

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

Adilia Warris<sup>1,7,8</sup>, Thomas Lehrnbecher<sup>2,7,8</sup>, Emmanuel Roilides<sup>2,7,8</sup>, Elio Castagnola<sup>4,7</sup>, Roger J.M. Bruggemann<sup>5,7</sup>, Andreas H. Groll<sup>6,7,8</sup>.

<sup>1</sup>MRC Centre for Medical Mycology, Institute of Medical Sciences, University of Aberdeen, Aberdeen, United Kingdom

<sup>2</sup>Division of Paediatric Haematology and Oncology, Hospital for Children and Adolescents, Johann Wolfgang Goethe-University, Frankfurt, Germany

<sup>3</sup>Infectious Diseases Unit, 3rd Department of Paediatrics, Faculty of Medicine, Aristotle University 96 School of Health Sciences, Thessaloniki, Greece

<sup>4</sup>Infectious Diseases Unit, IRCCS Istituto Giannina Gaslini Children's Hospital, Genoa, Italy

<sup>5</sup>Radboud Center for Infectious Diseases, Radboud University Medical Centre, Center of Expertise in Mycology Radboudumc/CWZ, ECMM Excellence Center of Medical Mycology, Nijmegen, Netherlands

<sup>6</sup>Infectious Disease Research Program, Center for Bone Marrow Transplantation and Department of Paediatric Hematology/Oncology, University Children's Hospital Münster, Münster, Germany

<sup>7</sup>ESCMID Fungal Infection Study Group (EFISG)

<sup>8</sup>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/](http://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 granulocytopenia and treatment with glucocorticosteroids); those with bone marrow failure syndromes (e.g. myelodysplastic syndrome (MDS) and very severe aplastic anaemia (VSAA)) with profound granulocytopenia; 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-IIIt). Options include itraconazole (A-IIIt); posaconazole for patients  $\geq 13$  years of age (A-IIIt); and voriconazole for patients  $> 2$  years of age (A-IIIt). Secondary alternatives include liposomal amphotericin B (B-IIIt); micafungin (B-IIIt); and, with less strength of evidence, aerosolised liposomal amphotericin B (C-IIIt) 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 ( $\geq 0.3$  mg/kg/day prednisone equivalent) or use of anti-inflammatory antibodies), prophylaxis against IA and other relevant IFDs is recommended (A-IIIt). Options include posaconazole for patients  $\geq 13$  years of age (A-IIIt); and voriconazole for patients  $> 2$  years of age (A-IIIt). Secondary alternatives are itraconazole (B-IIIt); 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-IIIt); the recommendation for prophylaxis in de novo ALL depends on the treatment protocol and additional risk factors including prolonged and profound ( $\geq 10$  days with an absolute neutrophil count  $< 500/uL$ ) granulocytopaenia and treatment with

glucocorticosteroids. Options include itraconazole (A-III); posaconazole for patients  $\geq 13$  years of age (A-III); and voriconazole for patients  $> 2$  years of age (A-III). Secondary alternatives include liposomal amphotericin B (B-III); micafungin (B-III); and, with less strength of evidence, aerosolised liposomal amphotericin B (C-III) 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 granulocytopenia (A-III). 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  $\geq 12$  months (A-III). In heart transplantation alone the risk for IA is low and there is no need of prophylaxis (D-III). However, heart transplantation with high-risk profile (e.g. acute rejection, re-exploration, haemodialysis) is an indication for antifungal prophylaxis (B-III).

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-III<sup>tt</sup>). 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-III<sup>tt</sup>).

### *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- $\gamma$  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 granulocytopenic 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 particularly 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-II<sub>t</sub>). 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-II<sup>t</sup>). 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,  $\beta$ -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 granulocytopenic 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-II); limited to children  $\geq 2$  years) and liposomal amphotericin B (B-II); 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-II); the combination of liposomal amphotericin B with an echinocandin (C-II); the combination of voriconazole with an echinocandin (C-II 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-II).

#### *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-II<sup>t</sup>) and liposomal amphotericin B (B-II<sup>t</sup>) [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 (All (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 (All, 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 (All, 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 (All, 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-It) 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-IIIt; limited to children  $\geq 2$  years) and liposomal amphotericin B in amphotericin B-naïve patients (B-IIIt), respectively. Further options approved in paediatric patients include amphotericin B lipid complex (B-II) and caspofungin (B-IIIt), and, for patients  $\geq 13$  years of age, posaconazole plus TDM (B-IIIt). Few and uncontrolled data exist on combination therapy with either voriconazole or an amphotericin B product plus an echinocandin for salvage treatment (C-IIIt), for micafungin (C-IIIt), 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-IIIt).

#### 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.

## ACKNOWLEDGEMENT

Prof Warris is supported by the Wellcome Trust Strategic Award (grant 097377) and the MRC Centre for Medical Mycology (grant MR/N006364/1) at the University of Aberdeen.

## FUNDING

European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the European Confederation of Medical Mycology (ECMM).

## REFERENCES

1. Steinbach WJ. Epidemiology of invasive fungal infections in neonates and children. *Clin Microbiol Infect.* 2010; **16**: 1321-1327.
2. Antachopoulos C. Invasive fungal infections in congenital immunodeficiencies. *Clin Microbiol Infect.* 2010; **16**: 1335-1342.
3. Pana ZD, Farmaki E, Roilides E. Host genetics and opportunistic fungal infections. *Clin Microbiol Infect.* 2014; **20**: 1254-1264.
4. Tragiannidis A, Kyriakidis I, Zundorf I, Groll AH. Invasive fungal infections in pediatric patients treated with tumor necrosis alpha (TNF- $\alpha$ ) inhibitors. *Mycoses.* 2017; **60**: 222-229.
5. Silva MF, Ferriani MP, Terreri MT, et al. A multicenter study of invasive fungal infections in patients with childhood-onset systemic lupus erythematosus. *J Rheumatol.* 2015; **42**: 2296-2303.
6. Zaoutis TE, Heydon K, Chu JH, Walsh TJ, Steinbach WJ. Epidemiology, outcomes, and costs of IA in immunocompromised children in the united states, 2000. *Pediatrics.* 2006; **117**: 711-716.
7. Pana ZD, Roilides E, Warris A, Groll AH, Zaoutis T. Epidemiology of Invasive Fungal Disease in Children. *J Pediatric Infect Dis Soc.* 2017; **6**: S3-S11.
8. 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**: 1813-1821.
9. Hovi L, Saarinen-Pihkala UM, Vettenranta K, Saxen H. Invasive fungal infections in pediatric bone marrow transplant recipients: single center experience of 10 years. *Bone Marrow Transplant.* 2000; **26**: 999-1004.
10. Benjamin DKJ, Miller WC, Bayliff S, Martel L, Alexander KA, Martin PL. Infections diagnosed in the first year after pediatric stem cell transplantation. *Pediatr Infect Dis J.* 2002; **21**: 227-234.



11. Walmsley S, Devi S, King S, Schneider R, Richardson S, Ford-Jones L. Invasive *Aspergillus* infections in a pediatric hospital: a ten year review. *Pediatr Infect Dis J*. 1993; **12**: 673-682.
12. Abbasi S, Shenep JL, Hughes WT, Flynn PM. Aspergillosis in children with cancer: a 34-year experience. *Clin Infect Dis*. 1999; **29**: 1210-1219.
13. Groll AH, Kurz M, Schneider W, et al. Five-year-survey of invasive aspergillosis in a paediatric cancer centre. Epidemiology, management and long-term survival. *Mycoses*. 1999; **42**: 431-442.
14. Burgos A, Zaoutis TE, Dvorak CC, et al. Pediatric invasive aspergillosis: A multicenter retrospective analysis of 139 contemporary cases. *Pediatrics*. 2008; **121**: e1286-1294.
15. Wattier RL, Dvorak CC, Hoffman JA, et al. A prospective, international cohort study of invasive mold infection in children. *J Pediatr Infect Dis Soc*. 2015; **4**: 313–322.
16. King J, Henriët S, Warris A. Aspergillosis in granulomatous disease. *J Fungi*. 2016; **2**: 15.
17. Groll AH, Jaeger G, Allendorf A, Herrmann G, Schloesser R, von Loewenich V. Invasive pulmonary aspergillosis in a critically ill neonate: case report and review of invasive aspergillosis during the first 3 months of life. *Clin Infect Dis*. 1998; **27**: 437-452.
18. Broenen E, Mavinkurve-Groothuis A, Kamphuis-van Ulzen K, Brüggemann R, Verweij PE, Warris A. Screening of the central nervous system in children with invasive pulmonary aspergillosis. *Med Mycol Case Rep*. 2014; **4**: 8-11.
19. Papouli M, Roilides E, Bibashi E, Andreou A. Primary cutaneous aspergillosis in neonates: case report and review. *Clin Infect Dis*. 1996; **22**: 1102-1104.
20. Beauté J, Obenga G, Le Mignot L, et al. Epidemiology and outcome of invasive fungal diseases in patients with chronic granulomatous disease: a multicenter study in France. *Pediatr Infect Dis J*. 2011; **30**: 57–62.
21. Blumental S, Mouy R, Mahlaoui N, et al. Invasive mold infections in chronic granulomatous disease: a 25-year retrospective survey. *Clin Infect Dis*. 2011; **53**: e159–e169.
22. Henriët S, Verweij PE, Holland SM, Warris A. Invasive fungal infections in patients with chronic granulomatous disease. *Adv Exp Med Biol*. 2013; **764**: 27–55.

23. Hope WW, Castagnola E, Groll AH, et al. 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.
24. Groll AH, Castagnola E, Cesaro S, et al. Fourth European conference on infections in leukaemia (ECIL-4): guidelines for diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or allogeneic haemopoietic stem-cell transplantation. *Lancet Oncol.* 2014; **15**(8): e327–40.
25. Ullmann AJ, Aguado JM, Arikan-Akdaglli S, et al. Diagnosis and management of aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clin Microbiol Infect.* 2018; **24**(Suppl 1): e1-e38.
26. Ullmann AJ, Cornely OA, Donnelly JP et al. ESCMID Diagnostic and management guideline for candida diseases 2012: developing european guidelines in clinical microbiology and infectious diseases. *Clin Microbiol Infect.* 2012; **18**(Suppl 7): 1–8.
27. 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](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf) (accessed Aug 10, 2018).
28. European Community. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 [https://ec.europa.eu/health/human-use/paediatric-medicines/developments\\_en](https://ec.europa.eu/health/human-use/paediatric-medicines/developments_en) (accessed Aug 10, 2018).
29. Fisher BT, Robinson PD, Lehrnbecher T, et al. Risk factors for invasive fungal disease in pediatric cancer and hematopoietic stem cell transplantation: A Systematic Review. *J Pediatric Infect Dis Soc.* 2017; **7**: 191-198.
30. Castagnola E, Bagnasco F, Bandettini R, et al. Role of acute graft versus-host disease in the risk of bacteremia and invasive fungal disease after allogeneic hemopoietic stem cell transplantation in children. Results from a single-center observational study. *Biol Blood Marrow Transplant.* 2014; **20**: 1056–1073.

31. Srinivasan A, Wang C, Srivastava DK, et al. Timeline, epidemiology, and risk factors for bacterial, fungal, and viral infections in children and adolescents after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2013; **19**: 94-101.
32. Crassard N, Hadden H, Piens MA, et al. Invasive aspergillosis in a paediatric haematology department: a 15-year review. *Mycoses*. 2008; **51**: 109-116.
33. Cesaro S, Tridello G, Castagnola E, et al. Retrospective study on the incidence and outcome of proven and probable invasive fungal infections in high-risk pediatric oncohematological patients. *Eur J Haematol*. 2017; **99**: 240–248.
34. Ducassou S, Rivaud D, Auvrignon A, et al. Invasive fungal infections in paediatric acute myeloid leukaemia. *J Pediatr Hematol Oncol*. 2015; **37**: 560-565.
35. Quarello P, Saracco P, Giacchino M, et al. Epidemiology of infections in children with acquired aplastic anaemia: a retrospective multicenter study in Italy. *Eur J Haematol*. 2012; **88**: 526-34.
36. Saxena S, Gee J, Klieger S, et al. Invasive fungal disease in pediatric solid organ transplant recipients. *J Pediatric Infect Dis Soc*. 2017; Jun 15.
37. Winston DJ, Maziarz RT, Chandrasekar PH, et al. Intravenous and oral itraconazole versus intravenous and oral fluconazole for long-term antifungal prophylaxis in allogeneic hematopoietic stem-cell transplant recipients. A multicenter, randomized trial. *Annals of internal medicine*. 2003; **138**: 705-713.
38. Marr KA, Crippa F, Leisenring W, et al. Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants. *Blood*. 2004; **103**: 1527-1533.
39. Wingard JR, Carter SL, Walsh TJ, et al. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. *Blood*. 2010; **116**: 5111-5118.
40. Marks DI, Pagliuca A, Kibbler CC, et al. Voriconazole versus itraconazole for antifungal prophylaxis following allogeneic haematopoietic stem-cell transplantation. *Br J Haematol*. 2011; **155**: 318-327.
41. Winston DJ, Bartoni K, Territo MC, Schiller GJ. Efficacy, safety, and breakthrough infections associated with standard long-term posaconazole antifungal prophylaxis in

allogeneic stem cell transplantation recipients. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2011; **17**: 507-515.

42. Bow EJ, Vanness DJ, Slavin M, et al. Systematic review and mixed treatment comparison meta-analysis of randomized clinical trials of primary oral antifungal prophylaxis in allogeneic hematopoietic cell transplant recipients. *BMC Infect Dis*. 2015; **15**: 128.
43. Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med*. 2007; **356**: 335-347.
44. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. Fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. 2007; **356**: 348-359.
45. Gavalda J, Meije Y, Fortun J, et al. Invasive fungal infections in solid organ transplant recipients. *Clin Microbiol Infect*. 2014; **20**(Suppl 7): 27-48.
46. Husain S, Zaldonis D, Kusne S, Kwak EJ, Paterson DL, McCurry KR. Variation in antifungal prophylaxis strategies in lung transplantation. *Transpl Infect Dis*. 2006; **8**: 213-218.
47. Husain S, Silveira FP, Azie N, Franks B, Horn D. Epidemiological features of invasive mold infections among solid organ transplant recipients: PATH Alliance® registry analysis. *Med Mycol*. 2017; **55**: 269-277.
48. Mead L, Danziger-Isakov LA, Michaels MG, Goldfarb S, Glanville AR, Benden C; International Pediatric Lung Transplant Collaborative (IPLTC). Antifungal prophylaxis in pediatric lung transplantation: an international multicenter survey. *Pediatr Transplant*. 2014; **18**: 393-7.
49. Munoz P, Guinea J, Pelaez T, Duran C, Blanco JL, Bouza E. Nosocomial invasive aspergillosis in a heart transplant patient acquired during a break in the hepa air filtration system. *Transpl Infect Dis*. 2004; **6**: 50-54.
50. Saliba F, Delvart V, Ichaï P, et al. Fungal infections after liver transplantation: outcomes and risk factors revisited in the MELD era. *Clin Transplant*. 2013; **27**: E454-61.
51. Saliba F, Pascher A, Cointault O, et al; TENPIN (Liver Transplant European Study Into the Prevention of Fungal Infection) Investigators; TENPIN Liver Transplant European

Study Into the Prevention of Fungal Infection Investigators. Randomized trial of micafungin for the prevention of invasive fungal infection in high-risk liver transplant recipients. *Clin Infect Dis*. 2015; **60**: 997-1006.

52. Pacholczyk M, Lagiewska B, Lisik W, Wasiak D, Chmura A. Invasive fungal infections following liver transplantation - risk factors, incidence and outcome. *Ann Transplant*. 2011; **16**: 14-6.
53. Teisseyre J, Kaliciński P, Markiewicz-Kijewska M, et al. Aspergillosis in children after liver transplantation: single center experience. *Pediatr Transplant*. 2007; **11**: 868-75.
54. Gallin JI, Alling DW, Malech HL, et al. Itraconazole to prevent fungal infections in chronic granulomatous disease. *N Engl J Med*. 2003; **348**: 2416-2422.
55. Menichetti F, Del Favero A, Martino P, et al. Itraconazole oral solution as prophylaxis for fungal infections in neutropenic patients with hematologic malignancies: A randomized, placebo-controlled, double-blind, multicenter trial. Gimema infection program. Gruppo italiano malattie ematologiche dell' adulto. *Clin Infect Dis*. 1999; **28**: 250-255.
56. Harousseau JL, Dekker AW, Stamatoullas-Bastard A, et al. Itraconazole oral solution for primary prophylaxis of fungal infections in patients with hematological malignancy and profound neutropenia: A randomized, double-blind, double-placebo, multicenter trial comparing itraconazole and amphotericin b. *Antimicrob Agents Chemother*. 2000; **44**: 1887-1893.
57. Glasmacher A, Hahn C, Molitor E, Marklein G, Sauerbruch T, Schmidt-Wolf I. 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.
58. Groll AH, Wood L, Roden M, et al. Safety, pharmacokinetics, and pharmacodynamics of cyclodextrin itraconazole in pediatric patients with oropharyngeal candidiasis. *Antimicrob Agents Chemother*. 2002; **46**: 2554-2563.
59. de Repentigny L, Ratelle J, Leclerc JM, et al. Repeated-dose pharmacokinetics of an oral solution of itraconazole in infants and children. *Antimicrob Agents Chemother*. 1998; **42**: 404-408.

60. Foot AB, Veys PA, Gibson BE. Itraconazole oral solution as antifungal prophylaxis in children undergoing stem cell transplantation or intensive chemotherapy for haematological disorders. *Bone Marrow Transplant*. 1999; **24**: 1089-1093.
61. Simon A, Besuden M, Vezmar S, et al. Itraconazole prophylaxis in pediatric cancer patients receiving conventional chemotherapy or autologous stem cell transplants. *Support Care Cancer*. 2007; **15**: 213-220.
62. Hennig S, Wainwright CE, Bell SC, Miller H, Friberg LE, Charles BG. Population pharmacokinetics of itraconazole and its active metabolite hydroxy-itraconazole in paediatric cystic fibrosis and bone marrow transplant patients. *Clin Pharmacokinet*. 2006; **45**: 1099-114.
63. Abdel-Rahman SM, Jacobs RF, Massarella J, et al. Single-dose pharmacokinetics of intravenous itraconazole and hydroxypropyl-beta-cyclodextrin in infants, children, and adolescents. *Antimicrob Agents Chemother*. 2007; **51**: 2668-73.
64. Ananda-Rajah MR, Grigg A, Downey MT, et al. Comparative clinical effectiveness of prophylactic voriconazole/posaconazole to fluconazole/itraconazole in patients with acute myeloid leukemia/myelodysplastic syndrome undergoing cytotoxic chemotherapy over a 12-year period. *Haematologica*. 2012; **97**: 459-463.
65. Jang SH, Colangelo PM, Gobburu JVS. Exposure--response of posaconazole used for prophylaxis against invasive fungal infections: Evaluating the need to adjust doses based on drug concentrations in plasma. *Clinical Pharmacology & Therapeutics*. 2010; **88**: 115-119.
66. Cornely OA, Duarte RF, Haider S, et al. Phase 3 pharmacokinetics and safety study of a posaconazole tablet formulation in patients at risk for invasive fungal disease. *J Antimicrob Chemother*. 2016; **71**: 718-26.
67. Krishna G, Martinho M, Chandrasekar P, Ullmann AJ, Patino H. Pharmacokinetics of oral posaconazole in allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease. *Pharmacotherapy*. 2007; **27**: 1627-1636.
68. Welzen ME, Bruggemann RJ, Van Den Berg JM, et al. A twice daily posaconazole dosing algorithm for children with chronic granulomatous disease. *Pediatr Infect Dis J*. 2011; **30**: 794-797.

69. Döring M, Müller C, Johann PD, et al. Analysis of posaconazole as oral antifungal prophylaxis in pediatric patients under 12 years of age following allogeneic stem cell transplantation. *BMC Infect Dis.* 2012; **12**: 263.
70. Lehrnbecher T, Attarbaschi A, Duerken M, et al. Posaconazole salvage treatment in paediatric patients: A multicentre survey. *Eur J Clin Microbiol Infect Dis.* 2010; **29**: 1043-1045.
71. Yunus S, Pieper S, Kolve H, Goletz G, Jürgens H, Groll AH. Azole-based chemoprophylaxis of invasive fungal infections in paediatric patients with acute leukaemia: an internal audit. *J Antimicrob Chemother.* 2014; **69**: 815-20.
72. Heinz WJ, Cabanillas Stanchi KM, et al. Posaconazole plasma concentration in pediatric patients receiving antifungal prophylaxis after allogeneic hematopoietic stem cell transplantation. *Med Mycol.* 2016; **54**: 128-37.
73. Döring M, Cabanillas Stanchi KM, et al. Posaconazole plasma concentrations in pediatric patients receiving antifungal prophylaxis during neutropenia. *Med Mycol.* 2017;**55**: 375-384.
74. Vanstraelen K, Colita A, Bica AM, et al. Pharmacokinetics of posaconazole oral suspension in children dosed according to body surface area. *Pediatr Infect Dis J.* 2016; **35**: 183-188.
75. Mattiuzzi GN, Cortes J, Alvarado G, et al. Efficacy and safety of intravenous voriconazole and intravenous itraconazole for antifungal prophylaxis in patients with acute myelogenous leukemia or high-risk myelodysplastic syndrome. *Support Care Cancer.* 2011; **19**: 19-26.
76. Barreto JN, Beach CL, Wolf RC, et al. The incidence of invasive fungal infections in neutropenic patients with acute leukemia and myelodysplastic syndromes receiving primary antifungal prophylaxis with voriconazole. *Am J Hematol.* 2013; **88**: 283-288.
77. 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**: 4782-4788.
78. Park WB, Kim N-H, Kim K-H, 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**: 1080-1087.

79. Luong ML, Al-Dabbagh M, Groll AH, et al. Utility of voriconazole therapeutic drug monitoring: a meta-analysis. *J Antimicrob Chemother.* 2016; **71**: 1786-99.
80. Walsh TJ, Karlsson MO, Driscoll T, et al. Pharmacokinetics and safety of intravenous voriconazole in children after single- or multiple-dose administration. *Antimicrob Agents Chemother.* 2004; **48**: 2166-2172.
81. Walsh TJ, Driscoll T, Milligan PA, et al. Pharmacokinetics, safety, and tolerability of voriconazole in immunocompromised children. *Antimicrob Agents Chemother.* 2010; **54**: 4116-4123.
82. Karlsson MO, Lutsar I, Milligan PA. Population pharmacokinetic analysis of voriconazole plasma concentration data from pediatric studies. *Antimicrob Agents Chemother.* 2009; **53**: 935-944.
83. Driscoll TA, Frangoul H, Nemecek ER, et al. Comparison of pharmacokinetics and safety of voriconazole intravenous-to-oral switch in immunocompromised adolescents and healthy adults. *Antimicrob Agents Chemother.* 2011; **55**: 5780-5789.
84. Driscoll TA, Yu LC, Frangoul H, et al. Comparison of pharmacokinetics and safety of voriconazole intravenous-to-oral switch in immunocompromised children and healthy adults. *Antimicrob Agents Chemother.* 2011; **55**: 5770-5779.
85. Friberg LE, Ravva P, Karlsson MO, Liu P. Integrated population pharmacokinetic analysis of voriconazole in children, adolescents and adults. *Antimicrob Agents Chemother.* 2012; **56**: 3032-3042.
86. Pieper S, Kolve H, Gumbinger HG, Goletz G, Wurthwein G, Groll AH. Monitoring of voriconazole plasma concentrations in immunocompromised paediatric patients. *J Antimicrob Chemother.* 2012; **67**: 2717-2724.
87. Molina JR, Serrano J, Sanchez-Garcia J, et al. Voriconazole as primary antifungal prophylaxis in children undergoing allo-sct. *Bone Marrow Transplant.* 2012; **47**: 562-567.
88. Martin JM, Macias-Parra M, Mudry P, et al. Safety, Efficacy, and exposure-response of voriconazole in pediatric patients with invasive aspergillosis, invasive candidiasis or esophageal candidiasis. *Pediatr Infect Dis J.* 2017; **36**: e1-e13.
89. Tollemar J, Ringden O, Andersson S, Sundberg B, Ljungman P, Tyden G. Randomized double-blind study of liposomal amphotericin b (ambisome) prophylaxis of invasive



- fungal infections in bone marrow transplant recipients. *Bone Marrow Transplant*. 1993; **12**: 577-582.
90. Kelsey SM, Goldman JM, McCann S, et al. Liposomal amphotericin (ambisome) in the prophylaxis of fungal infections in neutropenic patients: A randomised, double-blind, placebo-controlled study. *Bone Marrow Transplant*. 1999; **23**: 163-168.
91. Penack O, Schwartz S, Martus P, et al. Low-dose liposomal amphotericin b in the prevention of invasive fungal infections in patients with prolonged neutropenia: Results from a randomized, single-center trial. *Ann Oncol*. 2006; **17**: 1306-1312.
92. Cornely OA, Leguay T, Maertens J, et al; AmBiGuard Study Group. Randomized comparison of liposomal amphotericin B versus placebo to prevent invasive mycoses in acute lymphoblastic leukaemia. *J Antimicrob Chemother*. 2017; **72** : 2359-2367.
93. Ringden O, Meunier F, Tollemar J, et al. Efficacy of amphotericin b encapsulated in liposomes (ambisome) in the treatment of invasive fungal infections in immunocompromised patients. *J Antimicrob Chemother*. 1991; **28 Suppl B**: 73-82.
94. Hong Y, Shaw PJ, Nath CE, et al. Population pharmacokinetics of liposomal amphotericin b in pediatric patients with malignant diseases. *Antimicrob Agents Chemother*. 2006; **50**: 935-942.
95. Kolve H, Ahlke E, Fegeler W, Ritter J, Jurgens H, Groll AH. Safety, tolerance and outcome of treatment with liposomal amphotericin b in paediatric patients with cancer or undergoing haematopoietic stem cell transplantation. *J Antimicrob Chemother*. 2009; **64**: 383-387.
96. Bochennek K, Tramsen L, Schedler N, et al. Liposomal amphotericin B twice weekly as antifungal prophylaxis in paediatric haematological malignancy patients. *Clin Microbiol Infect*. 2011; **17**: 1868-1874.
97. Hand EO, Ramanathan MR. Safety and tolerability of high-dose weekly liposomal amphotericin B antifungal prophylaxis. *Pediatr Infect Dis J*. 2014; **33**: 835-836.
98. Lestner JM, Groll AH, Aljayyousi G, et al. Population pharmacokinetics of liposomal amphotericin B in immunocompromised children. *Antimicrob Agents Chemother*. 2016; **60**: 7340-7346.

99. Seibel NL, Shad AT, Bekersky I, et al. Safety, tolerability, and pharmacokinetics of liposomal amphotericin B in immunocompromised pediatric patients. *Antimicrob Agents Chemother.* 2017; **61**: e01477-16.
100. van Burik JA, Ratanatharathorn V, Stepan DE, et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. *Clin Infect Dis.* 2004; **39**: 1407-1416.
101. Huang X, Chen H, Han M, et al. Multicenter, randomized, open-label study comparing the efficacy and safety of micafungin versus itraconazole for prophylaxis of invasive fungal infections in patients undergoing hematopoietic stem cell transplant. *Biol Blood Marrow Transpl.* 2012; **18**: 1509-1516.
102. Seibel NL, Schwartz C, Arrieta A, et al. Safety, tolerability, and pharmacokinetics of Micafungin (FK463) in febrile neutropenic pediatric patients. *Antimicrob Agents Chemother.* 2005; **49**: 3317-3324.
103. Hope WW, Seibel NL, Schwartz CL, et al. Population pharmacokinetics of micafungin in pediatric patients and implications for antifungal dosing. *Antimicrob Agents Chemother.* 2007; **51**: 3714-3719.
104. Arrieta AC, Maddison P, Groll AH. Safety of micafungin in pediatric clinical trials. *Pediatr Infect Dis J.* 2011; **30**: e97-e102.
105. Mehta PA, Vinks AA, Filipovich A, et al. Alternate-day micafungin antifungal prophylaxis in pediatric patients undergoing hematopoietic stem cell transplantation: A pharmacokinetic study. *Biol Blood Marrow Transpl.* 2010; **16**: 1458-1462.
106. Benjamin DK Jr, Deville JG, Azie N, et al. Safety and pharmacokinetic profiles of repeated-dose micafungin in children and adolescents treated for invasive candidiasis. *Pediatr Infect Dis J.* 2013; **32**: e419-25.
107. Park HJ, Park M, Han M, et al. Efficacy and safety of micafungin for the prophylaxis of invasive fungal infection during neutropenia in children and adolescents undergoing allogeneic hematopoietic SCT. *Bone Marrow Transplant.* 2014; **49**: 1212-1216.
108. Bochennek K, Balan A, Müller-Scholden L, et al. Micafungin twice weekly as antifungal prophylaxis in paediatric patients at high risk for invasive fungal disease. *J Antimicrob Chemother.* 2015; **70**: 1527-1530.

109. Albano E, Azie N, Roy M, Townsend R, Arrieta A. Pharmacokinetic and safety profiles of repeated-dose prophylactic micafungin in children and adolescents undergoing hematopoietic stem cell transplantation. *J Pediatr Hematol Oncol*. 2015; **37**: e45-50.
110. Hope WW, Kaibara A, Roy M, et al. Population pharmacokinetics of micafungin and its metabolites M1 and M5 in children and adolescents. *Antimicrob Agents Chemother*. 2015; **59**: 905-13.
111. Rijnders BJ, Cornelissen JJ, Slobbe L, et al. Aerosolized liposomal amphotericin b for the prevention of invasive pulmonary aspergillosis during prolonged neutropenia: A randomized, placebo-controlled trial. *Clin Infect Dis*. 2008; **46**: 1401-1408.
112. Mattiuzzi GN, Alvarado G, Giles FJ, et al. Open-label, randomized comparison of itraconazole versus caspofungin for prophylaxis in patients with hematologic malignancies. *Antimicrob Agents Chemother*. 2006; **50**: 143-147.
113. Cattaneo C, Monte S, Algarotti A, et al. A randomized comparison of caspofungin versus antifungal prophylaxis according to investigator policy in acute leukaemia patients undergoing induction chemotherapy (PROFIL-C study). *J Antimicrob Chemother*. 2011; **66**: 2140-2145.
114. Walsh TJ, Adamson PC, Seibel NL, et al. Pharmacokinetics, safety, and tolerability of caspofungin in children and adolescents. *Antimicrob Agents Chemother*. 2005; **49**: 4536-4545.
115. Neely M, Jafri HS, Seibel N, et al. Pharmacokinetics and safety of caspofungin in older infants and toddlers. *Antimicrob Agents Chemother*. 2009; **53**: 1450-1456.
116. Zaoutis T, Lehrnbecher T, Groll AH, et al. Safety experience with caspofungin in pediatric patients. *Pediatr Infect Dis J*. 2009; **28**: 1132-1135.
117. Li CC, Sun P, Dong Y, et al. Population pharmacokinetics and pharmacodynamics of caspofungin in pediatric patients. *Antimicrob Agents Chemother*. 2011; **55**: 2098-2105.
118. Döring M, Hartmann U, Erbacher A, Lang P, Handgretinger R, Müller I. Caspofungin as antifungal prophylaxis in pediatric patients undergoing allogeneic hematopoietic stem cell transplantation: a retrospective analysis. *BMC Infect Dis*. 2012; **12**: 151.

119. Stader F, Wuerthwein G, Groll AH, Vehreschild JJ, Cornely OA, Hempel G. Physiology-based pharmacokinetics of caspofungin for adults and paediatrics. *Pharm Res.* 2015; **32**: 2029-2037.
120. Lempers VJ, Martial JC, Schreuder MF, et al. Drug-interaction of azole antifungals with selected immunosuppressants in transplant patients: strategies for optimal management in clinical practice. *Curr Opin Pharmacol.* 2015; **24**: 38-44.
121. Groll AH, Townsend R, Desai A, et al. Drug-drug interactions between triazole antifungal agents used to treat invasive aspergillosis and immunosuppressants metabolized by cytochrome P450 3A4. *Transpl Infect Dis.* 2017; Oct 19.
122. Pana ZD, Roilides E. Risk of azole-enhanced vincristine neurotoxicity in pediatric patients with hematological malignancies: old problem - new dilemma. *Pediatr Blood Cancer.* 2011; **57**: 30-35.
123. van Schie RM, Brüggemann RJ, Hoogerbrugge PM, te Loo DM. Effect of azole antifungal therapy on vincristine toxicity in childhood acute lymphoblastic leukaemia. *J Antimicrob Chemother.* 2011; **66**: 1853-1856.
124. Moriyama B, Henning SA, Leung J, et al Adverse interactions between antifungal azoles and vincristine: review and analysis of cases. *Mycoses.* 2012; **55**: 290-297.
125. Monforte V, Ussetti P, Gavalda J, et al. Feasibility, tolerability, and outcomes of nebulized liposomal amphotericin b for aspergillus infection prevention in lung transplantation. *J Heart Lung Transplant.* 2010; **29**: 523-530.
126. Husain S, Paterson DL, Studer S, et al. Voriconazole prophylaxis in lung transplant recipients. *Am J Transplant.* 2006; **6**: 3008-3016.
127. Castroagudin JF, Ponton C, Bustamante M, et al. Prospective interventional study to evaluate the efficacy and safety of liposomal amphotericin b as prophylaxis of fungal infections in high-risk liver transplant recipients. *Transplant Proc.* 2005; **37**: 3965-3967.
128. Fortun J, Martin-Davila P, Montejo M, et al. Prophylaxis with caspofungin for invasive fungal infections in high-risk liver transplant recipients. *Transplantation.* 2009; **87**: 424-435.
129. Mouy R, Veber F, Blanche S, et al. Long-term itraconazole prophylaxis against aspergillus infections in thirty-two patients with chronic granulomatous disease. *J Pediatr.* 1994; **125**: 998-1003.

130. The International Chronic Granulomatous Disease Cooperative Study Group. A controlled trial of interferon to prevent infection in chronic granulomatous disease. *N Engl J Med*. 1991; **324**: 509–516.
131. Gallin JI. Interferon- in the treatment of the chronic granulomatous diseases of childhood. *Clin Immunol Immunopathol*. 1991; **61**: S100–S105.
132. Weening RS, Leitz GJ, Seger RA. Recombinant human interferon- in patients with chronic granulomatous disease–European follow up study. *Eur J Pediatr*. 1995; **154**: 295–298.
133. Marciano BE, Wesley R, De Carlo ES, et al. Long-term interferon-gamma therapy for patients with chronic granulomatous disease. *Clin Infect Dis*. 2004; **39**: 692-699.
134. 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**: 709-718.
135. Kruger WH, Russmann B, de Wit M, et al. Haemopoietic cell transplantation of patients with a history of deep or invasive fungal infection during prophylaxis with liposomal amphotericin b. *Acta Haematol*. 2005; **113**: 104-108.
136. de Fabritiis P, Spagnoli A, Di Bartolomeo P, et al. Efficacy of caspofungin as secondary prophylaxis in patients undergoing allogeneic stem cell transplantation with prior pulmonary and/or systemic fungal infection. *Bone Marrow Transplant*. 2007; **40**: 245-249.
137. 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**: 734-742.
138. Cordonnier C, Rovira M, Maertens J, et al. Voriconazole for secondary prophylaxis of invasive fungal infections in allogeneic stem cell transplant recipients: Results of the vosifi study. *Haematologica*. 2010; **95**: 1762-1768.
139. Liu F, Wu T, Wang JB, et al. Risk factors for recurrence of invasive fungal infection during secondary antifungal prophylaxis in allogeneic hematopoietic stem cell transplant recipients. *Transpl Infect Dis*. 2013; **15**: 243-250.

140. Taccone A, Occhi M, Garaventa A, Manfredini L, Viscoli C. Ct of invasive pulmonary aspergillosis in children with cancer. *Pediatr Radiol*. 1993; 23: 177-180.
141. 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.
142. 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: 139-147.
143. Heussel CP, Kauczor HU, Heussel G, Fischer B, Mildenerger P, Thelen M. Early detection of pneumonia in febrile neutropenic patients: Use of thin-section ct. *AJR American journal of roentgenology*. 1997; 169: 1347-1353.
144. Caillot D, Couaillier JF, Bernard A, et al. Increasing volume and changing characteristics of invasive pulmonary aspergillosis on sequential thoracic computed tomography scans in patients with neutropenia. *J Clin Oncol*. 2001; 19: 253-259.
145. 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**: 558-564.
146. 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. *Pediatric blood & cancer*. 2007; **48**: 28-34.
147. Hayden R, Pounds S, Knapp K, et al. Galactomannan antigenemia in pediatric oncology patients with invasive aspergillosis. *Pediatr Infect Dis J*. 2008; **27**: 815-819.
148. Castagnola E, Furfaro E, Caviglia I, et al. Performance of the galactomannan antigen detection test in the diagnosis of invasive aspergillosis in children with cancer or undergoing haemopoietic stem cell transplantation. *Clin Microbiol Infect*. 2010; **16**: 1197-1203.
149. Fisher BT, Zaoutis TE, Park JR, et al. Galactomannan antigen testing for diagnosis of invasive aspergillosis in pediatric hematology patients. *J Pediatric Infect Dis Soc*. 2012; **1**: 103-111.

150. Jha AK, Bansal D, Chakrabarti A, Shivaprakash MR, Trehan A, Marwaha RK. Serum galactomannan assay for the diagnosis of invasive aspergillosis in children with haematological malignancies. *Mycoses*. 2013; **56**: 442-448.
151. Choi SH, Kang ES, Eo H, et al. Aspergillus galactomannan antigen assay and invasive aspergillosis in pediatric cancer patients and hematopoietic stem cell transplant recipients. *Pediatric blood & cancer*. 2013; **60**: 316-322.
152. Dinand V, Anjan M, Oberoi JK, et al. Threshold of galactomannan antigenemia positivity for early diagnosis of invasive aspergillosis in neutropenic children. *J Microbiol Immunol Infect*. 2016; **49**: 66-73.
153. Lehrnbecher T, Robinson PD, Fisher BT, et al. Galactomannan,  $\beta$ -D-glucan, and polymerase chain reaction-based assays for the diagnosis of invasive fungal disease in pediatric cancer and hematopoietic stem cell transplantation: a systematic review and meta-analysis. *Clin Infect Dis*. 2016; **63**: 1340-1348.
154. Loeffler J, Hafner J, Mengoli C, et al. Prospective biomarker screening for diagnosis of invasive aspergillosis in high-risk pediatric patients. *J Clin Microbiol*. 2016; **55**: 101-109.
155. Warris A, Lehrnbecher T. Progress in the diagnosis of invasive fungal disease in children. *Curr Fungal Infect Rep*. 2017; **11**: 35-44.
156. Vena A, Bouza E, Álvarez-Uría A, et al. The misleading effect of serum galactomannan testing in high-risk haematology patients receiving prophylaxis with micafungin. *Clin Microbiol Infect*. 2017; **23**: 1000.e1-1000.e4.
157. 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**: 750-770.
158. Lamoth F, Cruciani M, Mengoli C, et al.  $\beta$ -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**: 633-643.
159. 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**: 924-925.

160. Zhao L, Tang JY, Wang Y, et al. Value of plasma beta-glucan in early diagnosis of invasive fungal infection in children. *Zhongguo Dang Dai Er Ke Za Zhi*. 2009; **11**: 905-908.
161. 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**: 882-883.
162. Badiie P, Alborzi A, Karimi M, et al. Diagnostic potential of nested pcr, galactomannan eia, and beta-d-glucan for invasive aspergillosis in pediatric patients. *J Infect Dev Ctries*. 2012; **6**: 352-357.
163. Guitard J, Tabone MD, Senghor Y, et al. Detection of  $\beta$ -D-glucan for the diagnosis of invasive fungal infection in children with hematological malignancy. *J Infect*. 2016; **73**: 607-615.
164. Gupta P, Ahmad A, Khare V, et al. Comparative evaluation of pan-fungal real-time PCR, galactomannan and (1-3)- $\beta$ -D-glucan assay for invasive fungal infection in paediatric cancer patients. *Mycoses*. 2017; **60**: 234-240.
165. Becker MJ, Lugtenburg EJ, Cornelissen JJ, Van Der Schee C, Hoogsteden HC, De Marie S. Galactomannan detection in computerized tomography-based bronchoalveolar lavage fluid and serum in haematological patients at risk for invasive pulmonary aspergillosis. *Br J Haematol*. 2003; **121**: 448-457.
166. Clancy CJ, Jaber RA, Leather HL, et al. Bronchoalveolar lavage galactomannan in diagnosis of invasive pulmonary aspergillosis among solid-organ transplant recipients. *Journal of clinical microbiology*. 2007; **45**: 1759-1765.
167. Husain S, Paterson DL, Studer SM, et al. Aspergillus galactomannan antigen in the bronchoalveolar lavage fluid for the diagnosis of invasive aspergillosis in lung transplant recipients. *Transplantation*. 2007; **83**: 1330-1336.
168. 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**: 1688-1693.
169. Hsu LY, Ding Y, Phua J, et al. Galactomannan testing of bronchoalveolar lavage fluid is useful for diagnosis of invasive pulmonary aspergillosis in hematology patients. *BMC Infect Dis*. 2010; **10**: 44.



170. Bergeron A, Belle A, Sulahian A, et al. Contribution of galactomannan antigen detection in BAL to the diagnosis of invasive pulmonary aspergillosis in patients with hematologic malignancies. *Chest*. 2010; **137**: 410-415.
171. Eigl S, Hoenigl M, Spiess B, et al. Galactomannan testing and Aspergillus PCR in same-day bronchoalveolar lavage and blood samples for diagnosis of invasive aspergillosis. *Med Mycol*. 2017; **55**: 528-534.
172. 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**: 283-286.
173. de Mol M, de Jongste JC, van Westreenen M, et al. Diagnosis of invasive pulmonary aspergillosis in children with bronchoalveolar lavage galactomannan. *Pediatr Pulmonol*. 2013; **48**: 789-796.
174. Verweij PE, Brinkman K, Kremer HP, Kullberg BJ, Meis JF. Aspergillus meningitis: Diagnosis by non-culture-based microbiological methods and management. *Journal of clinical microbiology*. 1999; **37**: 1186-1189.
175. Viscoli C, Machetti M, Gazzola P, et al. Aspergillus galactomannan antigen in the cerebrospinal fluid of bone marrow transplant recipients with probable cerebral aspergillosis. *Journal of clinical microbiology*. 2002; **40**: 1496-1499.
176. Roilides E, Pavlidou E, Papadopoulos F, et al. Cerebral aspergillosis in an infant with corticosteroid-resistant nephrotic syndrome. *Pediatr Nephrol*. 2003; **18** :450-453.
177. Machetti M, Zotti M, Veroni L, et al. Antigen detection in the diagnosis and management of a patient with probable cerebral aspergillosis treated with voriconazole. *Transpl Infect Dis*. 2000; **2**: 140-144.
178. Reinwald M, Buchheidt D, Hummel M, et al. Diagnostic performance of an Aspergillus-specific nested PCR assay in cerebrospinal fluid samples of immunocompromised patients for detection of central nervous system aspergillosis. *PLoS One*. 2013; **8**: e56706.
179. Soeffker G, Wichmann D, Loderstaedt U, Sobottka I, Deuse T, Kluge S. Aspergillus galactomannan antigen for diagnosis and treatment monitoring in cerebral aspergillosis. *Prog Transplant*. 2013; **23**: 71-74.

180. Koltze A, Rath P, Schöning S, et al.  $\beta$ -D-Glucan screening for detection of invasive fungal disease in children undergoing allogeneic hematopoietic stem cell transplantation. *J Clin Microbiol*. 2015; **53**: 2605-2610.
181. Calitri C, Caviglia I, Cangemi G, et al. Performance of 1,3- $\beta$ -D-glucan for diagnosing invasive fungal diseases in children. *Mycoses*. 2017; **60**: 789-795.
182. Stanzani M, Sassi C, Lewis RE, et al. High resolution computed tomography angiography improves the radiographic diagnosis of invasive mold disease in patients with hematological malignancies. *Clin Infect Dis*. 2015; **60**: 1603-1610.
183. 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**: e101-104.
184. Armenian SH, Hoffman JA, Butturini AM, Kapoor N, Mascarenhas L. Invasive diagnostic procedures for pulmonary infiltrates in pediatric hematopoietic stem cell transplant recipients. *Pediatr Transplant*. 2007; **11**: 736-742.
185. Liss B, Vehreschild JJ, Bangard C, et al. Our 2015 approach to invasive pulmonary aspergillosis. *Mycoses*. 2015; **58**: 375-382.
186. Dekio F, Bhatti TR, Zhang SX, Sullivan KV. Positive impact of fungal histopathology on immunocompromised pediatric patients with histology-proven invasive fungal infection. *Am J Clin Pathol*. 2015; **144**: 61-67.
187. Mennink-Kersten MA, Ruegebrink D, Klont RR, et al. Bifidobacterial lipoglycan as a new cause for false-positive platelia *Aspergillus* enzyme-linked immunosorbent assay reactivity. *J Clin Microbiol*. 2005; **43**: 3925-3931.
188. Goudjil S, Kongolo G, Dusol L, et al. (1-3)-beta-D-glucan levels in candidiasis infections in the critically ill neonate. *J Matern Fetal Neonatal Med*. 2013; **26**: 44-48.
189. Armenian SH, Nash KA, Kapoor N, et al. Prospective monitoring for invasive aspergillosis using galactomannan and polymerase chain reaction in high risk pediatric patients. *J Pediatr Hematol Oncol*. 2009; **31**: 920-926.
190. 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**: 733-739.

191. Cesaro S, Stenghele C, Calore E, et al. Assessment of the lightcycler PCR assay for diagnosis of invasive aspergillosis in paediatric patients with onco-haematological diseases. *Mycoses*. 2008; **51**: 497-504.
192. Hummel M, Spiess B, Roder J, et al. Detection of aspergillus DNA by a nested PCR assay is able to improve the diagnosis of invasive aspergillosis in paediatric patients. *J Med Microbiol*. 2009; **58**: 1291-1297.
193. Landlinger C, Preuner S, Baskova L, et al. Diagnosis of invasive fungal infections by a real-time panfungal PCR assay in immunocompromised pediatric patients. *Leukemia*. 2010; **24**: 2032-2038.
194. Mandhaniya S, Iqbal S, Sharawat SK, Xess I, Bakhshi S. Diagnosis of invasive fungal infections using real-time PCR assay in paediatric acute leukaemia induction. *Mycoses*. 2012; **55**: 372-379.
195. Reinwald M, Konietzka CA, Kolve H, et al. Assessment of aspergillus-specific PCR as a screening method for invasive aspergillosis in paediatric cancer patients and allogeneic haematopoietic stem cell recipients with suspected infections. *Mycoses*. 2014; **57**: 537-543.
196. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin b for primary therapy of invasive aspergillosis. *N Engl J Med*. 2002; **347**: 408-415.
197. Maertens JA, Raad, II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by aspergillus and other filamentous fungi (secure): A phase 3, randomised-controlled, non-inferiority trial. *Lancet*. 2016; **387**: 760-769.
198. Denning DW, Ribaud P, Milpied N, et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clin Infect Dis*. 2002; **34**: 563-571.
199. Fortun J, Martin-Davila P, Sanchez MA, et al. Voriconazole in the treatment of invasive mold infections in transplant recipients. *Eur J Clin Microbiol Infect Dis*. 2003; **22**: 408-413.

200. Wieland T, Liebold A, Jagiello M, Retzl G, Birnbaum DE. Superiority of voriconazole over amphotericin b in the treatment of invasive aspergillosis after heart transplantation. *J Heart Lung Transplant*. 2005; **24**: 102-104.
201. Veroux M, Corona D, Gagliano M, et al. Voriconazole in the treatment of invasive aspergillosis in kidney transplant recipients. *Transplant Proc*. 2007; **39**: 1838-1840.
202. Doby EH, Benjamin DK, Jr., Blaschke AJ, et al. Therapeutic monitoring of voriconazole in children less than three years of age: A case report and summary of voriconazole concentrations for ten children. *Pediatr Infect Dis J*. 2012; **31**: 632-635.
203. Soler-Palacin P, Frick MA, Martin-Nalda A, et al. Voriconazole drug monitoring in the management of invasive fungal infection in immunocompromised children: A prospective study. *J Antimicrob Chemother*. 2012; **67**: 700-706.
204. Bartelink IH, Wolfs T, Jonker M, et al. Highly variable plasma concentrations of voriconazole in pediatric hematopoietic stem cell transplantation patients. *Antimicrob Agents Chemother*. 2013; **57**: 235-240.
205. Cornely OA, Maertens J, Bresnik M, et al. Liposomal amphotericin b as initial therapy for invasive mold infection: A randomized trial comparing a high-loading dose regimen with standard dosing (ambiloader trial). *Clin Infect Dis*. 2007; **44**: 1289-1297.
206. Kotwani RN, Gokhale PC, Bodhe PV, Kirodian BG, Kshirsagar NA, Pandya SK. A comparative study of plasma concentrations of liposomal amphotericin b (l-amp-lrc-1) in adults, children and neonates. *Int J Pharm*. 2002; **238**: 11-15.
207. Seibel NL, Shad AT, Bekersky I, et al. Safety, tolerability, and pharmacokinetics of liposomal amphotericin B in immunocompromised pediatric patients. *Antimicrob Agents Chemother*. 2017; **61**.
208. Groll AH, Silling G, Young C, et al. Randomized comparison of safety and pharmacokinetics of caspofungin, liposomal amphotericin b, and the combination of both in allogeneic hematopoietic stem cell recipients. *Antimicrob Agents Chemother*. 2010; **54**: 4143-4149.
209. Sunakawa K, Tsukimoto I, Tsunematsu Y, et al. Evaluation of the safety and efficacy of liposomal amphotericin b (l-amb) in children. *J Infect Chemother*. 2012; **18**: 456-465.

210. Herbrecht R, Maertens J, Baila L, et al. Caspofungin first-line therapy for invasive aspergillosis in allogeneic hematopoietic stem cell transplant patients: An european organisation for research and treatment of cancer study. *Bone Marrow Transplant*. 2010; **45**: 1227-1233.
211. Viscoli C, Herbrecht R, Akan H, et al. An eortc phase ii study of caspofungin as first-line therapy of invasive aspergillosis in haematological patients. *J Antimicrob Chemother*. 2009; **64**: 1274-1281.
212. Cornely OA, Vehreschild JJ, Vehreschild MJ, et al. Phase ii dose escalation study of caspofungin for invasive aspergillosis. *Antimicrob Agents Chemother*. 2011; **55**: 5798-5803.
213. Groetzner J, Kaczmarek I, Wittwer T, et al. Caspofungin as first-line therapy for the treatment of invasive aspergillosis after thoracic organ transplantation. *J Heart Lung Transplant*. 2008; **27**: 1-6.
214. Winkler M, Pratschke J, Schulz U, et al. Caspofungin for post solid organ transplant invasive fungal disease: Results of a retrospective observational study. *Transpl Infect Dis*. 2010; **12**: 230-237.
215. Maertens J, Egerer G, Shin WS, et al. Caspofungin use in daily clinical practice for treatment of invasive aspergillosis: Results of a prospective observational registry. *BMC Infect Dis*. 2010; **10**: 182.
216. 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.
217. Zaoutis T, Lehrnbecher T, Groll AH, et al. Safety experience with caspofungin in pediatric patients. *Pediatr Infect Dis J*. 2009; **28**: 1132-1135.
218. Zaoutis TE, Jafri HS, Huang LM, et al. A prospective, multicenter study of caspofungin for the treatment of documented candida or aspergillus infections in pediatric patients. *Pediatrics*. 2009; **123**: 877-884.
219. Ngai AL, Bourque MR, Lupinacci RJ, Strohmaier KM, Kartsonis NA. Overview of safety experience with caspofungin in clinical trials conducted over the first 15 years: A brief report. *Int J Antimicrob Agents*. 2011; **38**: 540-544.

220. Groll AH, Attarbaschi A, Schuster FR, et al. Treatment with caspofungin in immunocompromised paediatric patients: a multicentre survey. *J Antimicrob Chemother.* 2006; **57**: 527-535.
221. Caillot D, Thiebaut 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**: 2740-2746.
222. Candoni A, Caira M, Cesaro S, et al; SEIFEM GROUP (Sorveglianza Epidemiologica Infezioni Fungine nelle Emopatie Maligne). Multicentre surveillance study on feasibility, safety and efficacy of antifungal combination therapy for proven or probable invasive fungal diseases in haematological patients: the SEIFEM real-life combo study. *Mycoses.* 2014; **57**: 342-350.
223. Marr KA, Schlamm HT, Herbrecht R, et al. Combination antifungal therapy for invasive aspergillosis: A randomized trial. *Annals of internal medicine.* 2015; **162**: 81-89.
224. Singh N, Limaye AP, Forrest G, et al. Combination of voriconazole and caspofungin as primary therapy for invasive aspergillosis in solid organ transplant recipients: A prospective, multicenter, observational study. *Transplantation.* 2006; **81**: 320-326.
225. Raad II, Zakhem AE, Helou GE, Jiang Y, Kontoyiannis DP, Hachem R. Clinical experience of the use of voriconazole, caspofungin or the combination in primary and salvage therapy of invasive aspergillosis in haematological malignancies. *Int J Antimicrob Agents.* 2015; **45**: 283-288.
226. Walsh TJ, Hiemenz JW, Seibel NL, et al. Amphotericin b lipid complex for invasive fungal infections: Analysis of safety and efficacy in 556 cases. *Clin Infect Dis.* 1998; **26**: 1383-1396.
227. Kleinberg M. Aspergillosis in the clear outcomes trial: Working toward a real-world clinical perspective. *Medical mycology.* 2005; **43 Suppl 1**: S289-294.
228. Pappas PG. Amphotericin B lipid complex in the treatment of invasive fungal infections: results of the Collaborative Exchange of Antifungal Research (CLEAR), an industry-supported patient registry. *Clin Infect Dis.* 2005; **40 Suppl 6**: S379-383.
229. Walsh TJ, Whitcomb P, Piscitelli S, et al. Safety, tolerance, and pharmacokinetics of amphotericin B lipid complex in children with hepatosplenic candidiasis. *Antimicrob Agents Chemother.* 1997; **41**: 1944-1948.

230. Walsh TJ, Seibel NL, Arndt C, et al. Amphotericin B lipid complex in pediatric patients with invasive fungal infections. *Pediatr Infect Dis J*. 1999; **18**: 702-708.
231. Herbrecht R, Auvrignon A, Andrès E, et al. Efficacy of amphotericin B lipid complex in the treatment of invasive fungal infections in immunosuppressed paediatric patients. *Eur J Clin Microbiol Infect Dis*. 2001; **20**: 77-82.
232. Wiley JM, Seibel NL, Walsh TJ. Efficacy and safety of amphotericin B lipid complex in 548 children and adolescents with invasive fungal infections. *Pediatr Infect Dis J*. 2005; **24**: 167-174.
233. Denning DW, Lee JY, Hostetler JS, et al. Niaid mycoses study group multicenter trial of oral itraconazole therapy for invasive aspergillosis. *Am J Med*. 1994; **97**: 135-144.
234. Caillot D, Bassaris H, McGeer A, et al. Intravenous itraconazole followed by oral itraconazole in the treatment of invasive pulmonary aspergillosis in patients with hematologic malignancies, chronic granulomatous disease, or aids. *Clin Infect Dis*. 2001; **33**: e83-90.
235. Grigull L, Kuehlke O, Beilken A, et al. Intravenous and oral sequential itraconazole antifungal prophylaxis in paediatric stem cell transplantation recipients: a pilot study for evaluation of safety and efficacy. *Pediatr Transplant*. 2007; **11**: 261-266.
236. Kim H, Shin D, Kang HJ, et al. Successful empirical antifungal therapy of intravenous itraconazole with pharmacokinetic evidence in pediatric cancer patients undergoing hematopoietic stem cell transplantation. *Clin Drug Investig*. 2015; **35**: 437-446.
237. Starke JR, Mason EO Jr, Kramer WG, Kaplan SL. Pharmacokinetics of amphotericin B in infants and children. *J Infect Dis*. 1987; **155**: 766-774.
238. Benson JM, Nahata MC. Pharmacokinetics of amphotericin B in children. *Antimicrob Agents Chemother*. 1989; **33**: 1989-1993.
239. Koren G, Lau A, Klein J, et al. Pharmacokinetics and adverse effects of amphotericin B in infants and children. *J Pediatr*. 1988; **113**: 559-563.
240. Emminger W, Lang HR, Emminger-Schmidmeier W, Peters C, Gadner H. Amphotericin B serum levels in pediatric bone marrow transplant recipients. *Bone Marrow Transplant*. 1991; **7**: 95-99.

241. Nath CE, McLachlan AJ, Shaw PJ, Gunning R, Earl JW. Population pharmacokinetics of amphotericin B in children with malignant diseases. *Br J Clin Pharmacol.* 2001; **52**: 671-680.
242. White MH, Bowden RA, Sandler ES, et al. Randomized, double-blind clinical trial of amphotericin b colloidal dispersion vs. Amphotericin b in the empirical treatment of fever and neutropenia. *Clin Infect Dis.* 1998; **27**: 296-302.
243. Bowden R, Chandrasekar P, White MH, et al. A double-blind, randomized, controlled trial of amphotericin b colloidal dispersion versus amphotericin b for treatment of invasive aspergillosis in immunocompromised patients. *Clin Infect Dis.* 2002; **35**: 359-366.
244. Sandler ES, Mustafa MM, Tkaczewski I, et al. Use of amphotericin B colloidal dispersion in children. *J Pediatr Hematol Oncol.* 2000; **22**: 242-246.
245. Verweij PE, Varga J, Houbraken J, et al. *Emmericella quadrilineata* as cause of invasive aspergillosis. *Emerg Infect Dis.* 2008; **14**: 566–572.
246. Sugui JA, Peterson SW, Clark LP, et al. *Aspergillus tanneri* sp. nov., a new pathogen that causes invasive disease refractory to antifungal therapy. *J Clin Microbiol.* 2012; **50**: 3309-3317.
247. Vinh DC, Shea YR, Sugui JA, et al. Invasive aspergillosis due to *Neosartorya udagawae*. *Clin Infect Dis.* 2009; **49**: 102-111.
248. Scarcella A, Pasquariello MB, Giugliano B, Vendemmia M, de Lucia A. Liposomal amphotericin b treatment for neonatal fungal infections. *Pediatr Infect Dis J.* 1998; **17**: 146-148.
249. Juster-Reicher A, Flidel-Rimon O, Amitay M, Even-Tov S, Shinwell E, Leibovitz E. High-dose liposomal amphotericin b in the therapy of systemic candidiasis in neonates. *Eur J Clin Microbiol Infect Dis.* 2003; **22**: 603-607.
250. Karadag-Oncel E, Ozsurekci Y, Yurdakok M, Kara A. Is liposomal amphotericin b really safety in neonates? *Early Hum Dev.* 2013; **89**: 35-36.
251. Manzoni P, Rizzollo S, Farina D. Response to "is liposomal amphotericin b really safety in neonates?". *Early Hum Dev.* 2013; **89**: 37.
252. Le J, Adler-Shohet FC, Nguyen C, Lieberman JM. Nephrotoxicity associated with amphotericin B deoxycholate in neonates. *Pediatr Infect Dis J.* 2009; **28**: 1061-1063.



253. Würthwein G, Groll AH, Hempel G, Adler-Shohet FC, Lieberman JM, Walsh TJ. Population pharmacokinetics of amphotericin B lipid complex in neonates. *Antimicrob Agents Chemother.* 2005; **49**: 5092-5098.
254. Celik IH, Demirel G, Oguz SS, Uras N, Erdeve O, Dilmen U. Compassionate use of voriconazole in newborn infants diagnosed with severe invasive fungal sepsis. *Eur Rev Med Pharmacol Sci.* 2013; **17**: 729-734.
255. Odio CM, Araya R, Pinto LE, et al. Caspofungin therapy of neonates with invasive candidiasis. *Pediatr Infect Dis J.* 2004; **23**: 1093-1097.
256. Heresi GP, Gerstmann DR, Reed MD, et al. The pharmacokinetics and safety of micafungin, a novel echinocandin, in premature infants. *Pediatr Infect Dis J.* 2006; **25**: 1110-1115.
257. Smith PB, Walsh TJ, Hope W, et al. Pharmacokinetics of an elevated dosage of micafungin in premature neonates. *Pediatr Infect Dis J.* 2009; **28**: 412-415.
258. Sáez-Llorens X, Macias M, Maiya P, et al. Pharmacokinetics and safety of caspofungin in neonates and infants less than 3 months of age. *Antimicrob Agents Chemother.* 2009; **53**: 869-875.
259. Hope WW, Smith PB, Arrieta A, et al. Population pharmacokinetics of micafungin in neonates and young infants. *Antimicrob Agents Chemother.* 2010; **54**: 2633-2637.
260. Cohen-Wolkowicz M, Benjamin DK Jr, Piper L, et al. Safety and pharmacokinetics of multiple-dose anidulafungin in infants and neonates. *Clin Pharmacol Ther.* 2011; **89**: 702-707.
261. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. *J Antimicrob Chemother.* 2014; **69**: 1162-1176.
262. Brüggemann RJ, Aarnoutse RE. Fundament and prerequisites for the application of an antifungal TDM service. *Current Fungal Infection Reports.* 2015; **9**: 122-129.
263. Stockmann C, Constance JE, Roberts JK, et al. Pharmacokinetics and pharmacodynamics of antifungals in children and their clinical implications. *Clinical pharmacokinetics.* 2014; **53**: 429-454.

264. Perlin DS, Rautemaa-Richardson R, Alastruey-Izquierdo A. The global problem of antifungal resistance: prevalence, mechanisms, and management. *Lancet Infect Dis*. 2017; **17**: e383-e92.
265. Seyedmousavi S, Mouton JW, Melchers WJ, Bruggemann RJ, Verweij PE. The role of azoles in the management of azole-resistant aspergillosis: from the bench to the bedside. *Drug Resist Updat*. 2014; **17**: 37-50.
266. Verweij PE, Ananda-Rajah M, Andes D, et al. International expert opinion on the management of infection caused by azole-resistant *Aspergillus fumigatus*. *Drug Resist Updat*. 2015; **21-22**: 30-40.
267. Glasmacher A, Prentice A, Gorschlüter M, et al. Itraconazole prevents invasive fungal infections in neutropenic patients treated for hematologic malignancies: Evidence from a meta-analysis of 3,597 patients. *J Clin Oncol*. 2003; **21**: 4615-4626.
268. Tricot G, Joosten E, Boogaerts MA, Vande-Pitte J, Cauwenbergh G. Ketoconazole vs. Itraconazole for antifungal prophylaxis in patients with severe granulocytopenia: Preliminary results of two nonrandomized studies. *Rev Infect Diseases*. 1987; **9**: S94-S95.
269. Boogaerts MA, Verhoef GE, Zachee P, Demuynck H, Verbist L, De Beule K. Antifungal prophylaxis with itraconazole in prolonged neutropenia: Correlation with plasma levels. *Mycoses*. 1989; **32 Suppl 1**: 103-108.
270. Glasmacher A, Hahn C, Leutner C, et al. Breakthrough invasive fungal infections in neutropenic patients after prophylaxis with itraconazole. *Mycoses*. 1999; **42**: 443-451.
271. Boonsathorn S, Cheng I, Kloprogge F, et al. Clinical pharmacokinetics and dose recommendations for posaconazole in infants and children. *Clinical pharmacokinetics*. 2018; Apr 20.
272. Cornely OA, Robertson MN, Haider S, et al. Pharmacokinetics and safety results from the Phase 3 randomized, open-label, study of intravenous posaconazole in patients at risk of invasive fungal disease. *J Antimicrob Chemother*. 2017; **72**: 3406-3413.
273. 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.

274. Neely M, Rushing T, Kovacs A, Jelliffe R, Hoffman J. Voriconazole pharmacokinetics and pharmacodynamics in children. *Clin Infect Dis*. 2010; **50**: 27-36.
275. Neely M, Margol A, Fu X, et al. Achieving target voriconazole concentrations more accurately in children and adolescents. *Antimicrob Agents Chemother*. 2015; **59**: 3090-3097.
276. Job KM, Olson J, Stockmann C, Constance JE, Enioutina EY, Rower JE, et al. Pharmacodynamic studies of voriconazole: informing the clinical management of invasive fungal infections. *Expert review of anti-infective therapy*. 2016; **14**: 731-746.
277. Hope WW, Walsh TJ, Goodwin J, Peloquin CA, Howard A, Kurtzberg J, et al. Voriconazole pharmacokinetics following HSCT: results from the BMT CTN 0101 trial. *J Antimicrob Chemother*. 2016; **71**: 2234-2240.
278. Huurneman LJ, Neely M, Veringa A, Docobo Perez F, Ramos-Martin V, Tissing WJ, et al. Pharmacodynamics of voriconazole in children: further steps along the path to true individualized therapy. *Antimicrob Agents Chemother*. 2016; **60**: 2336-2342.
279. Pascual A, Csajka C, Buclin T, et al. Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety: Population pharmacokinetics-based analysis of adult patients with invasive fungal infections. *Clin Infect Dis*. 2012; **55**: 381-390.
280. Dolton MJ, Ray JE, Chen SCA, Ng K, Pont LG, McLachlan AJ. Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring. *Antimicrob Agents Chemother*. 2012; **56**: 4793-4799.
281. Cornely OA, Maertens J, Bresnik M, Ullmann AJ, Ebrahimi R, Herbrecht R. Treatment outcome of invasive mould disease after sequential exposure to azoles and liposomal amphotericin b. *J Antimicrob Chemother*. 2010; **65**: 114-117.
282. Auberger J, Lass-Flörl C, Aigner M, Clausen J, Gastl G, Nachbaur D. Invasive fungal breakthrough infections, fungal colonization and emergence of resistant strains in high-risk patients receiving antifungal prophylaxis with posaconazole: Real-life data from a single-centre institutional retrospective observational study. *J Antimicrob Chemother*. 2012; **67**: 2268-2273.
283. De la Serna J, Jarque I, López-Jiménez J, et al. Treatment of invasive fungal infections in high risk hematological patients. The outcome with liposomal amphotericin

B is not negatively affected by prior administration of mold-active azoles. *Rev Esp Quimioter.* 2013; **26**: 64-69.

284. Trifilio S, Singhal S, Williams S, et al. Breakthrough fungal infections after allogeneic hematopoietic stem cell transplantation in patients on prophylactic voriconazole. *Bone Marrow Transplant.* 2007; **40**: 451-456.
285. Winston DJ, Bartoni K, Territo MC, Schiller GJ. Efficacy, safety, and breakthrough infections associated with standard long-term posaconazole antifungal prophylaxis in allogeneic stem cell transplantation recipients. *Biol Blood Marrow Transplant.* 2011; **17**: 507-515.
286. Maertens J, Raad I, Petrikos G, et al; Caspofungin Salvage Aspergillosis Study Group. Efficacy and safety of caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy. *Clin Infect Dis.* 2004; **39**: 1563-1571.
287. Walsh TJ, Lutsar I, Driscoll T, et al. Voriconazole in the treatment of aspergillosis, scedosporiosis and other invasive fungal infections in children. *Pediatr Infect Dis J.* 2002; **21**: 240-248.
288. Maertens J, Glasmacher A, Herbrecht R, et al; Caspofungin Combination Therapy Study Group. Multicenter, noncomparative study of caspofungin in combination with other antifungals as salvage therapy in adults with invasive aspergillosis. *Cancer.* 2006; **107**: 2888-2897.
289. Denning DW, Marr KA, Lau WM, et al. Micafungin (fk463), alone or in combination with other systemic antifungal agents, for the treatment of acute invasive aspergillosis. *J Infect.* 2006; **53**: 337-349.
290. Kontoyiannis DP, Ratanatharathorn V, Young JA, et al. Micafungin alone or in combination with other systemic antifungal therapies in hematopoietic stem cell transplant recipients with invasive aspergillosis. *Transpl Infect Dis.* 2009; **11**: 89-93.
291. Kobayashi R, Suzuki N, Yoshida M, et al. Efficacy and safety of micafungin for febrile neutropenia in pediatric patients with hematological malignancies: a multicenter prospective study. *J Pediatr Hematol Oncol.* 2013; **35**: e276-279.
292. 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.

293. 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.
294. Maertens JA, Madero L, Reilly AF, et al. 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**: 415-420.
295. 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**: 249-255.
296. 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**: 1042-1051.
297. Girmenia C, Micozzi A, Gentile G, et al. Clinically driven diagnostic antifungal approach in neutropenic patients: A prospective feasibility study. *J Clin Oncol.* 2010; **28**: 667-674.
298. 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**: e350-356.
299. Yuan W, Ren J, Guo X, Guo X, Cai S. Preemptive antifungal therapy for febrile neutropenic hematological malignancy patients in China. *Med Sci Monit.* 2016; **22**: 4226-4232.
300. Castagnola E, Bagnasco F, Amoroso L, et al. Role of management strategies in reducing mortality from invasive fungal disease in children with cancer or receiving hemopoietic stem cell transplant: A single center 30-year experience. *Pediatr Infect Dis J.* 2014; **33**: 233-237.
301. Santolaya ME, Alvarez AM, Acuña M, et al. Efficacy of pre-emptive versus empirical antifungal therapy in children with cancer and high-risk febrile neutropenia: a randomized clinical trial. *J Antimicrob Chemother.* 2018; **73**: 2860-2866.
302. Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin b for empirical therapy in patients with persistent fever and neutropenia. National institute of allergy and infectious diseases mycoses study group. *N Engl J Med.* 1999; **340**: 764-771.

303. Walsh TJ, Tepler H, Donowitz GR, et al. Caspofungin versus liposomal amphotericin b for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med.* 2004; **351**: 1391-1402.
304. Koo A, Sung L, Allen U, et al. Efficacy and safety of caspofungin for the empiric management of fever in neutropenic children. *Pediatr Infect Dis J.* 2007; **26**: 854-856.