ESCMID-ECMM GUIDELINE: DIAGNOSIS AND MANAGEMENT OF INVASIVE ASPERGILLOSIS IN NEONATES AND CHILDREN.

Adilia Warris[1,7,8], Thomas Lehrnbecher[2,7,8], Emmanuel Roilides[2,7,8], Elio Castagnola[4,7], Roger J.M. Bruggemann[5,7], Andreas 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, ECMM Excellence Center of Medical Mycology, Nijmegen, 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]ESCMID Fungal Infection Study Group (EFISG)

[8]European Confederation of Medical Mycology (ECMM)

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 III 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.

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 neutrophil granulocytes are the major risk factors to develop IA. Consequently, paediatric patient groups vulnerable to IA include children with haematological malignancies and primary immunodeficiencies, children undergoing haematopoietic stem cell or solid organ transplantation, suffering from graft-versus-host disease, 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]. As neonates and children at risk for IA are in general also at risk for other invasive fungal infections caused by either yeasts or molds, and a proven diagnosis of an invasive mold infection is rarely obtained, epidemiological studies have focused on the incidence of invasive fungal disease (IFD) using the EORTC consensus criteria [8] or a modification of those. A retrospective cohort study using the U.S. 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, non-malignant 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 in up to 15% [18]. Exceptions are neonates, who are suffering more often from invasive cutaneous aspergillosis [17,19]. *Aspergillus fumigatus* and *A. flavus* are the most common species causing IA in neonates and children [14,15]. Invasive aspergillosis in children with CGD is predominantly caused by *A. fumigatus* and *A. nidulans*, with the latter species only sporadic encountered in other patient groups [16,20-22].

Motivation for guideline development

International professional organisations have noticed that the development of paediatric specific guidelines for the management of invasive fungal diseases 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 invasive

fungal disease. In the document presented here, the ESCMID-ECMM (European Confederation of Medical Mycology) guideline for the management of invasive aspergillosis in neonates and children is presented, the third paediatric specific guideline for management of invasive fungal diseases. It is related to the 2017 ESCMID-ECMM-ERS (European Respiratory Society) guideline covering the diagnosis and management of aspergillosis in all patient populations at high risk to develop either invasive or chronic aspergillosis whose executive summary has recently been 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 invasive aspergillosis and those diagnosed with invasive aspergillosis. 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 therapeutic drug monitoring 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 2012-2014, 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 ECCMID 2014. This summary was reviewed and approved by all authors and 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 USPSFTF grading system [www.uspreventiveservicetaskforce.org/] 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.

As the period between the development of the guideline and the publication of the executive summary was prolonged, 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 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: (i) underlying condition and cause of targeted disease and expected response to therapy are similar; (ii) data from clinical studies on pharmacokinetics, safety and tolerance are available for paediatric patients; and (iii) supportive paediatric efficacy data exists.

1WHICH PAEDIATRIC PATIENTS MAY BENEFIT FROM ANTIFUNGAL PROPHYLAXIS?

Primary antifungal chemoprophylaxis may be indicated in patients who are at high risk for developing invasive aspergillosis (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 leukemia (e.g. AML, recurrent AML and 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 (MDS) and very severe aplastic anaemia (VSAA)) with profound granulocytopaenia; allo-HSCT recipients; patients with chronic granulomatous disease 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, the local epidemiology is an important consideration for designing an appropriate prophylaxis strategy in a given institution. As IA in neonates is reported only occasionally, specific antifungal prophylaxis against IA in this patient group is not recommended (no grading).

3. WHAT ANTIFUNGAL AGENTS ARE AVAILABLE FOR MANAGEMENT OF INVASIVE ASPERGILLOSIS 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.

4. WHAT ANTIFUNGAL AGENTS ARE RECOMMENDED FOR THE PROPHYLAXIS OF INVASIVE ASPERGILLOSIS 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, 3, and 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, aerosolised liposomal amphotericin B (C-IIt) and caspofungin (C-II). In the absence of Graft-versus-Host Disease (GvHD), antifungal prophylaxis may be continued post 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/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, aerosolised liposomal amphotericin B (C-III) and caspofungin (C-III). If itraconazole, posaconazole, and voriconazole are selected, therapeutic drug monitoring (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].

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/uL) 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, aerosolised liposomal amphotericin B (C-IIt) and caspofungin (C-II). If itraconazole, posaconazole, and voriconazole are selected, therapeutic drug monitoring (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 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 leukemia.

Children undergoing lung and/or heart transplant

Prevention of IA in children with solid organ transplantation depends on the type of transplant. In children undergoing lung (+/-heart) transplantation, anti-*Aspergillus* prophylaxis is strongly recommended for ≥ 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 high-risk profile (e.g. acute rejection, re-exploration, haemodialysis) is an indication for antifungal prophylaxis (B-IIIt).

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

Children undergoing liver transplant

Antifungal prophylaxis is only recommended in those children exhibiting a high-risk profile (e.g. model for end-stage liver disease [MELD] score >30, liver failure, renal failure, re-intervention) (B-IIIt). Duration of prophylaxis is unclear but a 3 to 4-wk 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 IFI 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 transplant

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

Children with chronic granulomatous disease

Prevention of IA plays a central role in the clinical management of children with chronic granulomatous disease (CGD) and consists of reducing environmental exposure to molds and the prophylactic use of antifungals. Itraconazole prophylaxis has shown to significantly reduce invasive fungal disease 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 hematological 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 who had 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 invasive aspergillosis 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 prior to continuing anticancer treatment or starting the conditioning regimen.

5. HOW TO DIAGNOSE INVASIVE ASPERGILLOSIS IN NEONATES AND CHILDREN?

Early diagnosis of IA is particular challenging in children due to 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 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 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 non-neutropenic immunocompromised children following 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 (CNS) or the abdomen may be necessary. Similar to adults, invasive diagnostics such as broncho-alveolar lavage (BAL) 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 cut-off 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 fecal 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 mold-active prophylaxis may decrease the performance of the test, and the assay is not validated in non-neutropenic patients. In view of adult data, the limited studies in the paediatric population also suggest the usefulness of GM testing in BAL (B-IIt). Although not validated for detection in cerebrospinal fluid (CSF), a highly elevated GM in the CSF is indicative of CNS aspergillosis in the appropriate setting (B-II).

In addition to *Aspergillus* infections, ß-D-glucan (BG) may detect infections due to fungi such as *Candida* spp., *Pneumocystis jirovecii*, or *Fusarium* spp. Data on BG testing in serum or plasma are extremely limited in the paediatric population. In addition, the optimal cut-off in neonates and children is unknown, as mean BG levels are higher in immunocompetent children than in adults [162,180,187,188]. Therefore, at present, there is a recommendation against the use of BD 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 hematology patients at high risk for IA [162,189], 6 other studies showed a wide range of sensitivities and specificities when using a PCR assay (4 *Aspergillus* specific, 2 pan-fungal) as a diagnostic tool in immunocompromised children suspected of having IPA [190-195]. None of those studies included neonates. Due to the lack of paediatric data no recommendation can be made for its use in diagnosing IA in neonates and children.

6. WHAT ANTIFUNGAL AGENTS ARE RECOMMENDED FOR THE TREATMENT OF INVASIVE ASPERGILLOSIS 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 antifungal therapy should take into account clinical response, the degree of immunosuppression and/or recovery from neutropenia, engraftment post-HSCT and recovery of GvHD.

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

Recommendations for primary treatment of proven or probable IA (see 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 III trial was not a head-to-head comparison to voriconazole as the reference agent but a comparison between two different dosage 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 due to poor tolerability (D-IIt).

Children undergoing solid organ transplantation

There are no studies of primary treatment in paediatric SOT patients with IA. The recommendations are derived from children and/or adults with haematological malignancies and IA (see 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.

Children with chronic granulomatous disease

The recommendations for primary therapy in CGD patients with IA are derived from those for children with haematological malignancies as no studies have been performed in CGD patients (see 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 frequent compared to other patient groups [246,247]. In general it is more feasible to perform invasive diagnostics compared to children with underlying haematological 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

Invasive aspergillosis 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 dosages to be administered are unclear. Limited safety data for the use of liposomal amphotericin B in neonates is available [248-251], but PK studies are lacking. Amphotericin B deoxycholate (C-III) is an alternative as minimal toxicity is observed in neonates and is relatively safe and efficacious [237-239,252]. Other alternative agents are amphotericin lipid complex (C-III) [233], mold-active azoles (C-III) [238] and echinocandins (C-III) [255-260].

7. WHAT IS THE ROLE OF THERAPEUTIC DRUG MONITORING IN NEONATES AND CHILDREN?

Over the past two decades there has been a surge in information supporting the use of therapeutic drug monitoring (TDM) of azole antifungal agents [261,262]. Paediatric patients display differences in the clearance of antifungal azoles and display a high inter-individual 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].

As most azole antifungals are given 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 intra-individual variability [http://www.eci.-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 1-2 times per week for the first four weeks of treatment is recommended with a reduction in frequency thereafter. For drugs with limited intra-individual variability, monitoring once weekly at the start of therapy is recommended. This may be reduced after adequate exposure has been confirmed to once every two weeks [http://www.ecil-leukaemia.com/telechargements2015/ECIL6-Triazole-TDM-07-12-2015-

Lewis-R-et-al.pdf]. Patients on chronic/prophylactic therapy (such as CGD patients) typically are monitored on every outpatient visit (no grading due to the lack of data).

Itraconazole

For oral administration, the oral solution should be preferred over the tablet form due to better absorption of the parent. 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 0.5-4 mg/L (itraconazole +hydroxy-itraconazole) should be achieved; for treatment, trough concentrations of 1-4 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 IV 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 due to 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 IV formulation. The drug shows a high degree of both inter- and intra-individual variability in pharmacokinetics

[85,274-277] is both a substrate as well as inhibitor of CYP 450 mediated drug metabolism and carries a high potential for drug-drug interactions. TDM is recommended, and plasma trough concentrations of 1-5.5 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 CNS 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 in regular intervals during therapy regardless of previous concentrations.

8. HOW TO MANAGE BREAKTHROUGH INVASIVE ASPERGILLOSIS?

For children receiving mold-active azole prophylaxis, it is recommended to choose a non-azole 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) based on a salvage therapy study conducted in patients who had breakthrough infections while on amphotericin B [286].

9. WHAT ARE THE APPROACHES TO SALVAGE THERAPY?

Salvage- or second-line treatment refers to antifungal treatment in patients failing to respond or being 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 non-hematological patients, recommendations made here apply to all hematological and non-hematological patient populations (see table 7). Options for salvage treatment include voriconazole plus

TDM in voriconazole-naïve patients (A-IIt; limited to children ≥ 2 years) and liposomal amphotericin B in amphotericin B-naïve 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 due to poor tolerability (D-IIt).

10. WHICH MANAGEMENT STRATEGIES ARE AVAILABLE IN CHILDREN WITH A CLINICAL SUSPICION OF INVASIVE ASPERGILLOSIS?

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-oncological 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 on a chest-CT and/or a positive serum galactomannan

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 and 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-oncological population spanning several decades showed an increased survival from invasive fungal disease, 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 treatment strategy can be recommended in children (A-II) (see table 8), if the diagnostic infrastructure allows timely access to CT imaging, galactomannan testing and the ability to undertake bronchoscopies with bronchoalveolar lavage and appropriate microbiological work-up.

11. WHAT ANTIFUNGAL AGENTS ARE RECOMMENDED FOR EMPIRIC AND PRE-EMPTIVE TREATMENT IN NEONATES AND CHILDREN?

Summarizing the results of the 4 prospective randomized clinical trials in paediatric haemato-oncological 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) (see table 8).

TRANSPARENCY DECLARATION

Dr Brüggemann has received grants and consultancy fees as well as speaker fees from F2G, MSD, Pfizer, Gilead and Astellas. All contracts were with Radboudumc and all payments have been received by Radboudumc. Dr Castagnola reports personal fees from Astellas Pharma, non-financial support from Gilead, outside the submitted work. Dr Groll reports grants and personal fees from Gilead, Merck, Sharp & Dohme and Pfizer, personal fees from Astellas and Basilea, outside the submitted work. Dr Lehrnbecher reports grants, personal fees and non-financial support from Gilead Sciences, personal fees and non-financial support from Astellas and Merck/MSD, personal fees from Basilea, outside the submitted work. Dr Roilides reports grants, personal fees and non-financial support from Astellas, Gilead Merck and Pfizer, outside the submitted work. Dr Warris reports grants from Gilead, and personal fees for consultancy activities from Gilead and Basilea, outside the submitted work.

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