGD patients [54] and is recommended as prophylaxis (A-II). Posaconazole is a favourable alternative (A-III). The use of prophylactic recombinant human interferon-γ has shown to decrease the risk of severe infections (including fungal infections) in CGD by 70% [130], but controversy remains about its use in routine prophylaxis [131–133].

Secondary prophylaxis

Available data suggest a natural relapse rate of 30% to 50% in haematologic patients with proven or probable IFDs during subsequent courses of chemotherapy or allogeneic HSCT [134]. Cohort studies in adults indicate that voriconazole, itraconazole, caspofungin and liposomal amphotericin B may all be effective in reducing relapse rates in patients with disease that responded to initial antifungal therapy; data for paediatric patients are limited [24]. On the basis of these data, secondary prophylaxis to prevent recurrence or a second episode of IA is recommended for granulocytopaenic or immunocompromised patients as long as these risk factors are persisting (A-IIt). Prophylaxis should be implemented with an antifungal agent that is targeted against the *Aspergillus* species that caused the first episode and the site of infection [135–139]. No general recommendations can be made about the minimum duration of therapy and the extent of response before continuing anticancer treatment or starting the conditioning regimen.

How to diagnose IA in neonates and children?

Early diagnosis of IA is particularly challenging in children because of the difficulties in obtaining enough sample volumes, the need for anaesthesia to perform certain diagnostic procedures and limited clinical data with respect to the usefulness of fungal biomarkers and molecular detection methods. Standard diagnostic procedures for IA are not different between paediatric and adult patients. Both microscopy and culture should be attempted on appropriate specimens from patients at high risk for IA. The following recommendations are made with specific comments and systematic references in Table 5.

Imaging studies

Imaging studies, in particular computed tomography (CT) scan of the chest, should be used in high-risk patients as an early diagnostic modality to detect IA in an early phase triggered by persistent febrile neutropenia, clinical findings, positive serum galactomannan (GM) or *Aspergillus* positive sputum (A-IIt). Importantly, radiographic findings considered typical of pulmonary IA in adults, such as the halo sign, the air crescent sign and cavities, are not seen in the majority of children with pulmonary IA, whereas in immunocompromised children with invasive pulmonary aspergillosis (IPA), unspecific findings are detected more often. In neutropenic children, CT scans of the chest have a higher sensitivity in the early detection of IPA than conventional X-ray (C-II for the latter), whereas in nonneutropenic immunocompromised children after solid organ transplantation or those with CGD pulmonary infiltrates are in most cases visible on X-ray as well (A-III). However, for evaluation of extensiveness of disease, CT scan of the chest is recommended in this patient population (A-III). Whether pulmonary CT angiography will improve specificity in the diagnosis of IPA in children needs further evaluation [182]. In addition to chest imaging, evaluation of other sites such as the paranasal sinuses, the central nervous system or the abdomen may be necessary. Similar to adults, invasive diagnostics such as bronchoalveolar lavage or CT-guided biopsies should be strongly considered for the diagnosis of IA [183–186].

Non–culture-based assays

In paediatric patients, the GM assay in serum seems to have a sensitivity and specificity profile that is similar to that in adults [153]. However, careful interpretation is necessary due to limitations such as variations regarding the cutoff or the definition of test positivity. GM testing can be used both as a screening tool in paediatric patients considered at high risk for developing IA (B-II) as well as a diagnostic tool in paediatric patients suspected of having developed IA, e.g. those with clinical symptoms or imaging abnormalities (B-II). GM screening should not be performed in neonates and children at low risk for IA (D-III). Bifidobacteria, comprising over 75% of the total faecal microflora of neonates and young infants, have been shown to explain the high false-positive GM test results and is therefore of less value in this young patient population [187]. Systemic mould-active prophylaxis may decrease the performance of the test, and the assay is not validated in nonneutropenic patients. In view of adult data, the limited studies in the paediatric population also suggest the usefulness of GM testing in bronchoalveolar lavage (B-IIt). Although not validated for detection in cerebrospinal fluid, a highly elevated GM in the cerebrospinal fluid is indicative of central nervous system aspergillosis in the appropriate setting (B-II).

In addition to *Aspergillus* infections, β-D-glucan may detect infections due to fungi such as *Candida* spp., *Pneumocystis jirovecii* or *Fusarium* spp. Data on β-D-glucan testing in serum or plasma are extremely limited in the paediatric population. In addition, the optimal cutoff in neonates and children is unknown, as mean β-D-glucan levels are higher in immunocompetent children than in adults [162,180,187,188]. Therefore, at present, there is a recommendation against the use of β-D-glucan for screening or for the evaluation of suspected IA in immunocompromised children at high-risk to develop IA (D-III).

PCR-based assays are increasingly evaluated for the early detection of IA. Whereas two paediatric studies reported on a high negative predictive value of *Aspergillus*-specific PCR used for screening in haematology patients at high risk for IA [162,189], six other studies showed a wide range of sensitivities and specificities when using a PCR assay (four *Aspergillus* specific, two pan-fungal) as a diagnostic tool in immunocompromised children suspected of having IPA [190–195]. None of those studies included neonates. Because of the lack of paediatric data, no recommendation can be made for its use in diagnosing IA in neonates and children.

What antifungal agents are recommended for treatment of IA in neonates and children?

General management principles of IA are in line with those in adults and include prompt initiation of antifungal therapy, control of predisposing conditions (e.g. colony-stimulating factors for granulocytopaenic patients), reduction of immunosuppressive therapy and surgical interventions in individual patients [24,24]. Duration of treatment is not defined, and decisions when to stop

Table 5
Diagnostic modalities to detect IA in paediatric patient populations

Population	Intention	Intervention	SoR	QoE	Comments	References
Allogeneic HSCT, haematologic malignancies, bone marrow failure syndromes with prolonged and profound granulocytopaenia (considered to be at high risk to develop IA)	Early diagnostic modality to detect IA in early phase triggered by persistent febrile neutropenia, clinical findings or positive serum GM or *Aspergillus*-positive sputum	CT of 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 majority of children with pulmonary mould infections.	• Paediatric data: [14,140,141] • Adult data: [142–144]
		X-ray of chest	C	II	• Radiographic findings in immunocompromised children with invasive pulmonary fungal disease are often unspecific.	
Allogeneic HSCT, haematologic malignancies, bone marrow failure syndromes with prolonged and profound granulocytopaenia (considered to be at high risk to develop IA)	Early detection of IA	Screening by serum GM twice weekly	B	II	• Although assay seems to have sensitivity and specificity profile similar to that observed in adults, careful interpretation is necessary due to limitations such as wide variations regarding cutoff and definition of positivity. • Use of systemic mould-active antifungals may decrease performance of test. • GM assay not validated in nonneutropenic patients.	• [145–156]
		Screening by β-D-glucan in serum/plasma	D	III	• Data limited in children; optimal cutoff in children unknown (mean β-D-glucan levels higher in immunocompetent uninfected children than adults).	• Meta-analysis: [151,157,158] • Paediatric data: [155,158–163]
Immunocompromised patients including HSCT, haematologic 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)	GM in serum/plasma	B	II	• GM assay not validated in nonneutropenic patients and of low sensitivity in nonneutropenic patients. • Use of systemic mould-active antifungals may decrease performance of test.	• Paediatric Data: [152,153,155,164]
		GM in BAL	B	II t	• Although assay seems to have sensitivity and specificity profile similar to that observed in adults, careful interpretation necessary due to limitations such as wide variations regarding cutoff, definition of positivity and use of mould-active antifungals.	• Adult data: [165–171] • Paediatric data: [172,173]
		GM in CSF	B	II	• GM assay not validated for detection of GM in CSF.	• Case reports/series (3 kids/8 adults): [174–179]
		β-D-Glucan in serum/plasma	D	III	• Data limited in children; optimal cutoff in children unknown (mean β-D-glucan levels higher in immunocompetent uninfected children than adults).	• Meta-analysis: [153,157,158] • Paediatric data: [159–161,180,181]

BAL, bronchoalveolar lavage; CGD, chronic granulomatous disease; CSF, cerebrospinal fluid; GM, galactomannan; HSCT, haematopoietic stem-cell transplantation; IA, invasive aspergillosis; IFD, invasive fungal disease; QoE, quality of evidence; SoR, strength of recommendation; SOT, solid organ transplant.

antifungal therapy should take into account clinical response, the degree of immunosuppression and/or recovery from neutropenia, engraftment after HSCT and recovery of GvHD.

Children with HSCT, leukaemia, other cancers and bone marrow failure syndromes

Recommendations for primary treatment of proven or probable IA (Table 6) include intravenous voriconazole with TDM (A-IIt; limited to children ≥2 years) and liposomal amphotericin B (B-IIt); the weaker recommendation for liposomal amphotericin B is due to the fact that the pivotal phase 3 trial was not a head-to-head comparison to voriconazole as the reference agent but a comparison between two different dose strategies. Secondary options include caspofungin (C-IIt); the combination of liposomal amphotericin B with an echinocandin (C-IIt); the combination of voriconazole with an echinocandin (C-IIt a); amphotericin B lipid complex (C-III); and intravenous itraconazole with TDM (C-III). The use of amphotericin B deoxycholate and of amphotericin B colloidal dispersion is discouraged as a result of poor tolerability (D-IIt).

Children undergoing solid organ transplantation

There are no studies of primary treatment in paediatric solid organ transplant patients with IA. The recommendations are derived from children and/or adults with haematologic malignancies and IA (Table 6). Decreasing the degree of immunosuppression if possible but without jeopardizing graft viability is of importance to control IA. Primary treatment of proven or probable IA in children having received any solid organ transplant includes voriconazole (A-IIt) and liposomal amphotericin B (B-IIt) [199–201]. Secondary options [213–215,226] are similar to those recommended for paediatric haemato-oncology populations and are summarized in Table 6.

Table 6
Primary therapy of IA in paediatric patient populations

Population	Intention	Intervention	SoR	QoE	Comment	References
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 aged <2 years; TDM recommended	• Adult data: [196–201] • TDM: [77–79] • Paediatric PK: [80–85] • Paediatric safety and supportive efficacy: [86,88,202–204]
		Liposomal amphotericin	B	II t	Comparison between two dosages of L-AmB, no comparison to voriconazole	• Adult data: [205] • Paediatric PK: [94,98,206, 207] • Paediatric safety and supportive efficacy: [95,96,208,209]
		Caspofungin	C	II t	Pivotal study prematurely stopped due to low accrual	• Adult data: [210–212] • Paediatric PK: [114,115, 117,119] • Paediatric safety and supportive efficacy: [116,208,213–220]
		L-AmB + echinocandin	C	II t	Comparison made between high-dose L-AmB and combination of caspofungin and standard dose L-AmB	• Adult data: [221,222] • Paediatric safety and supportive efficacy: [208,216]
		Voriconazole + echinocandin	C	II t	Randomized comparison of voriconazole plus anidulafungin vs. voriconazole did not meet primary end point of improved survival at 6 weeks	• Adult data: [223–225] Paediatric safety and supportive efficacy: [216]
		AmB lipid complex	C	III	Data derived from large phase 2 trials in adult and paediatric patients and CLEAR registry	• Adult data: [226–228] • Paediatric PK: [229] • Paediatric safety and 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] • Paediatric PK: [63] • Paediatric safety and 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] • Paediatric PK and safety: [244]

AmB, amphotericin B; HSCT, haematopoietic stem-cell transplantation; IA, invasive aspergillosis; L-AmB, liposomal amphotericin B; PK, pharmacokinetics; QoE, quality of evidence; SoR, strength of recommendation; TDM, therapeutic drug monitoring.

Children with CGD

The recommendations for primary therapy in CGD patients with IA are derived from those for children with haematologic malignancies, as no studies have been performed in CGD patients (Table 6). In addition, the unique epidemiology of IA in CGD patients has been taken into account, which is characterized by the occurrence of *A. nidulans,* often resistant to amphotericin B [20–22,245]. To make a causative diagnosis is of utmost importance in this particular patient group, as unusual *Aspergillus* species with different susceptibility profiles are more frequently compared to other patient groups [246,247]. In general, it is more feasible to perform invasive diagnostic procedures compared to children with underlying haematologic malignancies. Posaconazole has been shown to be safe and effective in CGD patients with refractory IA, has good activity against *A. fumigatus* and *A. nidulans*, and is a reasonable alternative (no grading).

Neonates

IA in neonates is more often cutaneous [17,19]. Liposomal amphotericin B is the drug of choice (A-III), as voriconazole is not approved for children <2 years of age and the doses to be administered are unclear. Limited safety data for the use of liposomal amphotericin B in neonates are available [248–251], but pharmacokinetic studies are lacking. Amphotericin B deoxycholate (C-III) is an alternative, as minimal toxicity is observed in neonates and it is relatively safe and efficacious [237–239,252]. Other alternative agents are amphotericin lipid complex (C-III) [253], mould-active azoles (C-III) [254] and echinocandins (C-III) [255–260].

What is the role of TDM in neonates and children?

Over the past two decades, there has been a surge in information supporting the use of TDM of azole antifungal agents [261,262]. Paediatric patients display differences in the clearance of antifungal azoles and display a high interindividual variability in exposure [263]. Augmented TDM-guided exposure may be required in the setting of infection at sanctuary sites and for infections with strains with higher MICs. Other situations where TDM may be indicated is the setting of intravenous to oral step-down therapy or in the setting of drug–drug interactions. It should be noted that target trough concentrations have been defined mostly for adult populations and have not been fully validated in paediatric patients. In the setting of azole resistance, current recommended target concentrations are not valid, and alternative treatments should be used [264–266].

Because most azole antifungal agents are provided with a loading dose and steady-state conditions are reached at an early time point, it is feasible to have a first assessment on day 3 of therapy. The frequency of resampling is driven by the degree of intraindividual variability (http://www.ecil-leukaemia.com/

telechargements2015/ECIL6-Triazole-TDM-07-12-2015-Lewis-R-et-al.pdf). For compounds with a high degree of variability (i.e. voriconazole or itraconazole), sampling once or twice a week for the first 4 weeks of treatment is recommended, with a reduction in frequency thereafter. For drugs with limited intraindividual variability, monitoring once a week at the start of therapy is recommended. This may be reduced after adequate exposure has been confirmed to once every 2 weeks (http://www.ecil-leukaemia.com/telechargements2015/ECIL6-Triazole-TDM-07-12-2015-Lewis-R-et-al.pdf). Patients receiving chronic/prophylactic therapy (such as CGD patients) typically are monitored on every outpatient visit (no grading due to lack of data).

Itraconazole

For oral administration, the oral solution should be preferred over the tablet form because of better absorption of the parent agent. The pharmacokinetics of itraconazole have been well described for paediatric patients [58,60,63]. TDM is strongly recommended [57,231,267]. For prophylaxis, trough levels of 0.5 to 4 mg/L (itraconazole + hydroxy-itraconazole) should be achieved; for treatment, trough concentrations of 1 to 4 mg/L are recommended (AII (efficacy), B11 (safety)) [25,57,267–270]. Concentrations should be assessed after 5 days (3 days if loading dose is administered), and repeated during prophylaxis and therapy.

Posaconazole

Posaconazole is available as an oral suspension, as gastroresistant tablet and an intravenous formulation. Dosing in paediatric patients has not formally been established [271], and dosing recommendations in adults vary according to the formulation. For oral administration, the tablet formulation is preferred because of more consistent absorption. In the absence of established dosing regimens for children, TDM is recommended when administering posaconazole for prophylaxis [65,69,272] and targeted therapy [273]. For prophylaxis, trough concentrations of >0.7 mg/L (BII, efficacy) and for treatment trough concentrations >1 mg/L (AII, efficacy) are recommended [25]. Concentrations should be assessed on day 3 of administration, and repeated during prophylaxis and therapy.

Voriconazole

Voriconazole is available as a solid oral tablet, an oral solution and an intravenous formulation. The drug shows a high degree of both inter- and intraindividual variability in pharmacokinetics [85,274–277]. It is both a substrate and inhibitor of CYP 450–mediated drug metabolism and carries a high potential for drug–drug interactions. TDM is recommended, and plasma trough concentrations of 1 to 5.5 mg/L are considered adequate for prophylaxis and treatment of IA (AII, safety and efficacy) [25]. A slightly higher trough level (2–6 mg/L) is recommended for disseminated and/or central nervous system infections or infections caused by *Aspergillus* species with an elevated MIC of 2 mg/L (AII, safety and efficacy [25,77,78,278–280]. Concentrations should be assessed on day 3 of therapy and repeated at regular intervals during therapy, regardless of previous concentrations.

How to manage breakthrough IA?

For children receiving mould-active azole prophylaxis, it is recommended to choose a nonazole antifungal for empiric or pre-emptive therapy. Liposomal amphotericin B (A-IIt) is recommended as first-line antifungal therapy in those cases [281–285]. Caspofungin is recommended as an alternative (C-II) on the basis of a salvage therapy study conducted in patients who had breakthrough infections while receiving amphotericin B [286].

What are the approaches to salvage therapy?

Salvage or second-line treatment refers to antifungal treatment in patients with disease that fails to respond to initial treatment or in patients who are intolerant to the initial treatment. Identification to species level and the resistance profile of the causative *Aspergillus* sp. is of utmost importance. Although not formally investigated, a switch in class should be considered when antifungal therapy is changed for refractory disease. In the absence of separate data for nonhaematologic patients, recommendations made here apply to all haematologic and nonhaematologic patient populations (Table 7). Options for salvage treatment include voriconazole plus TDM in voriconazole-naive patients (A-IIt; limited to children ≥2 years) and liposomal amphotericin B in amphotericin B–naive patients (B-IIt), respectively. Further options approved in paediatric patients include amphotericin B lipid complex (B-II) and caspofungin (B-IIt), and, for patients ≥13 years of age, posaconazole plus TDM (B-IIt). Few and uncontrolled data exist on combination therapy with either voriconazole or an amphotericin B product plus an echinocandin for salvage treatment (C-IIt), for micafungin (C-IIt) and for itraconazole (C-III), and no strong recommendations can therefore be made. Similar to primary therapy, the use of amphotericin B deoxycholate and of amphotericin B colloidal dispersion is discouraged because of poor tolerability (D-IIt).

Which management strategies are available in children with clinical suspicion of IA?

The administration of empirical antifungal therapy is a common practice that consists of administering a systemic antifungal drug in a persistently febrile, neutropaenic cancer patient after a variable period of empirical antibacterial therapy (usually 4 to 7 days) in the absence of any further clinical, radiologic or microbiologic documentation of a fungal infection [292]. Empiric treatment is defined as a fever-driven treatment approach and aimed to treat IA as early as possible in patients at high risk for IA before further clinical signs and symptoms develop. Four prospective randomized clinical trials have been performed in paediatric haemato-oncologic populations [244,293–295].

The empirical approach has the potential to result in an overuse of antifungals, as most patients receiving empirical antifungal therapy ultimately do not have an invasive fungal infection. A pre-emptive or a diagnostic-driven approach has been advocated and has shown to be a safe alternative if diagnostic modalities are accessible in a timely way. In this approach, new abnormalities found on chest CT and/or a positive serum GM are used to define the start of antifungal therapy. A number of studies in adult high-risk populations have demonstrated the feasibility and safety of this approach as well as a reduction in the use of antifungal agents without increased mortality [296–299]. An observational study of a diagnostic treatment approach in a paediatric haemato-oncologic population spanning several decades showed an increased survival from IFD, a higher number of diagnosed infections and less antifungal consumption compared to historical controls with different management strategies [300]. Recently the results from the first randomized clinical trial comparing the efficacy of pre-emptive versus empirical antifungal therapy in children with high-risk febrile neutropenia were published [301]. The results showed that a pre-emptive approach was as effective as the empirical approach, with a significant reduction of antifungal use in the pre-emptive group. Therefore, a diagnostic-driven

Table 7
Salvage therapy of IA 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-naive patients; not approved for patients aged <2 years; TDM strongly recommended	• Adult data: [196,198,225] • TDM: [77–79] • Paediatric PK: [80–85] • Paediatric safety and supportive efficacy: [86,88,202–204,287]
		L-AmB	B	II t	Recommendation for patients with disease that fails to respond to adequate voriconazole treatment (based on TDM); comparison between 2 dosages in pivotal registration trial	• Adult data: [205] • Paediatric PK: [94,98,207] • Paediatric safety and supportive efficacy: [95,96,209]
		AmB lipid complex	B	II	Data derived from large phase 2 trials in adult and paediatric patients and CLEAR registry	• Adult data: [226,228] • Paediatric PK: [230] • Paediatric safety and supportive efficacy: [230–232]
		Caspofungin	B	II t	Open noncomparative multicentre clinical trial	• Adult data: [219,286] • Paediatric PK: [114,115,117,119] • Paediatric safety and supportive efficacy: [116,216–218,220]
		Posaconazole	B	II t	Not approved in EU in subjects aged <18 years; only supportive paediatric data ≥13 years of age. No paediatric data exist for IV formulation. TDM recommended for suspension	• Adult data: [273] • TDM: [65,66,272] • Paediatric PK: [67,68,121] • Paediatric safety and supportive efficacy: [69–73]
		L-AmB + echinocandin	C	II t		• Adult data: [208,221,288] • Paediatric safety: [216]
		Micafungin	C	II t	Indication not approved	• Adult data: [289,290] • Paediatric PK: [102,103,106,109,110] • Paediatric safety: [104,107,291]
		Voriconazole + echinocandin	C	II t	Randomized comparison of voriconazole plus anidulafungin vs. voriconazole did not meet primary end point of improved survival at 6 weeks	• Adult data: [223] • Paediatric safety and supportive efficacy: [216]
		Itraconazole	C	III	Not approved in subjects aged <18 years; sparse paediatric PK and safety data concerning intravenous itraconazole. TDM recommended	• Adult data: [233,234] • TDM: [57] • Paediatric PK: [63] • Paediatric safety and supportive efficacy: [235,236]
		AmB colloidal dispersion	D	II t	Recommendation based on increased rates of infusion related reactions	• Adult data: [242,243] • Paediatric PK and safety: [244]
		AmB deoxycholate	D	II t	Recommendation based on increased rates of renal AEs and infusion related reactions	• Adult data: [196] • Paediatric PK and safety: [237–241]

AE, adverse event; AmB, amphotericin B; HSCT, haematopoietic stem-cell transplantation; IA, invasive aspergillosis; L-AmB, liposomal amphotericin B; PK, pharmacokinetics; QoE, quality of evidence; SoR, strength of recommendation; TDM, therapeutic drug monitoring.

Table 8
Empiric and pre-emptive antifungal therapy in paediatric haemato-oncology patients considered to be at high risk of developing IA

Intention	Intervention/Method	SoR	QoE	Comments	References
Management of persistent (>96 hours) febrile neutropaenia without obvious cause and treatment of occult IFD (empiric therapy)	L-AmB	A	I	• Randomized 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 mould-active antifungal prophylaxis, switching to different class of mould-active antifungal is recommended (no grading due to lack of data). • Empirical antifungal treatment should be continued until resolution of fever and neutropenia.	• Paediatric data: [293–295] • Adult data: [302,303]
	Caspofungin	A	I		• Paediatric data: [294,295,304] • Adult data: [303]
	AmB colloidal dispersion	D	II		• Paediatric data: [244] • Adult data: [242]
	AmB deoxycholate	D	II		• Paediatric data: [241] • Adult data: [242]
Early treatment of IA based on at least one positive clinical, imaging or microbiologic feature suggesting IA (pre-emptive therapy)	Treatment recommendations correspond to those made for targeted therapy	A	II	• Studies have shown that use and cost of antifungals can be diminished substantially by pre-emptive approach compared to empirical approach without increase in mortality. • Pre-emptive treatment strategy only feasible if rapid imaging and mycology results are available. • If mould-active prophylaxis is provided, pre-emptive treatment is less useful due to lesser sensitivity of used diagnostic tools.	• Paediatric data: [300,301] • Adult data: [296–299]

AmB, amphotericin B; IA, invasive aspergillosis; IFD, invasive fungal disease; L-AmB, liposomal amphotericin B; QoE, quality of evidence; SoR, strength of recommendation.

treatment strategy can be recommended in children (A-II) (Table 8) if the diagnostic infrastructure allows timely access to CT imaging, GM testing and the ability to undertake bronchoscopies with bronchoalveolar lavage and appropriate microbiologic assessment.

What antifungal agents are recommended for empiric and pre-emptive treatment in neonates and children?

Summarizing the results of the four prospective randomized clinical trials in paediatric haemato-oncologic patients [244,293–295], similar efficacy was observed for caspofungin and liposomal amphotericin B, with liposomal amphotericin B being more efficacious than amphotericin B deoxycholate and amphotericin B colloidal dispersion. Caspofungin was better tolerated than liposomal amphotericin B, with the latter showing less toxicity compared to the other amphotericin B formulations. Therefore, caspofungin or liposomal amphotericin B are recommended and approved for use in an empiric treatment approach (A-I) (Table 8).

Transparency declaration

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