

Fourth European Conference on Infections in Leukaemia (ECIL-4): Guidelines for Diagnosis, Prevention and Treatment of Invasive Fungal Diseases in Paediatric Patients with Cancer or Allogeneic Haematopoietic Stem Cell Transplantation

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ABSTRACT

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

INTRODUCTION

Invasive opportunistic fungal diseases (IFDs) are important causes of morbidity and mortality in immunocompromised patients with cancer and/or undergoing allogeneic haematopoietic stem cell transplantation (HSCT). Whereas, relative to adults, paediatric patients are similarly vulnerable to acquire IFDs, relevant differences exist in the biology, treatment and outcome of the underlying conditions and age-dependent comorbidities, the populations at risk and the exact epidemiology of IFDs, the performance and usefulness of diagnostic tools, the pharmacology and dosing of systemic antifungal agents, and the availability of evidence generated by interventional phase III studies.¹⁻⁴

Cognizant of these differences, recommendations for diagnosis, prevention and treatment of IFDs in cancer and allogeneic HSCT patients elaborated for adults may not be directly transferred to infants, children and adolescents, but need to be adapted for their application based on scientific evidence and general principles in paediatric medicine. In order to specify its guidelines to the smaller, but relevant population of paediatric patients undergoing treatment for cancer and/or allogeneic HSCT, the 4th European Conference on Infection in Leukaemia (ECIL-4) has convened a Paediatric Group with the aim to specifically address paediatric issues that were not considered in previously published ECIL guidelines.⁵⁻⁹ The final considerations and recommendations of the ECIL-4 Paediatric Group constitute the first published international guidelines solely dedicated to diagnosis, prevention and treatment of IFDs in paediatric patients with cancer and allogeneic HSCT and are summarised in this manuscript.

METHODS

Guideline development overview

The ECIL is a joint initiative of the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT-IDWP), the Infectious Diseases Group of the European Organisation for Research and Treatment of Cancer (EORTC-IDG), the International Immunocompromised Host Society (ICHS), and the European Leukaemia Net (ELN). The objective of ECIL is to develop evidence-based guidelines for management of infectious complications in immunocompromised subjects with leukaemia, HSCT and other malignancies, as applicable.^{10,11}

The proceedings of the ECIL conferences have been previously described.^{10,11} In brief, considering the need to specifically address paediatric issues related to the management of IFDs, the ECIL organisation committee convened a paediatric working group. The ECIL Paediatric Group consisted of ten independent international experts identified on the basis of knowledge and publications in the field of paediatric IFDs. Under the guidance of a designated group leader, the group defined the relevant issues, questions and outcomes to be addressed, and evaluated these issues and questions prior to the consensus conference through a systematic literature review. Medical subject heading (MESH) terms were used as keywords to search articles published in English up to the date of the conference in Medline, PubMed or Cochrane databases. Abstracts presented during the period 2009–2011 at annual meetings of the American Society of Hematology (ASH), the Interscience Conference on Antimicrobial Agents and

Chemotherapy (ICAAC), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the American Society of Clinical Oncology (ASCO) and the European Group for Blood and Marrow Transplantation (EBMT) were also screened. Recommendations were formulated after discussion of the literature review within the group and graded for quality of evidence (I–III) and strength of recommendation (A–C) using the Infectious Diseases Society of America (IDSA) grading system (TABLE 1).¹²

The consensus conference was convened at ECIL-4 on September 09-10, 2011 and attended by 54 experts from 16 European countries, Russia, Israel and Turkey. Delegates were specialists in haematology, oncology, microbiology, infectious diseases and clinical research, and selected on the basis of expertise and active participation in the host organisations. The group presented the findings of the literature review and the proposed recommendations in an initial plenary session. After panel debate, the recommendations were revised as necessary, re-discussed in a second plenary session and a final consensus reached on the quality of evidence and the strength of each recommendation.

Grading system

While the grading system for interventions used in this document is similar to that of guidelines developed by the IDSA for adults,¹² there are, however, subtle but important differences for paediatric patients. These differences have been adopted by recently published paediatric guidelines on *Candida* infections¹³ and are consistent with paediatric drug development regulations and guidelines from the European Medicines Agency (EMA).^{14,15}

On the basis of this conceptual framework, the group considered four components for grading of recommendations for each intervention: (1) evidence for efficacy from adult phase II and III trials corresponding to the ECIL-3 recommendations,⁸ (2) existence and quality of paediatric pharmacokinetic data and dosing recommendations; (3) specific paediatric safety data and supportive efficacy data; and (4) regulatory approval for use in paediatric age group(s) by the EMA. For diagnostic interventions, however, the group assumed potential differences in children, and therefore, adult data were used merely as supportive and not as major evidence for useful performance in children. Of note, the group also had the option to provide no grading in cases where no evidence-based recommendations could be given due to the lack of data.

Intended use of the guidelines

These guidelines are intended to facilitate prevention, diagnosis and treatment of IFDs in paediatric patients with cancer and/or undergoing allogeneic HSCT. They are not necessarily exhaustive as they address only the most frequent and relevant clinical situations. Contra-indications, drug-drug interactions and specific warnings for each compound have to be considered. As recommended previously,¹³ these guidelines should be integrated into algorithms that are tailored to the specific patient population and the fungal epidemiology of each institution, and they should be implemented on the basis of a risk stratification strategy. A framework for a diagnostic and therapeutic algorithm that is consistent with the guidelines is provided in TABLE 2 (*appendix*).

OVERVIEW OF RISK FACTORS, EPIDEMIOLOGY AND ANTIFUNGAL AGENTS IN PAEDIATRIC CANCER/HSCT PATIENTS

Risk factors for invasive fungal diseases

The principal risk factors for development of IFDs in paediatric cancer/HSCT patients are similar to those in adults and include prolonged and profound granulocytopenia (absolute neutrophil count (ANC) of $\leq 500/\mu\text{L}$ for ≥ 10 days), the use of glucocorticosteroids in pharmacological doses (≥ 0.3 mg/kg/day prednisone equivalent), mucosal tissue damage, and, limited to invasive candidiasis, the presence of central venous catheters.^{18,19}

Risk constellations identified by contemporary multivariable analyses in paediatric cancer/HSCT patients include the diagnoses of acute myeloblastic leukaemia (AML), high risk acute lymphatic leukaemia (ALL), recurrent acute leukaemia, intensive care unit (ICU) admission, and, post allogeneic HSCT, the presence of graft-vs.-host disease (GVHD) (*references in appendix*)

Epidemiology of invasive fungal diseases

Evaluation of the natural incidence of IFDs in pediatric cancer/HSCT patients is greatly limited by the prophylactic and/or empiric use of systemic antifungal agents in the majority of contemporary series, and by differences in the use of diagnostic procedures, IFD definitions, population denominators, and fungal pathogens included.^{18,19} Considering cohort studies published during the past decade, incidence rates of IFDs of close to and $> 10\%$ are consistently observed among patients with AML, recurrent acute leukaemia, and following allogeneic HSCT; incidence rates of IFDs in patients with ALL are more variable, depending on the protocol and the cumulative presence of risk factors. Incidence rates are considerably lower ($< 5\%$) among patients with non-Hodgkin's lymphoma and following autologous HSCT, and sporadic in patients with paediatric solid tumors,

brain tumors, and Hodgkin's lymphoma (TABLE 3 (appendix)). Overall case fatality rates of IFDs in the series analysed were between 20 and 70% with poorest outcomes in patients with disseminated disease, central nervous system involvement, or persistent granulocytopenia (references in appendix).

Candida- and *Aspergillus* spp. account for the majority of proven and probable IFDs with variable relative distribution in different series, institutions, and countries.^{18,19} The spectrum of invasive candidiasis closely resembles that seen in adults with a predominance of catheter-associated candidaemia. In a recent 10-years pediatric cohort study of candidemia at European university hospital, one third of patients had solid tumors, not in itself considered to be a risk factor for candidemia. The presence of central vascular catheters in this pediatric population underscores the important role of central venous catheters in the pathogenesis of this syndrome and the potential for its occurrence in otherwise non high-risk populations.²⁰ While non-albicans *Candida* spp. account for the majority of infections, *C.albicans*, *C.parapsilosis* and *C.tropicalis* are the most frequent species isolated. Dissemination to secondary sites is observed in 10 to 20% of paediatric patients with candidaemia and severe sepsis and/or septic shock occurs in approximately 30%. Mortality rates range between 10 and 25% in most series and are close to 50% in patients admitted to the ICU¹⁸⁻²⁰ (references in appendix).

Similar to adults, most patients with invasive aspergillosis present with pulmonary aspergillosis; dissemination to other sites, particularly to the CNS, occurs in approximately 30% of cases. Sinusitis and primary cutaneous or gastrointestinal aspergillosis are less common or unusual, respectively.²¹ *A. fumigatus* is the most common cause of invasive aspergillosis followed by *A. flavus* and *A. terreus* although local differences may exist. Incidence rates for aspergillosis by underlying disease are highest with five to more than 10 % in patients with AML, recurrent leukaemia, and

allogeneic HSCT. The overall case fatality rate in most contemporaneous cohort studies ranges between 20 and 50 % and is around 80% in patients with allogeneic HSCT with allogeneic HSCT being predictive of poor outcome by multivariable analysis^{21,22} (references in appendix).

IFDs caused by non-*Aspergillus* moulds (i.e. *Fusarium* spp., *Scedosporium* spp., the agents of mucormycosis and others) present similar as invasive aspergillosis with the exception that some of them may cause fungaemia. Their incidence is variable and between zero and 35% of all proven/probable fungal infections. Prognosis is poor, and mortality rates generally appear to exceed those of invasive aspergillosis. While an increasing incidence of these infections has been noted in individual centers, no general trend can be observed in the paediatric population. Fungaemia and disseminated infections by rare yeasts and cryptococcosis are both sporadic in nature, and no incidence and mortality rates can be provided¹⁹ (references in appendix).

Antifungal agents

Despite substantial achievements and ongoing efforts, not all licensed antifungal agents are approved in pediatric patients, and for agents with a paediatric label, appropriate dosages may not have been studied and established for all age groups and indications.^{2,4,23} A summary of dosing ranges, principal pharmacokinetics, safety issues and the current status of regulatory approval of systemic antifungal agents used for management of IFDs in paediatric patients is provided in TABLE 4 (appendix); detailed references can be found in the appendix.

ECIL-4 RECOMMENDATIONS FOR DIAGNOSIS OF INVASIVE FUNGAL DISEASES

Early recognition and prompt antifungal treatment are key to the control of IFDs. Standard diagnostic procedures include blood cultures for yeasts and certain moulds; cultures and microscopic examination of appropriate liquid and solid diagnostic specimens; and imaging studies as mandated by clinical findings. Indications, validity, advantages and disadvantages of these diagnostic procedures are similar to adults. All appropriate efforts should be made to identify the causative pathogen and to allow for resistance testing.^{1,16}

Major advances in the early detection of IFDs have been made by the development of non-culture assays for fungal antigens or nucleic acids and by high resolution chest CT imaging. Although these diagnostic tools have been included in the EORTC/MSG definitions of IFDs,²⁴ their validity and usefulness in paediatric patients require separate assessment.¹⁷

Detection of fungal antigens

Galactomannan (GM) is a cell-wall component released by all *Aspergillus* spp which can be detected by an enzyme immunoassay (Platelia™, Bio-Rad) with high specificity, although false positive test results may occur for a variety of causes. Based on multiple studies in adults, GM positivity in serum, bronchoalveolar lavage (BAL) fluid and cerebrospinal fluid (CSF) has been accepted as mycological criteria of invasive aspergillosis in the revised EORTC/MSG definitions of IFDs.²⁴ The search of the literature revealed ten studies evaluating serum GM in children mostly in the setting of serial screening in children with haematological malignancies and after HSCT (appendix). The combined sensitivity and specificity of the five paediatric studies which included adequate information for individual patients and used EORTC/MSG criteria²⁵⁻²⁹ were 0.76 (95% CI 0.62-0.87)

and 0.86 (95%CI 0.68-0.95) respectively, which is consistent with the results from a meta-analysis for GM testing in adults (0.73, 95%CI 0.46-0.61 and 0.90, 95%CI 0.88-0.92, respectively) and two additional paediatric studies published in the interim (*references in appendix*).

Based on these data, prospective monitoring/serial screening of GM twice weekly in children at high risk for IFD should be considered for early diagnosis of invasive aspergillosis (A-II) (TABLE 5). Although the optimal cut-off value of GM in children is not well defined, the panel agreed on the threshold of an optical density index of ≥ 0.5 as positive test result which is consistent with the threshold used in adults (serum specimen) (B-III).

Based on inference from adult data,³⁰ systemic mould-active prophylaxis may decrease the diagnostic performance of the test in the serum in children (B-III). Of note, the performance of the GM assay as ad hoc testing such as in patients presenting with new pulmonary infiltrates is unclear and needs to be further evaluated. Corroborating results obtained in adult patients,³¹ limited data in children³² suggest that BAL-GM (cut-off 1) is a potentially useful adjunctive tool to conventional microbiologic and radiologic studies for diagnosis of invasive pulmonary aspergillosis (B-III).

Similarly, limited data also suggest the utility of GM testing in the CSF (cut-off ≥ 0.5) of both children and adults for involvement of the CNS (B-III) (TABLE 5).^{33,34}

Beta-D-glucan (BG) can be detected in patients with IFD due to *Aspergillus* and *Candida* spp., *Fusarium*, *Trichosporum* or *Saccharomyces*, and *Pneumocystis jirovecii*, but also in some bacterial infections. The Fungitell™ assay (Associates of Cape Cod) has been approved by the FDA and bears the European CE marking. BG is included as a mycological criterion in the revised IFD definitions of the EORTC/MSG consensus group.²⁴ In contrast to adults, in whom a meta-analysis demonstrated good diagnostic accuracy for early diagnosis of IFD,^{35,36} data on BG testing in children are

very limited.^{37,38} In addition, the optimal threshold for positivity of BG testing in children is unknown. Mean BG levels appear to be higher in immunocompetent uninfected children than in adults, with 15% of healthy children being within the adult-derived positive range for IFD.³⁹ Thus, data are too limited as to base any clinical decision on the results of BG testing in children (TABLE 5).

Further antigen detection systems, including but not limited to mannan antigen assays for diagnosis of invasive candidiasis and the so called *Aspergillus* lateral flow test device for diagnosis of invasive aspergillosis, have not been validated in pediatric patients so that no evidence-based recommendations can be made.

Detection of fungal nucleic acids

Standardised, polymerase chain reaction (PCR) based diagnostic methods in blood or serum are currently under evaluation for inclusion as diagnostic method in the MSG/EORTC consensus group criteria.⁴⁰ Use of PCR in these specimens in paediatric cancer patients has yielded variable performance data without indication for differences relative to adults¹⁶ (references in appendix). The use of PCR and other molecular methods on diagnostic aspirates or tissue biopsies has yielded promising performance in small non-paediatric patient series^{41,42} and may be very helpful in individual cases. However, due to the lack of standardisation and validation, no general recommendation can be made (TABLE 5).

Systematic pulmonary CT imaging

In adults, systematic CT-imaging of the chest allows for earlier diagnosis of invasive pulmonary aspergillosis and thereby, improved prognosis.^{43,44} Pulmonary nodules, in particular those with the halo sign, the air crescent sign or cavitation, are considered typical findings for mould-associated pneumonia in adult cancer/HSCT patients and are among the clinical criteria in the revised EORTC/MSG definitions of IFDs.²⁴ However, according to the limited data in persistently febrile granulocytopenic children with cancer and proven pulmonary IFD, imaging findings are often non-specific.^{22,45,46} Particularly in children <5 years of age, the signs considered typical of pulmonary IFD in adults are not observed in the majority of patients, whereas multiple nodules or fluffy masses and mass-like lesions are the two main types of abnormalities.¹⁷

Thus, in high-risk children with febrile granulocytopenia that persists beyond 96 hours or with focal clinical findings, imaging studies (e.g., CT-scan of the chest or adequate imaging of the symptomatic region) should be performed (B-II). Since typical signs of pulmonary IFD are often missing, even non-typical pulmonary infiltrates may be indicative of pulmonary IFD (B-II) (TABLE 5).

ECIL-4 RECOMMENDATIONS FOR PROPHYLAXIS OF INVASIVE FUNGAL DISEASES

Primary antifungal chemoprophylaxis

Primary antifungal prophylaxis may be indicated in paediatric patients who are at high risk for developing IFDs. While the term ‘high-risk’ is not properly defined, an incidence rate of IFDs of > 10% is usually considered as high-risk. However, although the patient population at high risk

is defined (TABLE 3 (appendix)), the local epidemiology is an important additional consideration for designing an appropriate institutional prophylaxis strategy.¹³ Furthermore, low or sporadic risk is not equal to no risk and a personalised assessment may be indicated for individual patients based on specific individual risk factors.

Two randomised, double-blind studies of antifungal chemoprophylaxis with inclusion of children compared micafungin and voriconazole, respectively, to fluconazole in the setting of allogeneic HSCT. With an enrolment rate of approximately 10% paediatric patients, these two studies provided important randomised safety data for micafungin and voriconazole and, in the absence of discriminative power, no signal for differences in efficacy relative to adults.^{47,48} A larger number of retrospective and prospective observational studies have been performed with different mould-active and mould non-active agents.^{18,19} However, due to differences in the design of the individual studies and the lack of randomised controls, these studies are not suitable as sole basis for scientifically sound recommendations. Considering the conceptual framework outlined in the methods section and the patient populations at high risk for IFDs, the following recommendations are made with dosages, specific comments and systematic references provided in the summary table (TABLE 6) and in the *appendix*, respectively:

In patients undergoing allogeneic HSCT, prophylaxis against IFDs is recommended during the granulocytopaenic phase until engraftment (B-II). Options include fluconazole (A-I; active only against yeasts and only to be used if the institutional incidence of invasive mould infections is low, or if there are active diagnostic and therapeutic algorithms for mould infections); itraconazole or voriconazole (B-I; therapeutic drug monitoring (TDM) recommended); micafungin (C-I); and liposomal amphotericin B (C-III). Other options may include aerosolised liposomal amphotericin B

and posaconazole plus TDM in patients ≥ 13 years of age (no grading). In the absence of GVHD, antifungal prophylaxis may be continued post engraftment until discontinuation of immunosuppression and immune recovery (no grading). In the presence of GVHD treated with augmented immunosuppression (including but not limited to use of glucocorticosteroids in therapeutic dosages (≥ 0.3 mg/kg/day prednisone equivalent) or use of anti-inflammatory antibodies), prophylaxis against mould and yeast infections is recommended (A-II). The following options exist: Posaconazole plus TDM for patients ≥ 13 years of age (B-I); voriconazole plus TDM for patients > 2 years of age (B-I); and itraconazole plus TDM (C-II). Other options may include intravenous liposomal amphotericin B and micafungin (no grading).

In high risk patients with de novo or recurrent acute leukaemia, primary antifungal prophylaxis should be considered (B-II). Options include: Itraconazole plus TDM (B-I); posaconazole plus TDM in patients ≥ 13 years of age (B-I); intravenous liposomal amphotericin B (B-II); and fluconazole (C-I; active only against yeasts). Other possible options include aerosolised liposomal amphotericin B, micafungin and voriconazole plus TDM (no grading). Special caution must be exerted with the concomitant use of itraconazole, posaconazole and voriconazole with vincristine and other anticancer agents.^{2,4,23}

Secondary antifungal chemoprophylaxis

As a term, secondary chemoprophylaxis is ill defined and may overlap with continued treatment for proven/probable IFDs arisen during a previous treatment course for leukaemia or being present prior to allogeneic HSCT. Although robust data are lacking, the available data suggest a natural IFD relapse rate of 30 to 50% in these settings.⁸ Small 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 (*appendix*). In a recent prospective multicentre study of secondary prophylaxis with voriconazole in 45 adult allogeneic HSCT patients with proven/ probable IFDs, the cumulative incidence of IFDs at 12 months post HSCT was 6.7%.⁵⁴ Data in paediatric patients are limited to 11 adolescents with acute leukaemia and possible/probable invasive aspergillosis who received liposomal amphotericin B followed by voriconazole during and post allogeneic HSCT. In the absence of chronic GVHD, two breakthrough infections occurred that were associated with recurrent leukaemia and graft failure.⁵⁵ On the basis of these mostly adult data, secondary antifungal chemoprophylaxis or continued antifungal treatment is recommended, targeted against the previous fungal pathogen, for as long as the patient is granulocytopenic or immunosuppressed [A-II]. In the absence of data, no general recommendations can be made about the minimum amount of therapy and the extent of response prior to continuing anticancer treatment or starting the conditioning regimen for allogeneic HSCT (no grading)

ECIL-4 RECOMMENDATIONS FOR EMPIRICAL AND PRE-EMPTIVE (DIAGNOSTIC DRIVEN) ANTIFUNGAL THERAPY

Whereas early clinical trials⁷ are difficult to interpret using current standards, a recent meta-analysis comparing empirical antifungal treatment to no treatment in adults with persistent febrile granulocytopenia concluded that empirical treatment significantly decreased IFDs, but did not lower mortality.⁵⁶ Although comparable data do not exist for the paediatric population, empirical antifungal therapy has been a common practice in granulocytopenic children with persistent fever despite appropriate empirical antibacterial therapy. Three prospective randomised clinical trials

compared different antifungal agents as empirical antifungal therapy in children with mostly leukaemia or allogeneic HSCT.⁵⁷⁻⁵⁹ In these comparisons, caspofungin was better tolerated than liposomal amphotericin B,⁵⁹ and liposomal amphotericin B was less nephrotoxic than amphotericin B deoxycholate.⁵⁷ Amphotericin B colloidal dispersion was less nephrotoxic relative to amphotericin B deoxycholate, but had more infusion-related toxicity.⁵⁸ In terms of efficacy, no differences were observed between caspofungin and liposomal amphotericin.⁵⁹ The efficacy of liposomal amphotericin was slightly better than that of amphotericin B deoxycholate,⁵⁷ whereas amphotericin B colloidal dispersion and amphotericin B deoxycholate had similar efficacy.⁵⁸ Equivalent efficacy of caspofungin and liposomal amphotericin is supported by a more recently published randomised paediatric trial,⁶⁰ and overall, the paediatric safety and efficacy data is in line with those of much larger randomised datasets in adults (*references in appendix*).

According to the approach used in the clinical registration trials, empirical antifungal therapy (if chosen as strategy) should be initiated in granulocytopenic children with newly diagnosed or recurrent acute leukaemia and in those undergoing allogeneic HSCT after 4 days of fever of unclear etiology that is unresponsive to broad-spectrum antibacterial agents (B-II), and continued until resolution of granulocytopenia in the absence of suspected or documented IFD (B-II). Empirical antifungal therapy may also be considered in individual persistently febrile patients with low risk conditions and profound and prolonged granulocytopenia and severe mucosal damage (no grading). The options include either caspofungin or liposomal amphotericin, which are both approved for this indication without age restriction in paediatric patients (A-I) (TABLE 7). A similar approach can be chosen in those granulocytopenic patients who develop recurrent fever after defervescence upon the initiation of broad spectrum antibacterial agents (no grading). Although there are no data for patients already receiving mould-active antifungal prophylaxis, switching

to a different class of mould-active antifungal agents seems reasonable; patients receiving antifungal prophylaxis without mould activity (i.e., fluconazole) should be given either caspofungin or liposomal amphotericin B for empiric therapy (no grading).

The intention of pre-emptive (or diagnostic driven) antifungal therapy, which uses clinical, mostly non-culture based microbiological, and radiographic parameters to determine whether or not to start antifungal therapy in granulocytopaenic patients is to reduce the exposure to potentially unnecessary antifungal treatment. The feasibility of this strategy has been demonstrated in adults⁶¹⁻⁶³ and it has been accepted as an alternative to the empiric approach in a subset of high-risk adult granulocytopaenic patients.⁶⁴ Although no study to date has evaluated this strategy in children, the panel agreed that pre-emptive therapy may also be applied as strategy in children (no grading) with the prerequisite of rapid availability of pulmonary CT-imaging and of GM-test results and ideally, the ability of performing bronchoscopies with bronchoalveolar lavage (TABLE 7).

ECIL-4 RECOMMENDATIONS FOR TARGETED TREATMENT OF INVASIVE FUNGAL DISEASES

Treatment recommendations for invasive *Candida* infections

General management principles of invasive *Candida* infections are not different to those in adults and include the prompt initiation of antifungal therapy, control of predisposing conditions, surgery as appropriate and consideration to remove indwelling intravenous catheters and/or other prosthetic devices. In all cases of candidaemia, clinical evaluation for deep sites of infection, including an ophthalmological examination, is

required. The optimal duration of therapy for uncomplicated candidaemia is 14 days after blood cultures are sterile. For tissue invasive candidiasis, the duration of treatment is determined by the site, the patient's response, and resolution of predisposing conditions.^{5,8,13}

The recommendations for initial antifungal treatment of candidemia and other forms of invasive candidiasis include (in alphabetical order): Caspofungin (B-II), fluconazole (B-II), liposomal amphotericin B (B-II), micafungin (B-II), voriconazole (B-II; limited to children ≥ 2 years), and amphotericin B lipid complex (C-II) (TABLE 8). A switch in class should be considered in patients with breakthrough infections on antifungal prophylaxis or empirical therapy (no grading). Of note, the absence of an A-I recommendation despite randomized phase III clinical trials conducted in adults, appropriate pharmacokinetic, safety and efficacy data and regulatory approval in pediatric patients is founded on the limited data for granulocytopenic patients and the very limited data base for tissue invasive disease.

Although there is no definite clinical evidence, fungicidal agents (i.e., amphotericin B or echinocandins) may be preferred over fungistatic agents (i.e., triazoles), particularly in granulocytopenic patients and in patients with cardiovascular instability¹³ (no grading). No fundamentally relevant pharmacological differences exist among the echinocandins;^{2,23} since the paediatric development of anidulafungin has not been completed, this compound is not included in the recommendations. Relative to other *Candida* spp., the echinocandins have higher MICs against *C.parapsilosis* group;⁶⁵ however, no diminished efficacy against these species has been noted in randomised clinical trials (references in appendix), and no recommendations against their use against members of the *C.parapsilosis* group can be made (no grading). It is recognised that the use of amphotericin B deoxycholate may be appropriate despite its unfavorable safety profile, if other amphotericin B formulations are not available (no

grading). Treatment with fluconazole is not recommended for infections by *C. krusei* and *C. glabrata*, since *C. krusei* is inherently resistant, and *C. glabrata* variably susceptible to this agent⁶⁶ (no grading). Because of the high pharmacokinetic variability of voriconazole, therapeutic drug monitoring is recommended when this compound is being used.^{51,52}

Combination antifungal chemotherapy (e.g., amphotericin B plus flucytosine and other combinations) may be considered in special situations (e.g. severe life threatening infection, compromised drug penetration in CNS infection, complicated bone and joint-, urinary tract- and intra-abdominal infections)¹³ (no grading).

Treatment recommendations for invasive *Aspergillus* infections

General management principles of invasive *Aspergillus* infections are consistent with those in adults and include the prompt initiation of antifungal therapy, control of predisposing conditions (e.g., colony-stimulating factors for granulocytopenic patients, reduction of immunosuppressive therapy, particularly discontinuation or taper of corticosteroids), and surgical interventions on a case by case basis using a multidisciplinary approach.^{5,8} Granulocyte transfusions may be considered in individual patients with profound and persistent granulocytopenia. A thorough evaluation for further sites of infection, in particular the CNS is required. The optimal duration of therapy is not defined but determined by the resolution of all signs and symptoms and reversal of the underlying deficit in host defenses.^{5,8}

The recommendations for initial antifungal treatment of invasive aspergillosis (TABLE 8) include intravenous voriconazole coupled with TDM (A-I; limited to children ≥ 2 years), liposomal amphotericin B (B-I), and amphotericin B lipid complex (B-II). The A-I recommendation for voriconazole is ultimately based on the pivotal phase III trial in adults; the somewhat weaker B-I recommendation for liposomal amphotericin B is due to the fact that the pivotal phase III trial was a comparison between two different dosage strategies and not a head-to-head comparison to the reference agent voriconazole (*references in appendix*). Review of the available data of the recently completed randomised, comparative clinical trial⁶⁷ indicates no general superiority of combination therapy of voriconazole plus anidulafungin for primary treatment of invasive aspergillosis (C-III). Of note, although specific data are lacking, a switch in class should be considered in patients with breakthrough infections on antifungal prophylaxis or empirical therapy (no grading).

Second-line treatment refers to antifungal treatment in patients failing to respond⁷² or being intolerant to the initial treatment. Although not formally investigated, a switch in class may be considered when antifungal chemotherapy is changed for refractory disease (no grading). Options for second line treatment include (TABLE 8) liposomal amphotericin B in amphotericin B-naïve patients (B-I) and voriconazole plus TDM in voriconazole-naïve patients (A-I; limited to children ≥ 2 years), respectively. Further options approved in paediatric patients include caspofungin (A-II) and amphotericin B lipid complex (B-II). Few and uncontrolled data exist on combination therapy with either voriconazole or an amphotericin B product plus an echinocandin for salvage treatment and no strong recommendation can therefore be made (C-II).

Treatment recommendations for infections by Mucorales and rare filamentous fungi

General principles in the management of invasive infections by rare filamentous fungi are similar to those outlined for invasive aspergillosis.⁹ In patients with mucormycosis, no recommendation for or against the routine use of hyperbaric oxygen can be made (no grading); on the basis of a randomised pilot trial, the adjunctive use of deferasirox is not recommended⁹ (A-I).

Independent of age, outcome of mucormycosis critically depends on the prompt initiation of treatment with amphotericin B and surgery^{74,75} (*appendix*). Recommendations for first line treatment of mucormycosis are similar to those in adults and include (TABLE 8) liposomal amphotericin B (B-II) and amphotericin B lipid complex (B-II). For pharmacokinetic/ pharmacodynamic reasons, liposomal amphotericin B is the preferred drug for CNS infections, and, due to its lower renal toxicity, for patients with renal failure. Options for second line therapy include posaconazole (B-II; limited to adolescents ≥ 13 years) and the combination of lipid amphotericin B with caspofungin (B-II)⁹ (*references in appendix*).

Recommendations for treatment of invasive fusariosis and scedosporiosis are based on preclinical *in vitro* and *in vivo* data and a few case series, and generally do not differ between paediatric and adult patients. With these premises, voriconazole coupled with TDM is the preferred agent for treatment of scedosporiosis and fusariosis (B-II; limited to children ≥ 2 years)⁷⁶⁻⁷⁸, while amphotericin B lipid complex, liposomal amphotericin B and posaconazole (limited to adolescents ≥ 13 years; plus TDM)^{79,80} may represent alternative choices (no grading due to paucity of data) (TABLE 8). For infections by other rare filamentous fungi, treatment must be individualised and be based on available preclinical data, case reports and small case series.

Treatment recommendations for infections by rare yeasts

Rare yeasts as well as cryptococcosis are sporadic causes of IFDs and are not specifically addressed in these guidelines. While treatment recommendations for cryptococcosis are not necessarily different from those made for other populations,⁸¹ treatment of infections by rare yeasts must be based on available preclinical data, case reports and small case series.⁸²

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Author's contributions

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REFERENCES

1. Dornbusch HJ, Manzoni P, Roilides E, Walsh TJ, Groll AH. Invasive fungal infections in children. *Pediatr Infect Dis J* 2009; **28**: 734–37.
2. Groll AH, Tragiannidis A. Update on antifungal agents for paediatric patients. *Clin Microbiol Infect* 2010; **16**: 1343–53.
3. Sung L, Phillips R, Lehrnbecher T. Time for paediatric febrile neutropenia guidelines - children are not little adults. *Eur J Cancer* 2011; **47**: 811–3.
4. Lestner JM, Smith PB, Cohen-Wolkowicz M, Benjamin DK Jr, Hope WW. Antifungal Agents and Therapy for Infants and Children with Invasive Fungal Infections: A Pharmacological Perspective. *Br J Clin Pharmacol* 2013; **75**: 1381–95.
5. Herbrecht R, Flückiger U, Gachot B, Ribaud P, Tiebaut A, Cordonnier C. Treatment of invasive candida and invasive aspergillus infections in adult haematological patients. *Eur J Cancer* 2007; **5 Suppl 2**: 49–59.
6. Maertens J, Frere P, Lass-Flörl C, Heinz W, Cornely OA. Primary antifungal prophylaxis in leukaemia patients. *Eur J Cancer* 2007; **5 Suppl 2**: 43–48.
7. Marchetti O, Cordonnier C, Calandra T. Empirical antifungal therapy in neutropenic cancer patients with persistent fever. *Eur J Cancer* 2007; **5 Suppl 2**: 32–42.
8. Maertens J, Marchetti O, Herbrecht R et al.; Third European Conference on Infections in Leukemia. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3--2009 update. *Bone Marrow Transplant* 2011; **46**: 709–18.
9. Skiada A, Lanternier F, Groll AH et al. Diagnosis and treatment of mucormycosis in patients with haematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia (ECIL 3). *Haematologica* 2013; **98**: 492–504.
10. Cordonnier C, Calandra T: The first European conference on infections in leukaemia: why and how? *Eur J Cancer* 2007; **5 Suppl 2**: 2–4.
11. Meunier F, Lukan C. The First European Conference on Infections in Leukaemia - ECIL1: a current perspective. *Eur J Cancer* 2008; **44**: 2112–17.
12. Kish MA. Guide to development of practice guidelines. *Clin Infect Dis* 2001; **32**: 851–54.
13. Hope WW, Castagnola E, Groll AH et al. ESCMID Fungal Infection Study Group. ESCMID guideline for the diagnosis and management of Candida diseases 2012: prevention and management of invasive infections in neonates and children caused by Candida spp. *Clin Microbiol Infect* 2012; **18 Suppl 7**: 38-52.

14. European Medicines Agency. ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population. Note for guidance on clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf (date last accessed: 15 August 2013)
15. European Community. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of medicinal products for paediatric use, amended by Regulation (EC) No 1902/2006. http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1902/reg_2006_1902_en.pdf (date last accessed; 15 August 2013).
16. Dornbusch HJ, Groll A, Walsh TJ. Diagnosis of invasive fungal infections in immunocompromised children. *Clin Microbiol Infect* 2010; **16**: 1328–34.
17. Lehrnbecher T, Phillips R, Alexander S et al. International Pediatric Fever and Neutropenia Guideline Panel. Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. *J Clin Oncol* 2012; **30**: 4427–38.
18. Dvorak CC, Fisher BT, Sung L et al. Antifungal prophylaxis in pediatric hematology/ oncology: new choices, new data. *Pediatr Blood Cancer* 2012; **59**: 21–6.
19. Tragiannidis A, Dokos C, Lehrnbecher T, Groll AH. Antifungal chemoprophylaxis in children and adolescents with haematological malignancies and following allogeneic haematopoietic stem cell transplantation: review of the literature and options for clinical practice. *Drugs* 2012; **72**: 685–704.
20. Tragiannidis A, Fegeler W, Rellensmann G et al. Candidaemia in a European Paediatric University Hospital: a 10-year observational study. *Clin Microbiol Infect* 2012; **18**: E27–30 doi: 10.1111/j.1469-0691.2011.03720.x.
21. Tragiannidis A, Roilides E, Walsh TJ, Groll AH. Invasive aspergillosis in children with acquired immunodeficiencies. *Clin Infect Dis* 2012; **54**: 258–67.
22. Burgos A, Zaoutis TE, Dvorak CC et al. Pediatric invasive aspergillosis: a multicenter retrospective analysis. *Pediatrics* 2008; **121**: e1286–1294. doi: 10.1542/peds.2007–2117.
23. Chiou CC, Walsh TJ, Groll AH. Clinical pharmacology of antifungal agents in pediatric patients. *Expert Opin Pharmacother* 2007; **8**: 2465–89
24. De Pauw B, Walsh TJ, Donnelly JP et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008; **46**: 1813–21.

25. Rohrlich P, Sarfati J, Mariani P et al. Prospective sandwich enzyme-linked immunosorbent assay for serum galactomannan: early predictive value and clinical use in invasive aspergillosis. *Pediatr Infect Dis J* 1996; **15**: 232–7
26. El-Mahallawy HA, Shaker HH, Ali Helmy H, Mostafa T, Razak Abo-Sedah A. Evaluation of pan-fungal PCR assay and Aspergillus antigen detection in the diagnosis of invasive fungal infections in high risk paediatric cancer patients. *Med Mycol* 2006; **44**: 733–9.
27. Hovi L, Saxen H, Saarinen-Pihkala UM, Vettenranta K, Meri T, Richardson M. Prevention and monitoring of invasive fungal infections in pediatric patients with cancer and hematologic disorders. *Pediatr Blood Cancer* 2007; **48**: 28–34.
28. Steinbach WJ, Addison RM, McLaughlin L et al. Prospective Aspergillus galactomannan antigen testing in pediatric hematopoietic stem cell transplant recipients. *Pediatr Infect Dis J* 2007; **26**: 558–64.
29. Challier S, Boyer S, Abachin E, Berche P. Development of a serum-based Taqman real-time PCR assay for diagnosis of invasive aspergillosis. *J Clin Microbiol* 2004; **42**: 844–6.
30. Marr KA, Laverdiere M, Gugel A, Leisenring W. Antifungal therapy decreases sensitivity of the Aspergillus galactomannan enzyme immunoassay. *Clin Infect Dis* 2005; **40**: 1762–9.
31. Maertens J, Maertens V, Theunissen K et al. Bronchoalveolar lavage fluid galactomannan for the diagnosis of invasive pulmonary aspergillosis in patients with hematologic diseases. *Clin Infect Dis* 2009; **49**: 1688–93.
32. Desai R, Ross LA, Hoffman JA. The role of bronchoalveolar lavage galactomannan in the diagnosis of pediatric invasive aspergillosis. *Pediatr Infect Dis J* 2009; **28**: 283–6.
33. Viscoli C, Machetti M, Gazzola P et al. Aspergillus galactomannan antigen in the cerebrospinal fluid of bone marrow transplant recipients with probable cerebral aspergillosis. *J Clin Microbiol* 2002; **40**: 1496–99.
34. Roilides E, Pavlidou E, Papadopoulos F et al. Cerebral aspergillosis in an infant with corticosteroid-resistant nephrotic syndrome. *Pediatr Nephrol* 2003; **18**: 450–3.
35. Karageorgopoulos DE, Vouloumanou EK, Ntziora F, Michalopoulos A, Rafailidis PI, Falagas ME. Beta-D-glucan assay for the diagnosis of invasive fungal infections: a meta-analysis. *Clin Infect Dis* 2011; **52**: 750–70.
36. Lamoth F, Cruciani M, Mengoli C et al. Third European Conference on Infections in Leukemia (ECIL-3). β -Glucan antigenemia assay for the diagnosis of invasive fungal infections in patients with hematological malignancies: a systematic review and meta-analysis of cohort studies from the Third European Conference on Infections in Leukemia (ECIL-3). *Clin Infect Dis* 2012; **54**: 633–43.
37. Zhao L, Tang JY, Wang Y et al. Value of plasma β -Glucan in early diagnosis of invasive fungal infection in children. *Chin J Contemp Pediatr* 2009; **11**: 905–8.

38. Mularoni A, Furfaro E, Faraci M et al. High Levels of beta-D-glucan in immunocompromised children with proven invasive fungal disease. *Clin Vaccine Immunol* 2010; **17**: 882–3.
39. Smith PB, Benjamin DK, Jr., Alexander BD, Johnson MD, Finkelman MA, Steinbach WJ. Quantification of 1,3-beta-D-glucan levels in children: preliminary data for diagnostic use of the beta-glucan assay in a pediatric setting. *Clin Vaccine Immunol* 2007; **14**: 924–25.
40. Loeffler J, Barnes R, Donnelly JP; European Aspergillus PCR Initiative. Standardization of Aspergillus PCR diagnosis. *Bone Marrow Transplant* 2012; **47**: 299–300.
41. Lass-Flörl C, Resch G, Nachbaur D et al. The value of computed tomography-guided percutaneous lung biopsy for diagnosis of invasive fungal infection in immunocompromised patients. *Clin Infect Dis* 2007; **45**: e101–4.
42. Rickerts V, Mousset S, Lambrecht E et al. Comparison of histopathological analysis, culture, and polymerase chain reaction assays to detect invasive mold infections from biopsy specimens. *Clin Infect Dis* 2007; **44**: 1 078–83.
43. Caillot D, Casasnovas O, Bernard A et al. Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. *J Clin Oncol* 1997; **15**: 139–47.
44. Heussel CP, Kauczor HU, Heussel GE et al. Pneumonia in febrile neutropenic patients and in bone marrow and blood stem-cell transplant recipients: use of high-resolution computed tomography. *J Clin Oncol* 1999; **17**: 796–805.
45. Taccone A, Occhi M, Garaventa A, Manfredini L, Viscoli C. CT of invasive pulmonary aspergillosis in children with cancer. *Pediatr Radiol* 1993; **23**: 177–80.
46. Archibald S, Park J, Geyer JR, Hawkins DS. Computed tomography in the evaluation of febrile neutropenic pediatric oncology patients. *Pediatr Infect Dis J* 2001; **20**: 5–10.
47. van Burik JA, Ratanatharathorn V, Stepan DE et al. National Institute of Allergy and Infectious Diseases Mycoses Study Group. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. *Clin Infect Dis* 2004; **39**: 1407–16
48. Wingard JR, Carter SL, Walsh TJ et al. Blood and Marrow Transplant Clinical Trials Network. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. *Blood* 2010; **116**: 5111–8.
49. Glasmacher A, Hahn C, Molitor E, Marklein G, Sauerbruch T, Schmidt-Wolf IG. Itraconazole trough concentrations in antifungal prophylaxis with six different dosing regimens using hydroxypropyl-beta-cyclodextrin oral solution or coated-pellet capsules. *Mycoses* 1999; **42**: 591–600
50. Marks DI, Pagliuca A, Kibbler CC et al. IMPROVIT Study Group. Voriconazole versus itraconazole for antifungal prophylaxis following allogeneic haematopoietic stem-cell transplantation. *Br J Haematol* 2011; **155**: 318–27.

51. Troke PF, Hockey HP, Hope WW. Observational study of the clinical efficacy of voriconazole and its relationship to plasma concentrations in patients. *Antimicrob Agents Chemother* 2011; **55**: 4782–88.
52. Park WB, Kim NH, Kim KH et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. *Clin Infect Dis* 2012; **55**: 1080–7.
53. Jang SH, Colangelo PM, Gobburu JV. Exposure-response of posaconazole used for prophylaxis against invasive fungal infections: evaluating the need to adjust doses based on drug concentrations in plasma. *Clin Pharmacol Ther* 2010; **88**: 115-9. doi: 10.1038/ clpt.2010.64.
54. Cordonnier C, Rovira M, Maertens J et al. Voriconazole for Secondary Prophylaxis of Invasive Fungal Infections in Patients With Allogeneic Stem Cell Transplants (VOSIFI) study group; Infectious Diseases Working Party, European Group for Blood and Marrow Transplantation. Voriconazole for secondary prophylaxis of invasive fungal infections in allogeneic stem cell transplant recipients: results of the VOSIFI study. *Haematologica* 2010; **95**: 1762–8.
55. Allinson K, Kolve H, Gumbinger HG, Vormoor HJ, Ehlert K, Groll AH. Secondary antifungal prophylaxis in paediatric allogeneic haematopoietic stem cell recipients. *J Antimicrob Chemother* 2008; **61**: 734–42.
56. Goldberg E, Gafter-Gvili A, Robenshtok E, Leibovici L, Paul M. Empirical antifungal therapy for patients with neutropenia and persistent fever: Systematic review and meta-analysis. *Eur J Cancer* 2008; **44**: 2192–2203.
57. Prentice HG, Hann IM, Herbrecht R, et al. A randomized comparison of liposomal versus conventional amphotericin B for the treatment of pyrexia of unknown origin in neutropenic patients. *Br J Haematol* 1997; **98**: 711–718.
58. Sandler ES, Mustafa MM, Tkaczewski I et al. Use of amphotericin B colloidal dispersion in children. *J Pediatr Hematol Oncol* 2000; **22**: 242–246.
59. Maertens JA, Madero L, Reilly AF et al. Caspofungin Pediatric Study Group. A randomized, double-blind, multicenter study of caspofungin versus liposomal amphotericin B for empiric antifungal therapy in pediatric patients with persistent fever and neutropenia. *Pediatr Infect Dis J* 2010; **29**: 415–20.
60. Caselli D, Cesaro S, Ziino O et al. A prospective, randomized study of empirical antifungal therapy for the treatment of chemotherapy-induced febrile neutropenia in children. *Br J Haematol* 2012; **158**: 249–55
61. Cordonnier C, Pautas C, Maury S et al. Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: a randomized, controlled trial. *Clin Infect Dis* 2009; **48**: 1042–51.
62. Girmenia C, Micozzi A, Gentile G et al. Clinical driven diagnostic antifungal approach in neutropenic patients: a prospective feasibility study. *J Clin Oncol* 2010; **28**: 667–74.

63. Tan BH, Low JG, Chlebicka NL et al. Galactomannan-guided preemptive vs. empirical antifungals in the persistently febrile neutropenic patient: a prospective randomized study. *Int J Infect Dis* 2011; **15**: e350–6 doi: 10.1016/j.ijid.2011.01.011.
64. Freifeld AG, Bow EJ, Sepkowitz KA et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Infect Dis* 2011; **52**: 427–31.
65. Pfaller MA, Diekema DJ, Andes D et al. CLSI Subcommittee for Antifungal Testing. Clinical breakpoints for the echinocandins and *Candida* revisited: integration of molecular, clinical, and microbiological data to arrive at species-specific interpretive criteria. *Drug Resist Updat*. 2011; **14**: 164–76. doi: 10.1016/j.drug.2011.01.004.
66. Pfaller MA, Diekema DJ, Gibbs DL et al. Global Antifungal Surveillance Group. Results from the ARTEMIS DISK Global Antifungal Surveillance Study, 1997 to 2007: a 10.5-year analysis of susceptibilities of *Candida* Species to fluconazole and voriconazole as determined by CLSI standardized disk diffusion. *J Clin Microbiol* 2010; **48**: 1366–77. doi: 10.1128/JCM.02117-09.
67. Marr KAS, Rottinghaus H, Jagannatha S et al. Mycoses Study Group. A randomised, double-blind study of combination antifungal therapy with voriconazole and anidulafungin versus voriconazole monotherapy for primary treatment of invasive aspergillosis. 22. European Congress of Clinical Microbiology and Infectious Diseases (ECCMID). European Society for Clinical Microbiology and Infectious Diseases, London, UK: Abstract LB2812 (2012).
68. Caillot D, Thiébaud A, Herbrecht R et al. Liposomal amphotericin B in combination with caspofungin for invasive aspergillosis in patients with hematologic malignancies: a randomized pilot study (Combistrat trial). *Cancer* 2007; **110**: 2740–6
69. Marr KA, Boeckh M, Carter RA, Kim HW, Corey L. Combination antifungal therapy for invasive aspergillosis. *Clin Infect Dis* 2004; **39**: 797-02.
70. Maertens J, Glasmacher A, Herbrecht R et al. Multicenter, noncomparative study of caspofungin in combination with other antifungals as salvage therapy in adults with invasive aspergillosis. *Cancer* 2006; 107: 2888–97.
71. Cesaro S, Giacchino M, Locatelli F et al. Safety and efficacy of a caspofungin-based combination therapy for treatment of proven or probable aspergillosis in pediatric hematological patients. *BMC Infect Dis* 2007; **7**: 28
72. Segal BH, Herbrecht R, Stevens DA et al. Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer consensus criteria. *Clin Infect Dis* 2008; **47**: 674–83.
73. Walsh TJ, Raad I, Patterson TF et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. *Clin Infect Dis* 2007; **44**: 2-12.
74. Zaoutis TE, Roilides E, Chiou CC et al. Zygomycosis in children: a systematic review and analysis of reported cases. *Pediatr Infect Dis J* 2007; **26**: 723–7.

75. Dehority W, Willert J, Pong A. Zygomycetes infections in pediatric hematology oncology patients: a case series and review of the literature. *J Pediatr Hematol Oncol* 2009; **31**: 911–9.
76. Perfect JR, Marr KA, Walsh TJ et al. Voriconazole treatment for less-common, emerging, or refractory fungal infections. *Clin Infect Dis* 2003; **36**: 1122–31
77. Troke P, Aguirrebengoa K, Arteaga C et al. Treatment of scedosporiosis with voriconazole: clinical experience with 107 patients. *Antimicrob Agents Chemother* 2008; **52**: 1743–50.
78. Lortholary O, Obenga G, Biswas P et al. French Mycoses Study Group. International retrospective analysis of 73 cases of invasive fusariosis treated with voriconazole. *Antimicrob Agents Chemother* 2010; **54**: 4446–50.
79. Raad II, Hachem RY, Herbrecht R et al. Posaconazole as salvage treatment for invasive fusariosis in patients with underlying hematologic malignancy and other conditions. *Clin Infect Dis* 2006; **42**: 1398–1403.
80. Raad I, Chapman S, Bradsher R, Morrison V, Goldman M, Graybill J. Posaconazole salvage therapy for invasive fungal infections. In Abstracts of the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology, Washington DC: Abstr. M-669 (2004)
81. Perfect JR, Dismukes WE, Dromer F et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2010; **50**: 291–322.
82. Arendrup MC, Boekhout T, Akova M et al. ESCMID/ECMM Joint Clinical Guideline for the Diagnosis and Management of Rare Yeast Infections. *Clin Microbiol Infect* 2013 Sep 18 doi: 10.1111/1469-0691.12360

Table 1: Infectious Diseases Society of America-United States Public Health Service grading system for ranking recommendations *

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
Quality of evidence	
I	Evidence from ≥ 1 properly randomized, controlled trial
II	Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

* Kish et al. 2001¹²

Table 5: Recommendations for use of non-culture diagnostic tools for diagnosis of invasive fungal diseases in paediatric patients with cancer or haematopoietic stem cell transplantation

Recommendation and grading	Comments	References
<p>Prospective monitoring of galactomannan in serum twice weekly for early diagnosis of invasive aspergillosis in children at high risk for IFD (A-II)</p> <p>Threshold for a positive test result in serum: optical density index of ≥ 0.5 (B-III)</p>	<p>Combined sensitivity and specificity of five paediatric studies with adequate data were 0.76 (95% CI 0.62-0.87) and 0.86 (95% CI 0.68-0.95)</p> <p>The performance of the galactomannan assay in serum under non-surveillance conditions (such as in patients presenting with new pulmonary infiltrates) is unclear and needs future evaluation.</p> <p>Causes of false-positive galactomannan test results include cross-reaction from an existing non-Aspergillus fungal infection (e.g., Histoplasma, Penicillium marneffeii), the intravenous administration of fungal-derived products such as betalactam antibiotics, various blood products or poor postextraction management of samples in the laboratory.</p>	16; 25-29
<p>Administration of systemic mould-active antifungal prophylaxis may decrease the performance of the galactomannan antigen assay in serum (B-III)</p>	<p>Posaconazole or voriconazole prophylaxis may prevent the circulation of galactomannan antigen</p>	30
<p>Galactomannan in bronchoalveolar lavage (BAL) with an optical density index threshold for a positive test of 1 is an adjunctive tool for diagnosis of invasive</p>	<p>Supported by adult data and retrospective data from 59 immunocompromised children</p>	31,32

pulmonary aspergillosis (B-III).		
Galactomannan in cerebrospinal fluid (CSF) with an optical density index threshold for a positive test of ≥ 0.5 is an adjunctive tool for diagnosis of invasive aspergillosis of the central nervous system (B-III).	Supported by adult data and few patients with probable central nervous system aspergillosis	33,34
Beta-D-Glucan (BG) testing in serum (no grading)	While included as a mycological criterion in the EORTC/MSG definitions of IFDs, data in children are very limited and the optimal threshold for positivity of BG testing in children is unknown	35-39
Detection of fungal nucleic acids in body fluids and tissues (no grading)	Standardised, polymerase chain reaction (PCR) based methods in blood/serum under evaluation by the MSG/EORTC consensus group. At present, no general recommendation can be made due to the lack of standardisation and clinical validation.	16; 40-42
Imaging studies (e.g., CT-scan of the lung or adequate imaging of the symptomatic region) should be performed in high-risk patients with febrile granulocytopenia that persists beyond 96 hours or with focal clinical findings (B-II). Typical and non-typical pulmonary infiltrates may be indicative of pulmonary IFD and should prompt further diagnostic work-up	Signs considered typical of IFDs in adults (e.g., halo sign, air crescent sign, and cavities) are not seen in the majority of children with pulmonary mould infections. Radiographic findings in immunocompromised children with invasive pulmonary fungal disease are often unspecific, in particular in children < 5-year of age	22; 43-46

and initiation of mould-active antifungal treatment (B-II).		
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Table 6: Recommendations for primary chemoprophylaxis of invasive fungal diseases in paediatric patients with cancer or haematopoietic stem cell transplantation

Recommendation and grading	Comments	Key References
Allogeneic HSCT		
<p>Antifungal prophylaxis is recommended during the granulocytopaenic phase until engraftment (B-II).</p> <p>In the absence of GVHD, prophylaxis may be continued post engraftment until discontinuation of immunosuppressive therapy and immune recovery (no grading).</p> <p><i>Options for prophylaxis include:</i></p>	<p>Inference from randomised studies in adults with non-absorbable antifungal agents as comparator</p> <p>Attention to drug-drug interaction is needed, particularly to those with immunosuppressive agents</p>	6,8; and appendix, section 4
Fluconazole 8-12 mg/kg/d IV/PO in one single dose (max. 400mg/d) (A-I)	Fluconazole is active only against yeasts and should only be used if the institutional incidence of invasive mould infections is low, or if there are active diagnostic and therapeutic algorithms for mould infections	<p>Clinical trials in adults: 6,8; and appendix, section 4</p> <p>PK, safety and efficacy in paediatric patients: Appendix, section 2</p>
Itraconazole 5 mg/kg/d PO (≥ 2 years of age) in two divided doses + TDM (B-I)	Spectrum includes both yeasts and moulds; not approved in subjects <18 years; TDM is suggested; dosing target: trough concentration of ≥ 0.5 mg/L	<p>Clinical trials in adults: 6,8; and appendix, section 4</p> <p>TDM dosing target: 49</p> <p>PK, safety and efficacy in</p>

		paediatric patients: Appendix, section 2
Voriconazole 2- <12 yrs /12-14 yrs and <50kg: 8 mg/kg BID (day 1: 9) IV and 9 mg/kg BID PO; / ≥15 yrs and 12-14 yrs and ≥50kg: 4 mg/kg BID (day 1: 6) IV; 200 mg BID PO +TDM (all) (B-I)	Spectrum includes both yeasts and moulds; compound not approved in subjects <2 years. Two randomized trials in adults exist; however, voriconazole is currently not approved for prophylaxis; TDM is suggested; dosing target: trough concentration of between 1.0 and 5.0 mg/L	Clinical trials in adults: 48,50 TDM dosing target: 51,52 PK, safety and efficacy in paediatric patients: Appendix, section 2
Micafungin 1 mg/kg/d (≥50kg: 50 mg) IV in one single dose (C-I)	Spectrum includes <i>Candida</i> and <i>Aspergillus</i> ; approved for prophylaxis of invasive <i>Candida</i> infections in granulocytopenic patients.	Clinical trial in adults: 47 PK, safety and efficacy in paediatric patients: 47 and appendix, section 2
Liposomal amphotericin B 1 mg/kg IV every other day or 2.5 mg/kg IV twice weekly (C-III)	Spectrum includes both yeasts and moulds; not approved for prophylaxis. Alternative option for patients who do not tolerate triazoles or have contraindications to triazoles	Clinical trials in adults: 6,8; and appendix, section 4 PK, safety and efficacy in paediatric patients: Appendix, section 2
Aerosolised liposomal amphotericin B 12,5 mg on 2 consecutive days per week (no grading)	Targeted against pulmonary mould infections; non-approved route of administration, appropriate doses and dosage schedule unknown in subjects < 18 years	Clinical trials in adults: 8; and appendix, section 4
Posaconazole plus TDM 600 mg/d PO in three divided doses +TDM in subjects ≥ 13 years (no grading)	Spectrum includes both yeasts and moulds; limited PK data in subjects ≥ 13 years, but not approved in the EU in subjects < 18 years and in this specific indication; TDM is suggested; dosing target: trough concentration of ≥ 0.5 mg/L	Clinical trials in adults: 6,8; and appendix, section 4 Suggested TDM dosing target: 53 PK, safety and efficacy in paediatric patients:

		Appendix, section 2
<p>In the presence of GVHD treated with augmented immunosuppression, prophylaxis against mould and yeast infections is recommended (A-II)</p> <p><i>Option for prophylaxis include:</i></p>	<p>Augmented immunosuppression refers to the use of additional immunosuppressive interventions with the aim to control overt GVHD and includes but is not limited to the use of glucocorticosteroids in therapeutic dosages (≥ 0.3 mg/kg/day prednisone equivalent) or use of anti-inflammatory antibodies</p>	
<p>Posaconazole plus TDM 600 mg/d PO in three divided doses +TDM in subjects ≥ 13 years (B-I)</p>	<p>Spectrum includes both yeasts and moulds; approved indication. Limited PK data in subjects ≥ 13 years, but not approved in the EU in subjects < 18 years; TDM is suggested; dosing target: trough concentration of ≥ 0.5 mg/L</p>	<p>Clinical trials in adults: 6,8; and appendix, section 4</p> <p>Suggested TDM dosing target: 53</p> <p>PK, safety and efficacy in paediatric patients: Appendix, section 2</p>
<p>Voriconazole 2- < 12 yrs /12-14 yrs and < 50kg: 8 mg/kg BID (day 1: 9) IV and 9 mg/kg BID PO; / ≥ 15 yrs and 12-14 yrs and ≥ 50kg: 4 mg/kg BID (day 1: 6) IV; 200 mg BID PO +TDM (all) (B-I)</p>	<p>Spectrum includes both yeasts and moulds; not approved in subjects < 2 years and not approved for prophylaxis; TDM is suggested; dosing target: trough concentration of between 1.0 and 5.0 mg/L</p>	<p>Clinical trials in adults: 48,50</p> <p>TDM dosing target: 51,52</p> <p>PK, safety and efficacy in paediatric patients: Appendix, section 2</p>
<p>Itraconazole 5 mg/kg/d PO (≥ 2 years of age) in two divided doses + TDM (C-II)</p>	<p>Spectrum includes both yeasts and moulds; not approved in subjects < 18 years and not in this specific indication; TDM is suggested; dosing target: trough concentration of ≥ 0.5 mg/L</p>	<p>Clinical trials in adults: 6,8; and appendix, section 4</p> <p>TDM dosing target: 49</p> <p>PK, safety and efficacy in paediatric patients:</p>

		Appendix, section 2
Liposomal amphotericin B 1 mg/kg IV every other day or 2.5 mg/kg IV twice weekly (no grading)	Spectrum includes both yeasts and moulds; not approved for prophylaxis. Alternative option for patients who do not tolerate triazoles or have contraindications to triazoles	Clinical trials in adults: 6,8; and appendix, section 4 PK, safety and efficacy in paediatric patients: Appendix, section 2
Micafungin 1 mg/kg/d (≥ 50 kg: 50 mg) IV in one single dose (no grading)	Spectrum includes <i>Candida</i> and <i>Aspergillus</i> ; approved for prophylaxis of invasive <i>Candida</i> infections in granulocytopenic patients but not in this indication	Clinical trial in adults: 47 PK, safety and efficacy in paediatric patients: 47 and appendix, section 2
<u>De novo or recurrent leukaemias</u>		
Antifungal prophylaxis should be considered in high risk patients with de novo or recurrent acute leukaemia (BII). <u>Options for prophylaxis include:</u>		
Itraconazole 5 mg/kg/d PO (≥ 2 years of age) in two divided doses + TDM (B-I)	Spectrum includes both yeasts and moulds; not approved in subjects <18 years; TDM is suggested; dosing target: trough concentration of ≥ 0.5 mg/L	Clinical trials in adults: 6,8; and appendix, section 4 TDM dosing target: 49 PK, safety and efficacy in paediatric patients: Appendix, section 2

Posaconazole plus TDM 600 mg/d PO in three divided doses +TDM in subjects \geq 13 years (B-I)	Spectrum includes both yeasts and moulds; approved indication in adults. Limited PK data in subjects \geq 13years, but not approved in the EU in subjects < 18 years; TDM is suggested; dosing target: trough concentration of \geq 0.5 mg/L	Clinical trials in adults: 6,8; and appendix, section 4 Suggested TDM dosing target: 53 PK, safety and efficacy in paediatric patients: Appendix, section 2
Liposomal amphotericin B 1 mg/kg IV every other day or 2.5 mg/kg IV twice weekly (B-II)	Spectrum includes both yeasts and moulds; not approved for prophylaxis. Option for patients who do not tolerate triazoles or have contraindications to triazoles	Clinical trials in adults: 6,8; and appendix, section 4 PK, safety and efficacy in paediatric patients: Appendix, section 2
Fluconazole 8-12 mg/kg/d IV/PO in one single dose (max. 400mg/d) (C-I)	Fluconazole is active only against yeasts and should only be used if the institutional incidence of invasive mould infections is low, or if there are active diagnostic and therapeutic algorithms for mould infections	Clinical trials in adults: 6,8; and appendix, section 4 PK, safety and efficacy in paediatric patients: Appendix, section 2
Aerosolised liposomal amphotericin B 12,5 mg on 2 consecutive days per week (no grading)	Targeted against pulmonary mould infections; non-approved route of administration, appropriate doses and dosage schedule unknown in subjects < 18 years	Clinical trials in adults: 8; and appendix, section 4
Micafungin 1 mg/kg/d (\geq 50kg: 50 mg) IV in one single dose (no grading)	Spectrum includes <i>Candida</i> and <i>Aspergillus</i> ; approved for prophylaxis of invasive <i>Candida</i> infections in persistently granulocytopenic patients	Clinical trial in adults: 47 PK, safety and efficacy in paediatric patients: 47 and appendix, section 2

<p>Voriconazole 2- <12 yrs /12-14 yrs and <50kg: 8 mg/kg BID (day 1: 9) IV and 9 mg/kg BID PO; / ≥15 yrs and 12-14 yrs and ≥50kg: 4 mg/kg BID (day 1: 6) IV; 200 mg BID PO +TDM (all) (no grading)</p>	<p>Spectrum includes both yeasts and moulds; not approved in subjects <2 years and not approved for prophylaxis; inference for efficacy from studies in the HSCT setting. TDM is suggested; dosing target: trough concentration of between 1.0 and 5.0 mg/L</p>	<p>Clinical trials in adults: 48,50 TDM dosing target: 51,52 PK, safety and efficacy in paediatric patients: Appendix, section 2</p>
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Table 7: Recommendations for empirical and pre-emptive (diagnostic driven) antifungal therapy in paediatric patients with cancer or haematopoietic stem cell transplantation

Recommendation and grading	Comments	References
<p>Empirical antifungal therapy, if chosen as strategy, should be initiated in high risk granulocytopaenic paediatric patients after 96 hours of fever of unclear aetiology that is unresponsive to broad-spectrum antibacterial agents (B-II), and be continued until resolution of neutropaenia in the absence of suspected or documented IFD (B-II).</p> <p>Both caspofungin (50 mg/m²/d, d 1: 70 mg/m²; max 70 mg/d) and liposomal amphotericin B (1-3 mg/kg/d) can be recommended (A-I)</p> <p>A similar approach can be chosen in those granulocytopaenic patients who develop recurrent fever after defervescence upon the initiation of broad spectrum antibacterial agents (no grading).</p> <p>In patients already receiving mould-active antifungal prophylaxis, switching to a different class of mould-active antifungal agents seems reasonable (no grading).</p>	<p>Randomised clinical trials with both caspofungin and liposomal amphotericin B conducted in paediatric patients show similar safety and efficacy relative to much larger trials in adults with similar study design. Both compounds are approved for empirical antifungal therapy in both children and adults.</p> <p>Empirical antifungal therapy may also be considered in individual persistently febrile patients with low risk conditions and profound and prolonged granulocytopaenia and severe mucosal damage (no grading).</p>	<p>Clinical trials in paediatric patients: 57-60</p> <p>PK studies in paediatric patients: Appendix, section 2</p> <p>Clinical trials in adults: 7,8; and appendix, section 5</p>
<p>Pre-emptive (diagnostic driven) therapy</p>	<p>No data in children; feasibility demonstrated in adults, and accepted</p>	<p>Clinical trials in adults:</p>

<p>may be an alternative to the empirical antifungal approach (no grading).</p>	<p>as an alternative to the empiric approach in high-risk adult granulocytopaenic patients. Rapid availability of pulmonary CT and galactomannan results a prerequisite; capability of performing bronchoscopies with bronchoalveolar lavage desirable.</p>	<p>61-63 Recommendations in adults: 8,64</p>
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Table 8: Recommendations for antifungal therapy of proven/probable invasive fungal diseases in paediatric patients with cancer or haematopoietic stem cell transplantation

Recommendation and grading	Comments	Key References
Invasive candidiasis		
Caspofungin 50 (d1:70) mg/m ² /d IV in one single dose (B-II)	Fungicidal activity, consider for granulocytopenic and cardiovascularly unstable patients; echinocandins have higher MICs against <i>C.parapsilosis</i> group; however, no diminished efficacy against these species has been noted in randomised clinical trials	Clinical trials in adults: 5,8; and appendix, section 6 PK, safety and efficacy in paediatric patients: Appendix, section 2
Fluconazole 8-12 mg/kg/d IV in one single dose (max. 800mg/d) (B-II)	Fungistatic activity; not recommended for infections by <i>C. krusei</i> and <i>C.glabrata</i>	Clinical trials in adults: 5,8; and appendix, section 6 PK, safety and efficacy in paediatric patients: Appendix, section 2
Liposomal amphotericin B 3 mg/kg/d IV in one single dose (B-II)	Fungicidal activity, consider for granulocytopenic and cardiovascularly unstable patients	Clinical trials in adults: 8; and appendix, section 6 PK, safety and efficacy in paediatric patients: Appendix, section 2
Micafungin 2-4 mg/kg/d IV (≥ 50kg: 100 -	Fungicidal activity, consider for granulocytopenic and	Clinical trials in adults:

200 mg) in one single dose (B-II)	cardiovascularly unstable patients; echinocandins have higher MICs against <i>C.parapsilosis</i> group; however, no diminished efficacy against these species has been noted in randomized clinical trials.	5,8; and appendix, section 6 PK, safety and efficacy in paediatric patients: Appendix, section 2
Voriconazole 2- <12 yrs /12-14 yrs and <50kg: 8 mg/kg BID (day 1: 9) IV and 9 mg/kg BID PO; / ≥15 yrs and 12-14 yrs and ≥50kg: 4 mg/kg BID (day 1: 6) IV; 200 mg BID PO +TDM (all) (B-II)	Fungistatic activity; relative to fluconazole, spectrum extends to <i>C.glabrata</i> and <i>C.krusei</i> . Not approved in subjects <2 years; TDM is suggested; dosing target: trough concentration of between 1.0 and 5.0 mg/L	Clinical trials in adults: 5,8; and appendix, section 6 TDM dosing target: 51,52 PK, safety and efficacy in paediatric patients: Appendix, section 2
Amphotericin B lipid complex 5 mg/kg/d IV in one single dose (C-II)	Fungicidal activity; lower grading because of absence of completely published first-line phase III data and limited paediatric pharmacokinetic studies.	Clinical trials in adults: 5,8; and appendix, section 6 PK, safety and efficacy in paediatric patients: Appendix, section 2
Invasive aspergillosis: First line		
Voriconazole 2- <12 yrs /12-14 yrs and <50kg: 8 mg/kg BID (day 1: 9) IV and 9 mg/kg BID PO; / ≥15 yrs and 12-14 yrs and ≥50kg: 4 mg/kg BID (day 1: 6) IV; 200 mg BID PO +TDM (all) (A-I)	A-I recommendation based on the pivotal phase III trial in adults. Not approved in subjects <2 years; TDM is suggested; dosing target: trough concentration of between 1.0 and 5.0 mg/L . Current treatment of choice for infections involving the CNS. A switch in class is to be considered in patients with breakthrough aspergillosis on mould-active azole prophylaxis	Clinical trials in adults: 5,8; and appendix, section 6 TDM dosing target: 51,52 PK, safety and efficacy in

		paediatric patients: Appendix, section 2
Liposomal amphotericin B 3 mg/kg/d IV in one single dose (B-I)	Pivotal phase III trial was comparison between two different dosage strategies but no head-to-head comparison to the reference agent at the time of its conduct (i.e., voriconazole)	Clinical trials in adults: 5,8; and appendix, section 6 PK, safety and efficacy in paediatric patients: Appendix, section 2
Amphotericin B lipid complex 5 mg/kg/d IV in one single dose (B-II)	No controlled first-line data but solid second line experience in treatment-naïve patients receiving the compound on the basis of its improved safety profile relative to amphotericin B deoxycholate	Clinical trials in adults: 5,8; and appendix, section 6 PK, safety and efficacy in paediatric patients: Appendix, section 2
Antifungal combination therapy (echinocandin plus polyene or triazole) (C-III).	Pivotal randomized clinical trial not fully published; preliminary data indicate no differences in the primary endpoint	Clinical trial in adults: 67-70 Safety and efficacy in paediatric patients: 71
Invasive aspergillosis: Second line		
Voriconazole 2- <12 yrs /12-14 yrs and <50kg: 8 mg/kg BID (day 1: 9) IV and 9 mg/kg BID PO; / ≥15 yrs and 12-14 yrs and ≥50kg: 4 mg/kg BID (day 1: 6) IV; 200 mg BID PO +TDM (all) (A-I)	Second line option for voriconazole-naïve patients. Not approved in subjects < 2 years; TDM is suggested; dosing target: trough concentration of between 1.0 and 5.0 mg/L. Inference for efficacy from the pivotal first-line phase III trial and a second line phase II trial.	Clinical trials in adults: 5,8; and appendix, section 6 TDM dosing target: 51,52 PK, safety and efficacy in paediatric patients:

		Appendix, section 2
Liposomal amphotericin B 3 mg/kg/d IV in one single dose (B-I)	Second-line option for patients not responding to or being intolerant of voriconazole; inference for efficacy from the pivotal first-line phase III trial	Clinical trials in adults: 5,8; and appendix, section 6 PK, safety and efficacy in paediatric patients: Appendix, section 2
Caspofungin 50 (d1:70) mg/m ² /d IV in one single dose (A-II)	Efficacy demonstrated in pivotal phase II trial; approved for second line therapy in both children and adults.	Clinical trials in adults: 5,8; and appendix, section 6 PK, safety and efficacy in paediatric patients: Appendix, section 2
Amphotericin B lipid complex 5 mg/kg/d IV in one single dose (B-II)	Solid second line experience based on data obtained through phase II and IV clinical studies	Clinical trials in adults: 5,8; and appendix, section 6 PK, safety and efficacy in paediatric patients: Appendix, section 2
Antifungal combination therapy (polyene or triazole plus echinocandin (C-II)	Assessment of efficacy based on small phase II study and retrospective cohort study and inference from one not fully published phase III first-line trial that failed to show differences in the primary endpoint	Clinical trial in adults: 67-70 Safety and efficacy in paediatric patients: 71
Itraconazole 5 mg/kg/d PO (\geq 2 years of age) in two divided doses + TDM (no grading)	Approved indication in adults, but not approved in subjects <18 years; limited PK in children \geq 2 years; TDM is suggested; dosing target: trough concentration of \geq 0.5 mg/L	Clinical trials in adults: 5,8; and appendix, section 6

		TDM dosing target: 49 PK, safety and efficacy in paediatric patients: Appendix, section 2
Posaconazole plus TDM 800 mg/d PO in two or four divided doses +TDM in subjects \geq 13 years (no grading)	Approved indication in adults, but not approved in the EU in subjects < 18 years; limited PK data in subjects \geq 13 years. TDM is suggested; dosing target: trough concentration of \geq 0.7 – 1.5 mg/L	Clinical trials in adults: 5,8; 73 <u>Suggested</u> TDM dosing target: 53,73 PK, safety and efficacy in paediatric patients: Appendix, section 2
Micafungin 2-4 mg/kg/d IV (\geq 50kg: 100 - 200 mg in one single dose (no grading)	Indication not approved; preclinical efficacy demonstrated, but no robust clinical data.	Clinical trials in adults: 5,8; and appendix, section 6 PK, safety and efficacy in paediatric patients: Appendix, section 2
Mucormycosis, first line:		
Amphotericin B lipid complex 5-7.5 mg/kg/d IV in one single dose (B-II)	Recommendations similar to those for adults	Clinical trials in adults: 9; and appendix, section 6 PK, safety and efficacy in paediatric patients: Appendix, section 2

Liposomal amphotericin B 5-10 mg/kg/d IV in one single dose (B-II)	Recommendations similar to those for adults. Preferred for infections involving the CNS or in patients with renal failure	Clinical trials in adults: 9; and appendix, section 6 PK, safety and efficacy in paediatric patients: Appendix, section 2
Antifungal combination therapy (lipid amphotericin B plus caspofungin or plus posaconazole (C-III)	Recommendations similar to those for adults	Clinical data in adults and preclinical data: 9; and appendix, section 6
Posaconazole 800 mg/d PO in 2 or 4 divided doses +TDM in subjects \geq 13 years (no grading)	Recommendations similar to those for adults. Non approved indication; limited PK data in subjects \geq 13 years. TDM is suggested; dosing target inferred from invasive aspergillosis: trough concentration of \geq 0.7 to 1.5 mg/L	Clinical trials in adults: 9; and appendix, section 6 <u>Suggested TDM dosing target:</u> 53,73 PK, safety and efficacy in paediatric patients: Appendix, section 2
Mucormycosis, second line:		
Posaconazole 800 mg/d PO in 2 or 4 divided doses +TDM in subjects \geq 13 years (B-II)	Recommendations similar to those for adults. Non approved indication; limited PK data in subjects \geq 13years. TDM is suggested; dosing target inferred from invasive aspergillosis: trough concentration of \geq 0.7 to 1.5 mg/L	Clinical trials in adults: 9; and appendix, section 6 <u>Suggested TDM dosing target:</u> 53,73 PK, safety and efficacy in

		paediatric patients: Appendix, section 2
Antifungal combination therapy (lipid amphotericin B plus caspofungin) (B-III)	Recommendations similar to those for adults.	Clinical data in adults and preclinical data: 9; and appendix, section 6
Antifungal combination therapy (lipid amphotericin B plus posaconazole) (C-III)	Recommendations similar to those for adults.	Preclinical data: 9; and appendix, section 6
Scedosporiosis and fusariosis:		
Voriconazole 2- <12 yrs /12-14 yrs and <50kg: 8 mg/kg BID (day 1: 9) IV and 9 mg/kg BID PO; / ≥15 yrs and 12-14 yrs and ≥50kg: 4 mg/kg BID (day 1: 6) IV; 200 mg BID PO +TDM (all) (B-II)	Approved indication in adults; approved in pediatric subjects >2 years; TDM is suggested; dosing target: trough concentration of between 1.0 and 5.0 mg/L	Clinical trials in adults: 76-78 TDM dosing target: 51,52 PK, safety and efficacy in paediatric patients: Appendix, section 2
Amphotericin B lipid complex 5 mg/kg/d IV in one single dose (no grading)	Inference made from in vitro data, animal models, and case series / case reports	Clinical trials in adults: Appendix, section 6 PK, safety and efficacy in paediatric patients: Appendix, section 2
Liposomal amphotericin B 3-5 mg/kg/d IV in	Inference made from in vitro data, animal models, and case series /	Clinical trials in adults: None

one single dose (no grading)	case reports	PK, safety and efficacy in paediatric patients: Appendix, section 2
Posaconazole 800 mg/d PO in 2 or 4 divided doses +TDM in subjects ≥ 13 years (no grading)	Treatment of fusariosis approved in adults. Limited PK data in subjects ≥ 13 years, but not approved in the EU in subjects < 18 years; TDM is suggested; dosing target inferred from invasive aspergillosis: trough concentration of ≥ 0.7 to 1.5 mg/L	Clinical trials in adults: 79,80 <u>Suggested</u> TDM dosing target: 53,72 PK, safety and efficacy in paediatric patients: Appendix, section 2